ISSN 0118-9034

# Philippine Heart Center Journal

Vol. 22 No. 1 January - June 2017



Official Publication of the Philippine Heart Center

# EDITORS AND CONSULTANTS



The Philippine Heart Center Journal is published by the Philippine Heart Center.

# PHILIPPINE HEART CENTER JOURNAL TABLE OF CONTENTS

*Volume 22 # 1 January-June, 2017*

## Editorial



## Original Articles

# Editorial

## Pushing for Publication

The Education, Training and Research Services (ETRS) of the Philippine Heart Center saw its conception middle of 2018 with the institution's government-mandated reorganization. New staff, new environ, renewed plans, redirected goals have reaffirmed the institution's mission to push the research agenda further and higher, with the continued publication of the research output of all residents, training fellows and members of the medical staff.

Motivation for publication stems primarily from the desire to share knowledge as a means to contribute towards the advancement of the sciences and eventually quality patient care. Research publication undoubtedly complements teaching and training, clinical care and public health. The far-reaching goal for the ETRS is to have the PHC Journal peer-reviewed. Research competitions among all the trainees of the various cardiovascular and allied specialties have continued to be held annually.

This issue of the Philippine Heart Center Journal compiles all the research that vied for the Philippine Heart Center's Research Competition for academic year 2016 - 2017. Albeit publication of these are temporally behind, it is believed that time has not made these articles any less relevant. The findings remain to be of intellectual value worth sharing with the rest of the scientific community.

Original articles from the various Departments – Pulmonary, Radiology, Adult Cardiology's Non-invasive and Invasive Divisions, Ambulatory and Emergency Care, Cardiovascular Surgery and Anesthesia, Pediatric Cardiology, Vascular Medicine and Cardiac Rehabilitation as well as Laboratory Medicine are all worthy of dissemination through this issue of the PHC Journal.

Altogether, their scientific significance provides the much-needed impetus towards pushing for publications not only in this journal but in international journals as well. The ETRS Strategic Narrative says it - that "we produce compassionate, globally competitive cardiovascular specialists and allied health professionals who can author internationally-acclaimed publications".

The drive towards a peer-reviewed journal foments. The hope is that the foment shall settle when the drive's end is reached in the not-too-distant future.

**Maria Belen O. Carisma, MD, FPCP, FPCC, FACC, MBAH**
Deputy Executive Director
Education, Training and Research Services

# In-hospital Outcomes of Patients with Thoracic and Abdominal Aortic Aneurysm Who Underwent Surgical, Endovascular and Conservative Medical Management

Ed D. Gabitoya, MD; Rosella S. Arellano, MD

***Background*** --- Aortic aneurysm is a life-threatening condition related to its catastrophic complications of rupture and dissection that warrants consideration of early surgical repair. The decision to intervene for aortic disease remained a challenging decision because of the concomitant high risk factors and comorbid illnesses as well as increased morbidity and mortality related to it.

***Method*** --- We performed a retrospective cohort of 275 patients with thoracic and abdominal aortic aneurysms with indication/s for intervention. The population was divided into three groups namely, surgical, endovascular or hybrid and medical management groups, respectively. Outcome measured included in-hospital mortality, cardiovascular, cerebrovascular, pulmonary and renal complications, embolic events and infection.

***Results*** --- Seventy-six percent of the subjects underwent surgical repair, 16% percent underwent endovascular or hybrid strategy while eight percent had conservative medical management. The over-all mortality rate is 16.36% with a statistically significant higher risk for in-hospital mortality in the medical group (p 0.001). Infection rate was higher in the surgical group (54.07%, p 0.001). There were no statistical differences in the cardiovascular events (p 0.069), neurologic complications (p 0.094), renal failure (p 0.082), respiratory failure (p 0.908), and embolic events (p 0.381) between the groups. Although, higher percentages of mortality in the surgical group, multivariate logistic regression analysis for in-hospital mortality showed that strategies of endovascular repair did not show a significant survival benefit (adjusted OR 0.987; 95% CI 0.219 – 4.436 p 0.986).

***Conclusion*** --- Prompt evaluation for early aortic aneurysm intervention either by open surgery or endovascular procedure is needed, because of high mortality related to medical management of large aortic aneurysms. A strategy of endovascular and/or hybrid repair was not associated with significant reduction in in-hospital mortality, when compared to open surgery, but evaluation of its intermediate and long-term outcomes is warranted. The use of endovascular or hybrid technique can be considered a feasible alternative to surgical repair especially in high-risk patients. ***Phil Heart Center J 2017;22(1):1-9.***

**Key Words: ■ open surgical repair ■ endovascular ■ medical management ■ thoracic aortic aneurysm ■ abdominal aortic aneurysm ■ 30-day mortality**

Over the past decades, studies[1-6] have demonstrated the natural history of thoracic and abdominal aortic aneurysms in order to improve survival and design new techniques in the management of the disease. Aortic aneurysm is highly lethal condition related to its catastrophic complications of rupture and dissection and that it warrants consideration of early surgical management.[1,2,5] The indications are related to the location, etiology, size, morphology and rate of expansion of the aneurysm.[5-8] Despite it being recommended in the guidelines, the mortality and morbidity of elective surgical management of aortic aneurysms remained high, with reports showing higher mortality for thoracic aortic aneurysm compared with abdominal aneurysms.[2] The decision of doing elective surgery remained an important factor, especially in asymptomatic patients and those with comorbid conditions, such as ischemic heart disease, chronic obstructive pulmonary disease and chronic renal insufficiency.[4,5,9] In another

*Finalist*, Oral Presentation - Original Paper. 24th PHC Annual Research Paper Competition and Poster Presentation held on February 26, 2016 at Philippine Heart Center. Correspondence *to Dr. Ed D. Gabitoya.* Department of Adult Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication**  2017 ISSN 0018-9034

spectrum of the disease, patients with genetically triggered aortic aneurysms like in Marfan Syndrome, requires early intervention because of the increase chances of complication particularly aortic dissection. The management of aortic aneurysms remained a challenging clinical decision, such that, a multidisciplinary approach to treatment and regular surveillance is needed.[1]

Earlier studies done in our institution regarding the in-hospital mortality associated with surgical management of thoracic aortic aneurysm showed a significant increased risk of 26.1% as reported in the study by Batoctoy, et al.[10] On the other hand, the institution's reported experience on the outcomes of abdominal aortic surgical management was limited. Also, the institution has no data on the outcomes of newer techniques in the management of aortic diseases particularly the strategy on endovascular repair and hybrid procedures.

This study aimed to review the in-hospital outcomes of patients with thoracic and abdominal aortic aneurysm who underwent either surgical, endovascular or conservative medical management. Essential information may be drawn from this study, that may support decision whether early surgical or endovascular interventions may benefit or are associated with increased mortality and complications.

## METHODS

The study was approved by the Institutional Review Board and informed consent was no longer obtained since the risk to the subject's privacy is minimal and no sensitive information were obtained. This is a retrospective cohort study involving patients with thoracic and abdominal aneurysms admitted at the Philippine Heart Center from January 2012 to December 2015. Patients age 19 years and above with presence of thoracic and/or abdominal aneurysm with indications to intervention were included in the study. The following indications were included: focal aortic dilatation measuring 5.5 cm and above as diagnosed by imaging like, echocardiography, abdominal duplex scan, computed tomography, magnetic resonance imaging and conventional aortography; genetically triggered aortic aneurysms (e.g. Marfan Syndrome) with aortic aneurysm measurement of 5.0 cm and above; thoracoabdominal aneurysm measuring 6.0 cm and above; saccular aneurysms of any size; and those symptomatic, ruptured or leaking aneurysms of any morphology and size. The presence of aortic dissection is excluded because of its difference in the natural history. Likewise, patient with prior endovascular and/or surgical interventions were also excluded.

Patients with thoracic and abdominal aneurysms were identified using medical and surgical database and radiographic data. Review of charts and imaging studies were done. A data abstraction tool was filled up which includes the patients' demographic profile, clinical presentation, co-morbid illness, risk factors, characteristics of aneurysm (size, location, morphology), and whether medical, surgical or endovascular interventions were instituted. Patients who underwent hybrid procedure were included in the endovascular group. Outcomes of the study include in-hospital mortality that encompasses death from any cause within the 30 days of hospitalization; cardiovascular events such as acute myocardial infarction, congestive heart failure and arrhythmia; neurologic complications including cerebrovascular accident (stroke), paraplegia and or paraparesis; renal failure which is defined as increase of creatinine to 2mg/dl or those requiring hemodialysis; respiratory failure as manifested by hypoxemia or hypercapnia or that requiring prolonged intubation, and ventilatory support either by intubation or non-invasive ventilation; other embolic events that include atheroembolism and lower limb ischemia; and infection from respiratory, urinary tract, and surgical site foci.

Using Epi Info version 7, the minimum sample size requirement was estimated to be at least 201 based on the following parameters: alpha = 5%, overall mortality rate 15.48 as reported in the study by Batoctoy, et al[10] and margin of error = 5%.

Data analysis was done using Stata SE version 13. Quantitative variables were summarized and presented as mean ± standard deviation while qualitative variables were tabulated and presented as frequency and percent distribution. Categorical and continuous variables were compared between groups using Fisher exact test and analysis of variance (ANOVA), respectively. A multivariate logistic regression analysis was performed to determine the likelihood for increased risk of mortality between the surgical and the endovascular group.

## RESULTS

A total of 275 patients were included in the study, seventy-six percent underwent surgical repair, sixteen percent underwent endovascular or hybrid procedure and eight percent had medical management. Majority of the subjects were male (78.91%), with a mean age of 65 ± 11.64 years; however, patients in the endovascular group were slightly older and younger patients were noted in the medical group (p 0.037). Baseline characteristics were presented in Table 1. Many patients have hypertension and history of smoking, being the most common risk factors and dyslipidemia was noted commonly in the surgical and endovascular groups (p 0.043). More than sixty percent of patients with aortic aneurysms have concomitant coronary artery disease, which is significantly higher in the endovascular group (p 0.013). Peripheral artery disease is seen in 50% of patients in the endovascular group (p 0.038). Upon presentation, the average size of both abdominal and thoracic aortic aneurysm was 7.08 ± 1.57 cm. Based on location, majority were abdominal aortic aneurysms (67.64%), then followed by thoracic aortic aneurysm (25.45%) and thoracoabdominal aneurysm (6.91%). The distribution based on location of the thoracic and abdominal aortic aneurysms were presented in Figures 1 and 2, respectively. Most common etiology was atherosclerotic. Majority of these aneurysms are of fusiform in morphology (81.09%), and 30.91% presented as ruptured aneurysm upon admission, with majority of them underwent emergency surgical repair. For abdominal aortic aneurysm, 33.17% presented as ruptured while in patients with thoracic aortic aneurysms, 14.29% presented as ruptured upon admission. Of the ruptured aneurysm, the average sizes for abdominal aortic fusiform and saccular aneurysms were 7.62 ± 1.20 cm and 5.62 ± 1.17 cm respectively, while for thoracic aortic fusiform and saccular aneurysms, the average sizes were 8.91 ± 1.40 cm and 6.63 ± 1.07, respectively.

Although, there was a trend of higher percentages of mortality rates in the surgical group when compared to endovascular group, multivariate logistic regression analysis of patients with abdominal and thoracic aneurysm revealed that there was no significant survival benefit using strategy for endovascular repair (adjusted OR 0.987; 95% CI 0.219 – 4.436 p 0.986) when adjusted to confounder such as sex and taking into consideration the presence of ruptured aortic aneurysms and emergency procedures done in the surgical group.

Table 2 showed the in-hospital outcomes of patient with thoracic and abdominal aneurysm who underwent surgical, endovascular and conservative medical management. The overall mortality rate was 16.36%, with highest in the medical group (p 0.001) and infection rate was high in the surgical group (54.07%, p 0.001). When analyzed based on the location of the aneurysm, the mortality rate for abdominal aortic aneurysm was 16.59% and was comparable to thoracic aortic aneurysm which was at 15.71%. Tables 3 and 4 showed the subanalysis of in-hospital outcomes of patients with aortic aneurysms according to location. In-hospital outcomes are higher in the medically treated group with significant increased risk in mortality. There was increased risk for infection in patients who underwent surgical repair of the aortic aneurysms (abdominal aneurysm p 0.035 and thoracic aneurysm p 0.001) and renal complications for those who underwent open surgery for abdominal aortic aneurysm (p 0.044). Embolic phenomenon such as acute limb ischemia and atheroembolism were noted in some patients admitted for abdominal aortic aneurysm.

**Table 1.** Baseline Characteristics

| Clinical Characteristics | Surgical Group n = 209 | Endovascular Group n = 44 | Medical Group n = 22 | p - value |
|---|---|---|---|---|
| Risk factors | | | | |
| Age (in years) | 64 ± 11.06 | 70 ± 11.73 | 60 ± 13.69 | 0.001 |
| Male | 172 (82.30) | 31 (70.45) | 14 (63.64) | 0.037 |
| Hypertension | 178 (85.17) | 38 (86.36) | 17 (77.27) | 0.558 |
| Diabetes | 41 (19. 62) | 10 (22.73) | 7 (31.82) | 0.364 |
| Dyslipidemia | 140 (66.99) | 31 (70.45) | 9 (40.91) | 0.043 |
| Smoking history | 154 (73.68) | 27 (61.36) | 13 (59.09) | 0.126 |
| Family history of aneurysm | 50 (23.92) | 7 (15.91) | 7 (31.82) | 0.329 |
| Co-morbid illness | | | | |
| CAD | 125 (59.81) | 36 (81.82) | 12 (54.55) | 0.013 |
| COPD | 37 (17.70) | 10 (22.73) | 3 (13.64) | 0.653 |
| CKD | 40 (19.14) | 5 (11.36) | 3 (13.64) | 0.483 |
| PAD | 63 (31.04) | 22 (50.0) | 6 (27.27) | 0.038 |
| CVA | 33 (15.79) | 6 (13.64) | 3 (13.64) | 0.957 |
| VHD | 15 (7.18) | 3 (6.82) | 4 (18.18) | 0.176 |
| Marfans Syndrome | 9 (4.31) | 0 (0.00) | 1 (4.55) | 0.421 |
| Takayasus Arteritis | 3 (1.44) | 1 (2.27) | 2 (9.09) | 0.062 |
| Characteristics of aneurysm | | | | |
| Size | 7.16 ± 1.63 | 6.85 ± 1.31 | 6.79 ± 1.48 | 0.336 |
| Morphology | | | | |
| Fusiform | 176 (84.21) | 32 (72.73) | 15 (68.18) | 0.051 |
| Saccular | 36 (17.22) | 12 (27.27) | 7 (31.82) | 0.087 |
| Location | | | | |
| Thoracic | 45 (21.53) | 17 (38.64) | 8 (36.36) | |
| Abdominal | 149 (71.29) | 25 (56.82) | 12 (54.55) | 0.091 |
| Thoracoabdominal | 15 (7.18) | 2 (9.09) | 2 (9.09) | |
| Ruptured | 77 (36.84) | 0 (0.00) | 8 (36.36) | 0.000 |
| Emergency procedure | 75 (35.89) | 0 (0.00) | 0 (0.00) | 0.000 |

CAD – Coronary artery disease; COPD – Chronic obstructive pulmonary disease; CKD – Chronic kidney disease; CVA – Cerebrovascular accident; PAD – Peripheral artery disease; VHD – Valvular heart disease

**Table 2.** In-hospital Outcomes of Patients with Abdominal and Thoracic Aortic Aneurysms Who Underwent Surgical, Endovascular and Conservative Medical Management

| Outcome | Surgical Group n = 209 | Endovascular Group n = 44 | Medical Group n = 22 | p - value |
|---|---|---|---|---|
| Mortality | 31 (14.83) | 3 (6.82) | 11 (50.00) | 0.001 |
| Cardiovascular events | 16 (7.66) | 4 (9.09) | 5 (22.73) | 0.069 |
| Neurologic complications | 12 (5.74) | 3 (6.82) | 14 (18.18) | 0.094 |
| Renal failure | 53 (25.36) | 5 (11.36) | 3 (13.64) | 0.082 |
| Respiratory failure | 30 (14.35) | 6 (13.64) | 2 (9.09) | 0.908 |
| Other embolic events | 8 (3.83) | 1 (4.55) | 0 (0.00) | 0.381 |
| Infection | 113 (54.07) | 12 (27.27) | 7 (31.82) | 0.001 |

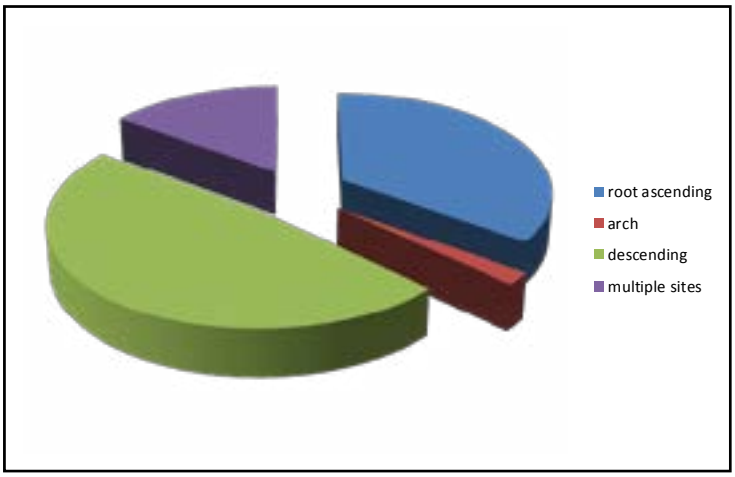


**Figure 1.** Distribution of thoracic aortic aneurysm based on location

**Table 3.** Sub-analysis of In-hospital Outcomes of Patients with Thoracic Aortic Aneurysm Who Underwent Surgical, Endovascular and Conservative Medical Management

| Outcome | Surgical Group n = 45 | Endovascular Group n = 17 | Medical Group n = 8 | p - value |
|---|---|---|---|---|
| Mortality | 5 (11.11) | 1 (5.88) | 5 (62.50) | 0.003 |
| Cardiovascular events | 4 (8.89) | 1 (5.88) | 2 (25.00) | 0.323 |
| Neurologic complications | 5 (11.11) | 2 (11.76) | 1 (12.50) | 1.000 |
| Renal failure | 5 (11.11) | 3 (17.65) | 0 (0.00) | 0.625 |
| Respiratory failure | 8 (17.78) | 4 (23.53) | 0 (0.00) | 0.452 |
| Other embolic events | 0 (0.00) | 0 (0.00) | 0 (0.00) | - |
| Infection | 27 (60.00) | 5 (29.41) | 0 (0.00) | 0.001 |

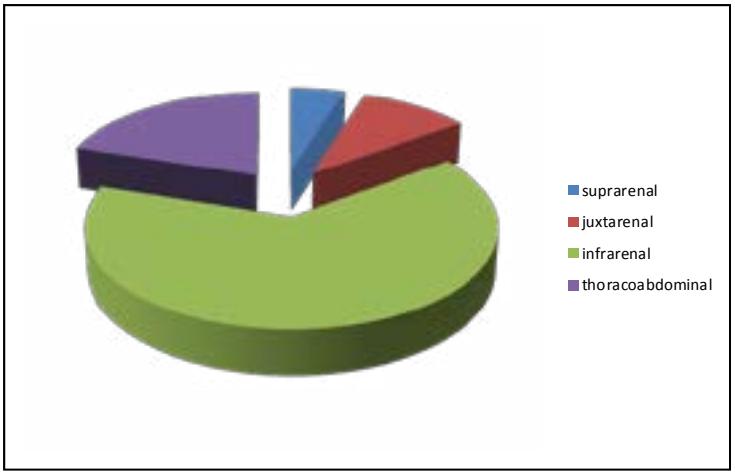


**Figure 2.** Distribution of abdominal aortic aneurysm based on location

**Table 4.** Sub-analysis of In-hospital Outcomes of Patients with Thoracic Abdominal Aneurysm Who Underwent Surgical, Endovascular and Conservative Medical Management

| Outcome | Surgical Group n = 164 | Endovascular Group n = 27 | Medical Group n = 14 | p - value |
|---|---|---|---|---|
| Mortality | 26 (15.85) | 2 (7.41) | 6 (42.86) | 0.023 |
| Cardiovascular events | 12 (7.32) | 3 (11.11) | 3 (21.43) | 0.122 |
| Neurologic complications | 7 (4.27) | 1 (3.70) | 3 (21.43) | 0.041 |
| Renal failure | 48 (29.27) | 2 (7.41) | 3 (21.43) | 0.044 |
| Respiratory failure | 2 (13.41) | 2 (7.41) | 2 (14.29) | 0.721) |
| Other embolic events | 6 (4.76) | 0 (0.00) | 0 (0.00) | 1.000 |
| Infection | 86 (52.44) | 7 (25.93) | 7 (50.00) | 0.035 |

## DISCUSSION

Findings in this retrospective cohort showed a significant increased risk in the in-hospital outcomes of patient with thoracic and abdominal aneurysm, who were medically managed, particularly 30-day mortality. When compared to endovascular or hybrid procedure, surgical management has higher percentages of in-hospital mortality, but the risk of increased mortality was not statistically significant. Overall, open surgery for aortic aneurysm was associated with increased infection rates, and open surgery for abdominal aortic aneurysm was associated with increased renal complications.

Several observational studies and systematic reviews[11-16] also showed a similar trend of increased 30-day mortality in patients who underwent open surgical repair versus endovascular and/or hybrid procedures for both thoracic and abdominal aortic aneurysms. However medical therapies for aortic aneurysms are available to slow the growth and reduce the risk of aneurysm-related dissection or rupture,[1] data on its role as the only therapy for larger aneurysms were limited, and guidelines[17] recommend medical management for smaller and asymptomatic aneurysms in conjunction with serial imaging to monitor growth and size of aneurysms. The increased in in-hospital outcomes seen in the medically treated group, particularly mortality, is associated with aneurysm related complications such as rupture and eventual hypovolemic shock and death.

In the treatment of thoracic aortic aneurysm, a recent study by Lee et al[11] showed that the 30-day mortality in the endovascular group was 3.5% versus open surgical repair group, which was at 9.4% in patients with isolated descending aortic aneurysm. However, subset of patients in this study has dissecting aortic aneurysms, which is an exclusion criterion in our study. On the other hand, another observational study[18] showed a similar perioperative 30-day mortality between endovascular and open surgical technique, same with what has been observed in our study, in the sub-analysis of outcomes of patients with thoracic aortic aneurysm. In subset of patients with ruptured thoracic aneurysms, the composite of death, stroke and permanent paraplegia occurred in 36.2% of the open surgical repair and 21.7% of the endovascular group.[12] In a multivariate analysis of this observational study, age and hypovolemic shock were noted to increase the risk for the composite outcome whereas endovascular technique was associated with significant lower risk of composite endpoint. Overall, for thoracic aneurysm, there was evident significant decreased risk in-hospital mortality in the endovascular and/or hybrid strategies compared to open surgical repair in both intact and ruptured thoracic aortic aneurysm. Moreover, the use of endovascular stent grafting was also introduced for ascending aortic repair especially in high-risk individuals and was considered feasible alternative to medical therapy in this group of patients.[19] But, these practices were not yet being done in our institution. When compared to previous study by Batoctoy et al,[10] the mortality for thoracic aortic aneurysm repair decreased to 11.11% from 26.1%, meaning that improved skills and use of newer techniques have evolved over time.

For abdominal aortic aneurysm repair, pooled relative risk for all-cause 30-day mortality was lower in the endovascular group than in the open surgical repair group.[13] The UK EVAR trial investigators[14] reported a significantly lower 30-day operative mortality rate for endovascular repair group (1.8%) compared to open surgical repair group (4.3%). Endovascular repair was also associated with early benefit with respect to aneurysm-related mortality. Similarly, even in patients 80 years and above, the pooled analysis showed higher immediate postoperative mortality after open surgical repair compared with endovascular repair.[15] This was associated with significantly higher risk of postoperative cardiac, pulmonary and renal complications. Like in ruptured thoracic aortic aneurysm, open surgical repair for ruptured abdominal aortic aneurysms was also associated with increased perioperative mortality of 47.7% compared to endovascular repair, which was 33.8%.[16] In contradistinction, the IMPROVE trial investigators[20] reported no significant difference in the 30-day mortality for both endovascular and open surgical repair groups (35.4% vs 37.4%). This was a similar observation noted in patients with abdominal aortic aneurysm in our study.

Furthermore, the overall in-hospital mortality benefit was evident for endovascular repair of aortic aneurysms compared with open surgical repair in all spectrum of the disease presentation. However, the intermediate outcomes showed increased endovascular-related complication and need for re-intervention with equal survival benefit in the long-term analysis.[12,13,16] An important findings in this retrospective study, was the increased mortality related to abdominal aortic repair compared to thoracic aortic repair, which is in contrast with what we have learned regarding aortic aneurysm repair.[2] One plausible explanation may be related to the increased cases of ruptured abdominal aortic aneurysms during presentation (33.17% vs. 14.29%).

Other outcomes such as cardiovascular, cerebrovascular, respiratory and renal complications and infections are related to risk factors and baseline profile of patients with aortic aneurysm.[2,15] Majority of these aortic aneurysms are degenerative in etiology and were related to significant risk of atherosclerosis and concomitant cardiovascular diseases. Elderly and those with concomitant comorbid conditions were considered high-risk for aortic aneurysm repair.[1,17,19] In our study, majority have concomitant coronary artery disease, noted to be higher in the endovascular group and some required prior or concomitant revascularization during aortic aneurysm intervention. On the other hand, infection rates were significantly increased in the patients who underwent open surgery. The increased in infection rate in this group maybe related to the use of several catheters perioperatively and associated prolonged hospitalization related to open surgery compared to endovascular procedures. Renal complications were also seen to be significantly associated with open surgery for abdominal aortic aneurysm. Postoperative renal failure is relatively common following aortic aneurysm surgery and is associated with poor outcome.[21] The interdependence of aneurysm and renal failure may be related to traditional method of surgical repair such as application of vascular clamps and the duration of the ischemic time. Likewise, aneurysm-related complication such as hypovolemia from ruptured aneurysm can also contribute to renal complications, which was also observed in this study.

Another important implication of this study is the increased rate of rupture aortic aneurysm at the time of presentation, particularly in patients with abdominal aortic aneurysm. Almost one-third of patients came in at the emergency room with ruptured AAA, and necessitates emergency repair. The importance of screening for abdominal aortic aneurysm has been reiterated by the U.S. Preventive Services Task Force and several guidelines[5,17] and has been shown to significantly reduced rates of AAA rupture, emergent surgery, and AAA-related deaths, particularly in elderly male smokers.

Although no statistical significance, the result of this retrospective study showed a trend toward increased risk of mortality for open surgical repair compared to endovascular and/or hybrid procedures and certain limitations should be considered which affects the result of this observation. In our institution none of the ruptured aortic aneurysms was managed by

emergency endovascular repair. In this study, all ruptured aortic aneurysms, whether, thoracic or abdominal, underwent emergency surgical repair, which may explain the associated increased risk for mortality in open surgical group. In our study, the over-all mortality for ruptured aortic aneurysms was 35.29% (thoracic 54.55%; abdominal 32.43%). This was addressed by doing a multivariate regression analysis to offset the effects of these variables. Second, although only a few in the subset of population, all ascending aortic aneurysms were also managed surgically and none with endovascular approach, making comparison of the two treatment modalities difficult. Likewise, the associated valvular heart disease complicating these ascending aneurysms may also considerably increased morbidity and mortality due to concomitant valvular repair or replacement procedures. Third, since the advent of guideline-directed management and increased knowledge of the natural history for aortic aneurysms, the number of patients for conservative medical management had decreased. When compared to the study done in our institution about a decade ago, a significant number of these large aneurysms, particularly thoracic aortic aneurysm, are now being managed surgically or by endovascular techniques. Moreover, the outcomes in this study were only limited to in-hospital or 30-days, and intermediate and long-term outcomes were warranted. Other outcomes for endovascular procedure such as endoleaks and other endovascular-related complications were also important. Further studies were recommended focusing on these outcomes.

## CONCLUSION

In conclusion, in-hospital outcomes for aortic aneurysm management were significantly higher in the medically treated group, particularly 30-day mortality, therefore prompt evaluation for early aortic aneurysm intervention by open surgery or endovascular procedure is needed. A strategy of endovascular and/or hybrid repair was not associated with significant reduction in in-hospital mortality, but has lower infection and renal complication rates, when compared with open surgery. Evaluation of its intermediate and long-term outcomes is warranted before definitive conclusions can be drawn about the relative merit of endovascular procedures in aortic aneurysm repair. The use of endovascular or hybrid technique can be considered a feasible alternative to surgical repair especially in high-risk patients.

## REFERENCES


1. Isselbacher EM. Thoracic and abdominal aortic aneurysms. Circulation. 2005 Feb 15;111(6):816-28.
2. Clouse WD, Hallett JW Jr, Schaff HV, Gayari MM, Ilstrup DM, Melton LJ 3rd. Improved prognosis of thoracic aortic aneurysms: a population-based study. JAMA. 1998 Dec 9;280(22):1926-9.
3. Crawford ES, DeNatale RW. Thoracoabdominal aortic aneurysm: observations regarding the natural course of the disease. J Vasc Surg. 1986 Apr;3(4):578-82.
4. Griepp RB, Ergin MA, Lansman SL, Galla JD, Pogo G. The natural history of thoracic aortic aneurysms. Semin Thorac Cardiovasc Surg. 1991 Oct;3(4):258-65.
5. U.S. Preventive Services Task Force. Screening for abdominal aortic aneurysm recommendation statement. Ann Intern Med. 2005 Feb 1;142(3):198-202.
6. Chaikof EL, Brewster DC, Dalman RL, Makaroun MS, Illig KA, Sicard GA, et al. The care of patients with an abdominal aortic aneurysm: the Society for Vascular Surgery practice guidelines. J Vasc Surg. 2009 Oct;50(4 Suppl):S2-49.
7. Davies RR, Goldstein LJ, Coady MA, Tittle SL, Rizzo JA, Kopf GS, Elefteriades JA. Yearly rupture or dissection rates for thoracic aortic aneurysms: simple prediction based on size. Ann Thorac Surg. 2002 Jan;73(1):17-27; discussion 27-8.
8. Coady MA, Rizzo JA, Hammond GL, Kopf GS, Elefteriades JA. Surgical intervention criteria for thoracic aortic aneurysms: a study of growth rates and complications. Ann Thorac Surg. 1999 Jun;67(6):1922-6; discussion 1953-8.
9. Lucas P, Tuano N. Cardiovascular profile and risk factors of Filipino patients with infra-renal abdominal aneurysm at the Philippine Heart Center from January 2005 to March 2012. Philippine Heart Center. 2010. [Unpublished].
10. Batoctoy BZ, Junia AT, Abola MT, Garcia F. In-hospital outcome of patients with thoracic aortic aneurysm admitted at Philippine Heart Center from 1994 to 2003. Philippine Heart Center. 2004. [Unpublished].
11. Lee HC, Joo HC, Lee SH, Lee S, Chang BC, Yoo KJ, Youn YN. Endovascular repair versus open repair for isolated descending thoracic aortic aneurysm. Yonsei Med J. 2015 Jul;56(4):904-12.

12. Jonker FH, Verhagen HJ, Lin PH, Heijmen RH, Trimarchi S, Lee WA, et al. Open surgery versus endovascular repair of ruptured thoracic aortic aneurysms. J Vasc Surg. 2011 May;53(5):1210-6.
13. Dangas G, O'Connor D, Firwana B, Brar S, Ellozy S, Vouyouka A, et al. Open versus endovascular stent graft repair of abdominal aortic aneurysms: a meta-analysis of randomized trials. JACC Cardiovasc Interv. 2012 Oct;5(10):1071-80.
14. United Kingdom EVAR Trial Investigators, Greenhalgh RM, Brown LC, Powell JT, Thompson SG, Epstein D, Sculpher MJ. Endovascular versus open repair of abdominal aortic aneurysm. N Engl J Med. 2010 May 20;362(20):1863-71.
15. Biancari F, Catania A, D'Andrea V. Elective endovascular vs. open repair for abdominal aortic aneurysm in patients aged 80 years and older: systematic review and meta-analysis. Eur J Vasc Endovasc Surg. 2011 Nov;42(5):571-6.
16. Edwards ST, Schermerhorn ML, O'Malley AJ, Bensley RP, Hurks R, Cotterill P, Landon BE. Comparative effectiveness of endovascular versus open repair of ruptured abdominal aortic aneurysm in the Medicare population. J Vasc Surg. 2014 Mar;59(3):575-82.
17. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, Evangelista A, Falk V, Frank H, Gaemperli O, Grabenwöger M, Haverich A, Iung B, Manolis AJ, Meijboom F, Nienaber CA, Roffi M, Rousseau H, Sechtem U, Sirnes PA, Allmen RS, Vrints CJ; ESC Committee for Practice Guidelines. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2014 Nov 1;35(41):2873-926.
18. von Allmen RS, Anjum A, Powell JT. Outcomes after endovascular or open repair for degenerative descending thoracic aortic aneurysm using linked hospital data. Br J Surg. 2014 Sep;101(10):1244-51.
19. Roselli EE, Idrees J, Greenberg RK, Johnston DR, Lytle BW. Endovascular stent grafting for ascending aorta repair in high-risk patients. J Thorac Cardiovasc Surg. 2015 Jan;149(1):144-51.
20. IMPROVE trial investigators. Endovascular or open repair strategy for ruptured abdominal aortic aneurysm: 30 day outcomes from IMPROVE randomised trial. BMJ 2014; 348:f7661.
21. Taylor PR, Reidy J, Scoble JE. Endovascular abdominal aortic aneurysm repair and renal function. Nephrol Dial Transplant. 2006 Sep;21(9):2362-5.

# Correlation of ST2 with Global LV Function in Filipinos with Acute Coronary Syndrome: a Quantitative Assessment Using 2-Dimensional Speckle Tracking Echocardiography 2D and 3D LV Analysis

Roy M. Sasil, MD; Edwin S. Tucay, MD; Viannely Berwyn F. Flores, MD; Romeo J. Santos, MD

***Background*** --- Philippine data on utilization of serum Suppression of Tumorigenicity 2 (sST2) and 2-dimensional speckle tracking echocardiography (2D- STE) among patients with acute coronary sydrome (ACS) post "acute phase" is non existent. This study aimed to determine the association between LV function utilizing 2-dimensional left ventricular ejection fraction (2D-LVEF), 2D-STE and sST2 then also determine whether changes in global longitudinal strain (GLS), global radial strain (GRS), and global circumferential strain (GCS) measurements during an acute myocardial infarction (AMI) correlates with the level of concentration of sST2.
***Methods*** --- This is a prospective cross sectional study of ACS patients admitted at the Philippine Heart Center (PHC) from September 2015 to January 2016 who underwent 2D-LVEF, 2D-STE measurements and sST2 (Presage) sampling within 48-72 hours after successful primary or rescue PCI for ST-segment elevation myocardial infarction (STEMI) and also within 48-72 hours of admission for stable non-ST elevation myocardial infarction (NSTEMI), unstable angina (UA) and STEMI treated medically.
***Results*** --- Eighty seven patients were included. There were 70% males and the majority were hypertensive (70%). Half of patients have STEMI yet, less than 20% underwent primary coronary intervention (PCI). The mean 2D-LVEF of the study population was (51.70 $\pm$ 48.71 %) by Simpson's method. Baseline 2D-LV EF (r=0.055, p=0.60) was not correlated with sST2. GLS(r=0.14,p=0.17) and GCS (r=0.10,p=0.35) exhibit direct but weak non-significant correlation while GRS (r=-0.14, p=0.18) showed inverse but weak non-significant correlation with sST2 during AMI.
***Conclusion*** --- 2D-LVEF did not show correlation while 2D-STE measurements are weakly correlated with sST2 during AMI among Filipinos. This confirms that sST2 may not be purely a marker of hemodynamic stress, fibrosis and adverse myocardial remodeling but may likely reflect to reater degree the state inflammatory response. ***Phil Heart Center J 2017;22(1):10-19.***

**Key Words: Acute Coronary Syndrome ■ Acute Myocardial Infarction ■ 2D Speckle Tracking Echocardiography ■ Global Longitudinal Strain ■ Global Radial Strain ■ Global Circumferential Strain ■ Serum Suppression of Tumorigencity 2**

Risk stratification and prognosis assessment among patients with acute myocardial infarction (AMI) is dependent on prognostically significant biomarkers coupled with imaging parameters. One such marker is Suppression of Tumorigenicity 2 (sST2, also known as an interleukin (IL)-l receptor-like-l) whose levels are elevated early after AMI and correlates with creatinine kinase and inversely with 2-dimensional left ventricular ejection fraction (2D-LVEF).[1] It predicts subsequent 30-day mortality and heart failure (HF).[2,3] Left ventricular (LV) volume, ejection fraction (EF), wall motion score index (WMSI) as well as the presence of increased left atrial volume and mitral regurgitation are echocardiographic imaging parameters also shown to provide prognostic information.[4-7] Among these, 2D-LVEF remains the most commonly used parameter to quantify global systolic function and predict cardiac mortality and morbidity.[8,9] Despite its widespread use, it is limited by dependence on

*Finalist*, Poster-Original Paper Presentation - Original Paper. 24th PHC Annual Research Paper Competition and Poster Presentation held on February 26, 2016 at Philippine Heart Center. Correspondence *to Dr. Roy M. Sasil., Jr.* Department of Adult Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication**  ISSN 0018-9034

image quality, subjective interpretation and LV geometric assumptions.[10]

Two-dimensional speckle tracking echocardiography (2D-STE) has allowed advances in quantification of LV function beyond traditional assessment of 2D-LVEF. 2D-STE global strain measurements: global longitudinal strain (GLS), global radial strain (GRS), and global circumferential strain (GCS) have excellent correlations with LVEF validated by three-dimensional (3D) echocardiography and cardiac magnetic resonance (CMR) imaging.[11] Of the three measures, assessment of GLS is a robust method for evaluating LV systolic function[12] as it provides incremental diagnostic and prognostic value and is a more sensitive marker of LV systolic function.[13-19]

That sST2 predicts adverse cardiovascular outcome and related to 2D-LVEF after AMI, suggest a role in adverse LV remodeling and as a potential pathophysiologic mediator of myocardial fibrosis. Weir et al. noted direct relationship between sST2, infarct magnitude, infarct remodeling assessed through CMR and they have shown that measurements of sST2 after AMI assists in the prediction of medium term LV functional recovery after AMI.[16] However, as to date there are no published papers that define the association of sST2 measurements with LV function utilizing 2D-STE in the Philippines. On the basis of its fibrosis modulating effect and the interaction between cardiac fibrosis and LV systolic function, we hypothesized that there is a direct correlation with sST2 and GLS, GRS and GCS in addition to an inverse relationship between sST2 and 2D-LVEF.

## METHODS

The study was a prospective cross-sectional, conducted in compliance with the ethical principles set forth in the Declaration of Helsinki and approved by the PHC Institutional Ethics Review Board. A written informed consent was obtained from both patients and attending physicians after explaining to them the aims, methods, significance, anticipated benefits and potential risks of the study and right to refuse or withdraw.

*Research Setting and Time Frame.* sST2 (Presage), speckle tracking measurements GLS, GRS and GCS were performed at the Non-invasive laboratory within 48-72 hours after successful primary or rescue percutaneous coronary intervention (PCI) for STEMI within 12 hours of symptom onset and within 48-72 hours of admission among stable non ST-segment elevation myocardial infarction (NSTEMI) or unstable angina (UA) and STEMI patients treated medically and admitted at the emergency room (ER), chest pain unit (CPU) or coronary care unit (CCU) of the Philippine Heart Center (PHC) from September 2015 to January 2016.

*Inclusion Criteria*: The subjects include patients aged >19 years, admitted at PHC ER, CPU and CCU with a diagnosis of ACS by medical history with the following criteria: patients with STEMI: 3 out of 4 criteria were met: 1) sudden onset of severe chest pain at rest or during minimal exertion, 2) ST-segment elevation or new LBBB indicating acute ischemic injury, 3) positive biomarker indicating myocardial necrosis (Troponin I or CKMB), 4) primary PCI or thrombolysis planned. Patients with NSTEMI ACS: at least 2 of the 3 criteria were met: 1) ST- segment changes on ECG indicating ischemia, 2) positive biomarker indicating myocardial necrosis, 3) one of the following risk indicators: a) ≥60 years of age, b) previous ischemic stroke without residual deficits, TIA, carotid stenosis (2:50%), c) chronic renal dysfunction (creatinine clearance <60 ml/l min), d) coronary artery disease (CAD) with 2:50% stenosis in 2:2 vessels, e) diabetes mellitus. Patients with UA: at least 1 of the 3 were met: 1) angina pectoris occurring at rest (or with minimal exertion) and usually lasting more than 20 minutes (if not interrupted by nitroglycerin), 2) being severe and described as frank pain and of new onset (within 1 month), 3) occurring with crescendo pattern (more severe, prolonged, or frequent than previously noted).

*Exclusion Criteria:* 1. Patients with congenital heart disease (CHD), concomitant valvular heart disease (VHD), chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, obvious chest trauma, autoimmune disease, severe hepatic disorders, chronic kidney disease (CKD) requiring dialysis, cancer patients, with known psychiatric disorders, anemia or febrile conditions, patients with recent surgery, previous

myocardial infarction (MI), pregnant, patients not mentioned with (a) unstable clinical condition, (b) suboptimal image quality for analysis (defined as more than three poorly visualized segments), or (c) arrhythmias such as atrial fibrillation with rapid ventricular response, atrial flutter, or frequent ventricular ectopy and lastly patients with previous history of heart failure symptoms.

*Sampling:* The participants were all ACS patients admitted for ACS from September to January 2016. The computed sample size was 84 patients yet recruitment was maximized to 107. Finally, 87 successfully participated. The 18 patients who were excluded had sST2 taken yet without 2D-STE studies. Among these patients, 6 had events within 72 hours (3 died, 1 had stroke and 2 had acute heart failure), 1 had an emergency coronary artery bypass, 2 went home against advise, 1 transferred to another hospital while the rest had poor echo windows with suboptimal image quality.

*Study Population:* Baseline parameters of the participants were gathered that include demographics, medical history and smoking history. Killip class, Lipid profile and FBS levels were likewise documented.

*Study Maneuver:* Blood samples were taken at the ER, CPU or CCU even without fasting. Venous blood were drawn from the antecubital vein with minimal tourniquet pressure into serum separator tubes. Samples were allowed to clot for 30 minutes (min) before centrifugation (4°C; 3,000 g for 15 min) and stored at -80°C until use.

*Laboratory Measurements:* sST2 were measured with specific enzyme-linked immunosorbent assays (ELISA) using Food and Drug Administration (FDA) Critical Diagnostics; Presage ST2. Minimum detection limit for sST2 was 1.3 ng/mL; laboratory determinations were performed using the ST2 assay kit in microplate configuration and read at 450nm with a microtiter well reader by medical technologists blinded to clinical characteristics of patients.

*Echocardiography:* **2D-LVEF**. Images were obtained at the non-invasive laboratory with patient in the left lateral decubitus position with a commercially available Acuson S2000 PRIME (Siemens Ultrasound Mountain View, California) using transducer at a depth of 14 to 16cm. Standard data on bi-dimensional echocardiography was collected according to American Society of Echocardiography (ASE) guidelines,[20] with LV size evaluated on M-Mode on a parasternal long axis view. LV volumes were estimated using the biplane Simpson's method from apical four-chamber and two-chamber views. These studies were done within 48-72 hours and read by Level 3 echocardiographers.

**2D-STE.** For strain analysis, experienced senior sonographers (A.C.S, M.V.A, M.M.A and J.H.V.) used transducer of the same machine to obtain images at the non-invasive laboratory within 48h to 72h of revascularization for STEMI and within 48h to 72h among NSTEMI/UA and STEMI patients treated medically. For GLS, endocardial borders of apical four-, three- and two-chamber views were manually defined and myocardial motion tracked by a semi-automated algorithm of Acuson SC2000 Prime. Parasternal short axis views at the level of the mitral valve, papillary muscle and apex were defined and traced manually for analysis of GRS and GCS. Based on frame by frame tracking of natural acoustic markers,[21] peak systolic LS were obtained for each of the 16 LV myocardial segments. All acquisitions were carried out by a single experienced echocardiographer blinded to the sST2 results and 2D LVEF measurements.

*Sample size.* Using NCSS-PASS 2013 software, the minimum sample size requirement was estimated to be at 84 based on the following parameters: Alpha (a)=5%, power (1-β) 80%, correlation between sST2 and 2D-LVEF= -0.3

*Statistical Analysis*. Data analysis was done using NCSS-PASS 2013 software. Quantitative variables were summarized and presented as mean and standard deviation and median, while qualitative variables were presented as frequency and percent distribution. Correlation between sST2 and 2D-LVEF and strain measurements (GLS, GRS and GCS) taken were assessed using Spearman's rho correlation coefficient and graphically presented using scatterplot. A further substudy was done categorizing patients accord-

ing to sST2 and type of MI as well as sST2 and type of intervention. P values <0.05 were considered statistically significant.

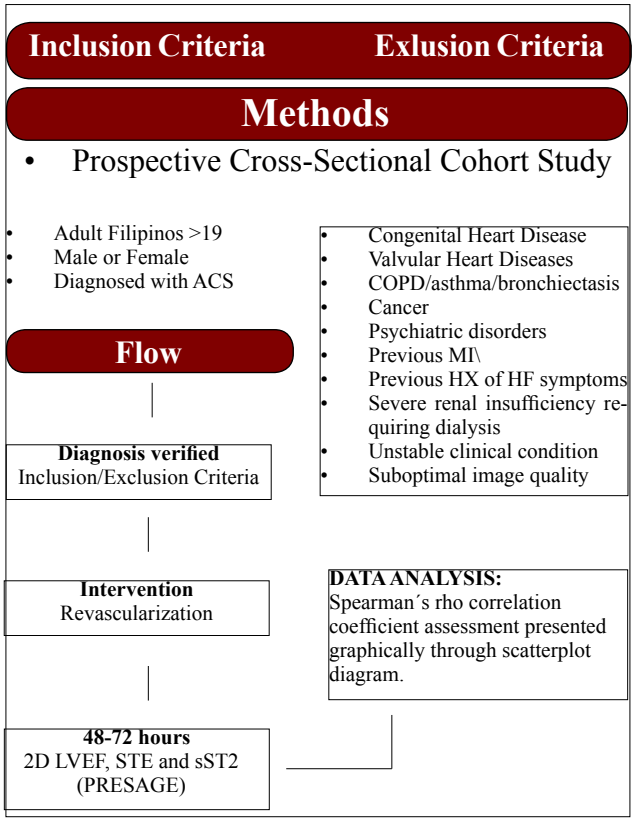


**Figure 1.** Simplified Flow of Study Manuever

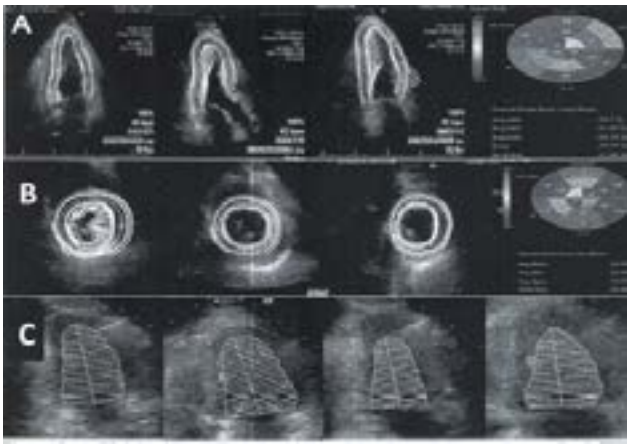


**Figure 2.** A GLS by 2D-STE (using 4, 3 and 2 apical chamber views) B. GCS and GRS by 2D-STE (obtained in the short axis view at the level of the MV, papillary muscle and apex) with each segment represented in the Bull's eye illustration using Accuson SC2GOOPRIME C. 2 D-LVEF obtained by Simpson's method

## RESULTS

**Study Population Characteristics:** Table 1 summarizes the baseline characteristics of 87 Filipino patients enrolled with acute coronary syndrome (ACS). The mean age, sex predominance as well as the medical history conforms with the findings of the Philippine Heart Association Acute Coronary Syndrome Registry in 2014. However, more than 50% enrolled in the study have STEMI yet less than 20% underwent immediate revascularization through PCI. The mean 2D-LVEF of the study population is 51.70% by Simpson's method.

**Serum ST2 Levels in Relation to Diagnosis**: Sixty three percent of patients (63%) had significant sST2 values (i.e. >35ng/ml: cut off value used in heart failure prognostication and studies in acute myocardial infarction). Seventy one (71%) in the STEMI subgroup and 64% among those with NSTEMI had elevated sST2 levels.

**Serum ST2 Levels in Relation to Events**: One out of 87 patients died within hospital admission due to acute heart failure. Six patients who had sST2 taken within 48 hours but were not included in the final analysis of this study because of death, acute heart failure and stroke within 72 hours had higher sST2 levels than those without events within 72 hours (55-1.99ng/ml).

**Ejection Fraction and Speckle Tracking Echocardiography:** Even with a preserved mean 2D-LVEF (51.70%), the mean GLS (-8.58 ± 5%) for the group and mean GCS (-12.76 ± 9.36%) is reduced compared to normal (-19±5% for GLS and -23.3± 3.4% for GCS).

**Correlation of Serum ST2 and Echocardiographic Parameters**: Of main importance in this study are the echocardiographic parameters namely GLS, GRS and GCS as well as the biomarker sST2 which revealed a skewed distribution of measurements (*Table 1*).

Figure 3 depicts the scatterplot diagram representation on the degree of correlation between sST2 and 2D-LVEF, GLS, GRS, and GCS. Baseline sST2 did not correlate with baseline 2D-L VEF (r=.05,p=0.6). GRS(r=-0.14, p=0.18) show inverse but weak non-significant correlation while GLS (r=0.14, p=0.17) and

**Correlation of Serum ST2 and Type of MI with Echocardiographic Parameters:** Table 2 shows the weak but non-significant relationship between sST2 among NSTEMI/UA patients and the different echocardiographic parameters namely: 2D-LVEF, GLS and GCS. GRS however remain to have an inverse but weak non-significant correlation with sST2 in both NSTEMI/UA and STEMI population.

**Correlation of Serum ST2 and Type of MI with Echocardiographic Parameters:** Table 3 also shows the weak but non-significant relationship between sST2 among patients who underwent PCI and the different echocardiographic parameters namely: 2D-LVEF and GLS. However, with medical management sST2 is weakly related only to 2D-STE measurements wherein GRS remain to show an inverse but weak non-significant correlation.

**Table 1.** Baseline Characteristics of Filipino Patients Enrolled with ACS

| Variable | N = 87(%) | |
|---|---|---|
| Age, y(mean ± SD) | 58 ±.09 | |
| Male | 61 (70) | |
| Smoking | 29 (33) | |
| **Medical History** | | |
| Diabetes | 16 (18) | |
| Hypertesion | 62 (70) | |
| **Echocardiographic data** | (Mean ± SD) | Mean (25P, 75P) |
| 2D EF | 51.70 ± 48.71 | 51 (42, 60) |
| 2D EF>50 | 46 (52%) | |
| 2D GLS | -8.58 ± 5.09 | -9.22 (11.545,-5.8) |
| 2D GRS | 16.71 ± 12.71 | 17.35 (10.2, 25.24) |
| 2D GCS | -12.60 ± 9.36 | -13.22 (-18.62,-9.07) |
| **Biomarker** | | |
| sST2 | 63.44 ± 48.71 | 51 (29.5, 82.5) |
| sST2>35 | 55 (63.2%) | |
| STEMI (n=45) | 32 (71%) | |
| NSTEMI (n=36) | 23 (64%) | |
| UA (n=6) | 1 (17%) | |
| **Blood Chemistries** | | |
| LDL (n=57) | 112.28 ± 36.3 | |
| FBS (n=66) | 6.23 ± 2.14 | |
| **Killip Score >1** | 22 (25) | |
| **Diagnosis** | | |
| STEMI | 45 (51) | |
| NSTEMI/UA | 42 (49) | |
| **Treatment** | | |
| PCI | 16 (18) | |
| Medical | 71 (82) | |

**Table 2.** Correlation of sST2 and Type of Myocardial Infarction with the Different Echocardioraphic Parameters.

| Echocardiographic Parameters | sST2 and Type of Myocardial Infarction | | | |
|---|---|---|---|---|
| | NSTEMI (n=42) | | STEMI (n=45) | |
| | Spearman´s rho | P Value | Spearman´s rho | P Value |
| 2D LVEF | 0.19 | 0.22 | -0.03 | 0.82 |
| GLS | 0.13 | 0.39 | 0.07 | 0.64 |
| GRS | -0.15 | 0.34 | -0.18 | 0.24 |
| GCS | 0.10 | 0.52 | 0.06 | 0.67 |

**Table 3.** Correlation of sST2 and Type of Treatment with the Different Echocardiographic Parameters

| Echocardiographic Parameters | sST2 and Type of Treatment | | | |
|---|---|---|---|---|
| | PCI (n=16) | | MEDICAL (n=71) | |
| | Spearman´s rho | P Value | Spearman´s rho | P Value |
| 2D LVEF | 0.32 | 0.22 | -0.02 | 0.88 |
| GLS | 0.10 | 0.70 | 0.12 | 0.36 |
| GRS | -0.05 | 0.86 | -0.14 | 0.22 |
| GCS | -0.04 | 0.88 | 0.12 | 0.30 |

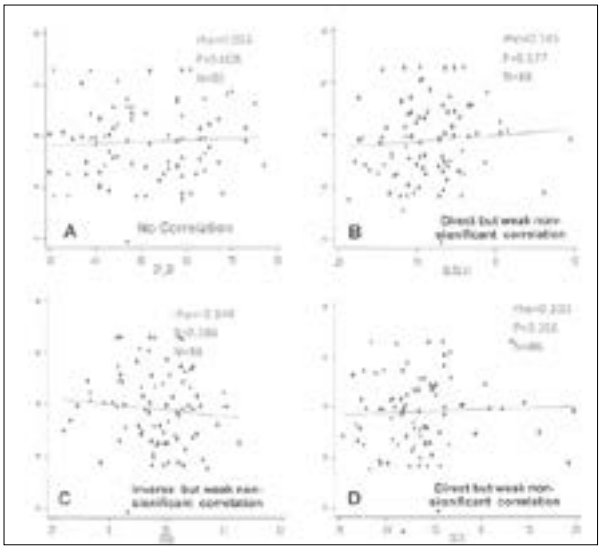


**Figure 3.** Scatterplot diagram between ST2, 2D-LVEF, and 2D-STE measurements A.)2D- LVEF B.)global longitudinal strain (GCS) C.)global radial strain (GRS) D.) global circumferential strain (GCS).

## DISCUSSION

Although there was a statistically significant but weak negative correlation between ST2 and 2D-LVEF in the MERLIN-TIMI 36 trial (Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome Thrombolysis In Myocardial Infarction 36 with 4426 patents in the ST2 sub-study),[22] CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy-Thombolysis in Myocardial Infarction 28 with 551 STEMI patients),[3] arid HEART (Healing and Early Afterload Reducing Therapy with 69 predominantly STEMI patients),[1] the present study which evaluated the correlation of ST2 levels among Filipinos with acute coronary syndrome (ACS) with measurements using the newer STE technology (for defining global myocardial function) vis a vis use of 2D-LVEF did not show correlation with 2D-LVEF. There is however an inverse but weak non significant correlation with GRS and a direct but weak non significant correlation with GLS and GCS. These findings using the above techniques support the idea that sST2 is not merely a surrogate for the degree of ventricular dysfunction at the time of measurement.[22] Our findings, integrated with those of others, espouses that sST2 may not be purely a marker of hemodynamic stress, fibrosis and adverse myocardial remodeling but may likely reflect to a greater degree the state of inflammatory response using pathways different from those detected by established biomarkers.[22]

The motivation for this paper comes from HF studies showing sST2 to be strongly associated with adverse outcomes, lower pre-discharge EF,[1] higher New York Heart Association functional class[23] and correlation with echocardiographic predictors of HF.[24] The value of sST2 as a biomarker to predict future clinical heart failure in patients with CAD which is the leading cause of death in the Philippines attracted the authors' interest.

We have presented that among the majority of Filipinos with STEMI and NSTEMI serum levels of sST2 are already increased within 48 hours. This result show similarity to other studies that demonstrate higher sST2 values in ACS compared to levels in patients with stable CAD and in individuals without CAD.[25] Though not part of the objectives of this work, we also observed that the sST2 levels are markedly elevated in patients with major adverse cardiovascular events or MACE (i.e. CV death, stroke, re-MI and re-hospitalization due to heart failure). The in-hospital MACE noted during recruitment (6 patients) and analysis (1 patient) support that sST2 concentration at presentation maybe associated with the risk of death or HF at 30 days among Filipinos. As of this writing, an ongoing follow-up study is conducted among our patients to evaluate the prognostic value of sST2 in predicting MACE. Published reports also showed association of higher levels with death within 6-months[26] and 43-months after STEMI,[25] independent of traditional risk indicators.[3,27] The relationship however between sST2 and acute change in the LV function using newer modalities like STE has not been previously characterized especially in our local setting.

Wall motion abnormalities and 2D-LVEF information on the other hand, are the main echocardiographic parameters relevant to the attending physician at the Emergency Department (ED) as these parameters are strongly predictive of all-cause mortality following AMI.[28,29] However, both 2D-LVEF (assessed by Simpson's biplane method) and

WMSI (a regional functional parameter) have inherent limitations.[10] Since cardiac mechanics is complex, these two parameters do not allow us to study the spatial organization of myocardial fibers.[30] 2D-STE, a relatively new, largely angle-independent technique provide new insights into cardiac mechanics.[31] The speckles seen in gray scale B-mode images results from the constructive and destructive interference of ultrasound back scattered from structures smaller than ultrasound wavelength. With the help of this technology, random noise is filtered out while keeping small temporary stable unique myocardial features known as speckles.[31] These speckles can be tracked from frame to frame (simultaneously in multiple regions within an image plane) using block matching and provide displacement information (velocity, strain and strain rate) depending on spatial resolution of the epicardium, midwall and endocardium.[31] The sub-endocardial layers, organized in oblique clockwise orientation accounts for the longitudinal function (long-axis) function while the circumferentially oriented mid-layers and outer layer arranged in an oblique anti-clockwise direction accounts for the short axis function[16] seen in 2D echocardiography as myocardial thickening. Longitudinal, radial, and circumferential strain can then be quantified, reflecting these different deformations. During AMI, GLS is first altered function due to early necrosis of sub-endocardial layers of myocardial fibers,[32] while radial function remains preserved. This is the reason why the correlation between sST2 and GRS is weakly negative but weakly positive in relation to GLS and GCS. Furthermore, GCS provide information on the extent of infarction whether sub-endocardial and transmural infarction[33,34] while GLS exhibit a predictive value for infarct size and 2D-LVEF recovery.[35,36-40] Though load-dependent, these parameters provide a more accurate insight into regional myocardial function and its impact on global function. In this study, we demonstrated the feasibility of measuring these 3 strain parameters in the AMI setting similar to the studies published.[5,37] GLS reproducibility and feasibility have been validated in the AMI setting,[35-37,40] which underlines the parameter's value as a prognostic tool. We assessed radial and circumferential strain and also correlate it with sST2 on account of the complex organization and interaction between these deformation parameters.[41]

Why there appears to be weak correlation remains intriguing and possibly because of smaller sample size, different timing of getting sST2 and the 2D-STE measurements (although within the 48-72 hours time-frame) and maybe perhaps on the inherent nature of sST2. sST2 is an interleukin (IL)-1 receptor family member with transmembrane (ST2L) and soluble isoforms (sST2).[44-46] ST2L is membrane-bound receptor, and IL-33 is it's functional ligand. sST2, a soluble truncated form of ST2L is being secreted into the circulation and believed to function as a "decoy" receptor for IL-33, inhibiting the effects of IL-33/ST2L signaling.[44-46] IL-33 functions as a danger signal or an alarm by signaling the presence of tissue damage to local immune cells after exposure to pathogens, injury-induced stress, or death by necrosis. IL-33/ST2L signaling leads to transcription of inflammatory genes and ultimately to the production of inflammatory cytokines/chemokines necessary for an appropriate and adequate immune response. In contrast, once sST2 binds to IL-33, it can function as a "decoy" receptor for IL-33, inhibiting IL-33/ST2L signaling. With a consequent increase in the concentration of sST2 in the circulation, the systemic biological effects of IL-33 is mitigated.[47] The source of circulating sST2 in cardiac disease was presumed to be myocardial following in vitro data.[1] Currently, it appears in this study that though sST2 is significantly elevated in 63% of patients with ACS and there is evidence of myocardial dysfunction based on depressed GLS, GRS and GCS values compared to normal, these 2 parameters (sST2 and STE measurements) are independent of each other. Further analysis of our data intriguingly showed that in STEMI patients, only GRS showed a weak and inverse non-significant relationship with sST2 when in fact it would be that last to be affected during acute infarction due to a totally occluded vessel. On the other hand, all 4 echocardiographic parameters are weakly related with sST2 among NSTEMI patients. Categorizing the data into treatment revealed a direct but weak non-significant correlation with sST2 and 2D-LVEF and GLS after PCI but only with GLS and GCS when medically treated. This finding is consistent with the observation of other authors that

among the echocardiographic parameters evaluated, GLS is consistently a robust and a more sensitive marker of LV systolic function. Our data also tend to support that the myocardium may not be the major source of increased sST2 with cardiac disease.[48] Some authors propose that vascular endothelial cells might be the predominant source of mRNA expression and for secretion of sST2 in AMI[49] Bartuneck et al. showed no difference in arterial and coronary sinus levels of sST2 and found that IL-33 protein to be localized to endothelial cells in the human coronary artery.[49] Furthermore, Svitlana et al. also showed that both human macrovascular (aortic and coronary artery) and heart microvascular endothelial cells secrete sST2 protein, whereas human adult cardiac myocytes, cardiac fibroblasts and vascular smooth muscle cells do not secrete detectable amounts of sST2 antigen in vitro.[25] sST2 was shown to be upregulated in human endothelial cells, by the inflammatory cytokines IL-I b, TNF -a and by phorbol ester.[49] Additionally, proinflammatory mediators IL-Ia, IL-Ib, and TNF-a as well as supematants of LPS-stimulated peripheral blood mononuclead cells led to an enhanced secretion of sST2 in cultured human adult cardiac myocytes, but not in cardiac fibroblasts.[30] With these published facts, our study provides yet another evidence that sST2 may not just be a pure marker of hemodynamic stress, fibrosis, and adverse myocardial remodeling but it may also reflect to a greater degree the state of inflammatory response independent of the information provided by 2D-STE measurements.

## LIMITATION

Our study was exclusively based on 2D strain analysis, itself limited to the quality of view acquisition and to its 2D nature. In plane and out-of-plane motion may, in fact, pose a problem for strain analysis, which not encountered when using the 3D or MR tagging approach.[32] We have a small sample size and interobserver and intraobserver variability was also not assessed due to time constraints. Furthermore, extraction of sST2 was not done at the same time images for strain and 2D-LVEF measurements were completed.

## CONCLUSION

2D-LVEF did not correlate while 2D-STE measurements are weakly and nonsignificantly correlated with sST2 concentrations during an AMI among Filipinos. This confirms that sST2 may not be purely a marker of hemodynamic stress, fibrosis and adverse myocardial remodelling but may likely reflect to a greater degree the state of inflammatory response.

## REFERENCES


1. Weinberg EO, Shimpo M, De Keulenaer GW, MacGillivray C, Tominaga S, Solomon SD, Rouleau JL, Lee RT. Expression and regulation of ST2, an interleukin-1 receptor family member, in cardiomyocytes and myocardial infarction.Circulation. 2002 Dec 3;106(23):2961-6.
2. Shimpo M, Morrow DA, Weinberg EO, Sabatine MS, Murphy SA, Antman EM, Lee RT. Serum levels of the interleukin-1 receptor family member ST2 predict mortality and clinical outcome in acute myocardial infarction. Circulation. 2004 May 11;109(18):2186-90. Epub 2004 Apr 26.
3. Sabatine MS, Morrow DA, Higgins LJ, MacGillivray C, Guo W, Bode C, Rifai N, et al. Complementary roles for biomarkers of biomechanical strain ST2 and N-terminal prohormone B-type natriuretic peptide in patients with ST-elevation myocardial infarction. Circulation. 2008 Apr 15;117(15):1936-44.
4. Gibbons RJ, Valeti US, Araoz PA, Jaffe AS. The quantification of infarct size. J Am Coll Cardiol. 2004 Oct 19;44(8):1533-42.
5. Møller JE, Hillis GS, Oh JK, Reeder GS, Gersh BJ, Pellikka PA. Wall motion score index and ejection fraction for risk stratification after acute myocardial infarction. Am Heart J. 2006 Feb;151(2):419-25.
6. Solomon SD, Skali H, Anavekar NS, Bourgoun M, Barvik S, Ghali JK, Warnica JW, et al. Changes in ventricular size and function in patients treated with valsartan, captopril, or both after myocardial infarction. Circulation. 2005 Jun 28;111(25):3411-9. Epub 2005 Jun 20.
7. Mollema SA, Nucifora G, Bax JJ. Prognostic value of echocardiography after acute myocardial infarction. Heart. 2009 Nov;95(21):1732-45.
8. Quiñones MA, Greenberg BH, Kopelen HA, Koilpillai C, Limacher MC, Shindler DM, Shelton BJ, et al. Echocardiographic predictors of clinical outcome in patients with left ventricular dysfunction enrolled in the SOLVD registry and trials: significance of left ventricular hypertrophy. Studies of Left Ventricular Dysfunction. J Am Coll Cardiol. 2000 Apr;35(5):1237-44.

9. Thune JJ, Køber L, Pfeffer MA, Skali H, Anavekar NS, Bourgoun M, Ghali JK, et al. Comparison of regional versus global assessment of left ventricular function in patients with left ventricular dysfunction, heart failure, or both after myocardial infarction: the valsartan in acute myocardial infarction echocardiographic study. J Am Soc Echocardiogr. 2006 Dec;19(12):1462-5.
10. Quiñones MA, Douglas PS, Foster E, Gorcsan J 3rd, Lewis JF, Pearlman AS, Rychik J, et al.ACC/AHA clinical competence statement on echocardiography: a report of the American College of Cardiology/American Heart Association/American College of Physicians-American Society of Internal Medicine Task Force on clinical competence. J Am Soc Echocardiogr. 2003 Apr;16(4):379-402.
11. Luis SA, Yamada A, Khandheria BK, Speranza V, Benjamin A, Ischenko M, Platts DG, et al. Use of three-dimensional speckle-tracking echocardiography for quantitative assessment of global left ventricular function: a comparative study to three-dimensional echocardiography. J Am Soc Echocardiogr. 2014 Mar;27(3):285-91.
12. Reisner SA, Lysyansky P, Agmon Y, Mutlak D, Lessick J, Friedman Z. Global longitudinal strain: a novel index of left ventricular systolic function. J Am Soc Echocardiogr. 2004 Jun;17(6):630-3.
13. Nesbitt GC, Mankad S, Oh JK. Strain imaging in echocardiography: methods and clinical applications. Int J Cardiovasc Imaging. 2009 Apr;25 Suppl 1:9-22.
14. Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. Heart. 2014 Nov;100(21):1673-80.
15. Spethmann S, Rieper K, Riemekasten G, Borges AC, Schattke S, Burmester GR, Hewing B, et al. Echocardiographic follow-up of patients with systemic sclerosis by 2D speckle tracking echocardiography of the left ventricle. Cardiovasc Ultrasound. 2014 Mar 29;12:13.
16. Bière L, Donal E, Terrien G, Kervio G, Willoteaux S, Furber A, Prunier F. Longitudinal strain is a marker of microvascular obstruction and infarct size in patients with acute ST-segment elevation myocardial infarction. PLoS One. 2014 Jan 28;9(1):e86959.
17. Rhea IB, Uppuluri S, Sawada S, Schneider BP, Feigenbaum H. Incremental prognostic value of echocardiographic strain and its association with mortality in cancer patients. J Am Soc Echocardiogr. 2015 Jun; 28 (6):667-73.
18. Saito M, Negishi K, Eskandari M, Huynh Q, Hawson J, Moore A, Koneru S, et al. Association of left ventricular strain with 30-day mortality and readmission in patients with heart failure. J Am Soc Echocardiogr. 2015 Jun; 28(6):652-66.
19. Dahou A, Bartko PE, Capoulade R, Clavel MA, Mundigler G, Grondin SL, Bergler-Klein J, et al. Usefulness of global left ventricular longitudinal strain for risk stratification in low ejection fraction, low-gradient aortic stenosis: results from the multicenter True or Pseudo-Severe Aortic Stenosis study. Circ Cardiovasc Imaging. 2015 Mar;8(3):e002117.
20. Hanekom L, Jenkins C, Jeffries L, Case C, Mundy J, Hawley C, Marwick TH. Incremental value of strain rate analysis as an adjunct to wall-motion scoring for assessment of myocardial viability by dobutamine echocardiography: a follow-up study after revascularization. Circulation. 2005 Dec 20;112(25):3892-900.
21. Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, Kaluski E, et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. J Am Soc Echocardiogr. 2004 Oct;17(10):1021-9.
22. Kohli P, Bonaca MP, Kakkar R, Kudinova AY, Scirica BM, Sabatine MS, Murphy SA, et al. Role of ST2 in non-ST-elevation acute coronary syndrome in the MERLIN-TIMI 36 trial. Clin Chem. 2012 Jan;58(1):257-66.
23. Rehman SU, Mueller T, Januzzi JL Jr. Characteristics of the novel interleukin family biomarker ST2 in patients with acute heart failure. J Am Coll Cardiol. 2008 Oct 28;52(18):1458-65.
24. Shah RV, Chen-Tournoux AA, Picard MH, van Kimmenade RR, Januzzi JL. Serum levels of the interleukin-1 receptor family member ST2, cardiac structure and function, and long-term mortality in patients with acute dyspnea. Circ Heart Fail. 2009 Jul;2(4):311-9.
25. Demyanets S, Speidl WS, Tentzeris I, Jarai R, Katsaros KM, Farhan S, Krychtiuk KA, et al. Soluble ST2 and interleukin-33 levels in coronary artery disease: relation to disease activity and adverse outcome. PLoS One. 2014 Apr 21;9(4):e95055. doi: 10.1371/journal.pone.095055. eCollection 2014.
26. Zhang K, Zhang XC, Mi YH, Liu J. Predicting value of serum soluble ST2 and interleukin-33 for risk stratification and prognosis in patients with acute myocardial infarction. Chin Med J (Engl). 2013;126(19):3628-31.
27. Sanada S, Hakuno D, Higgins LJ, Schreiter ER, McKenzie AN, Lee RT. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. J Clin Invest. 2007 Jun;117(6):1538-49. Epub 2007 May 10.
28. Savoye C, Equine O, Tricot O, Nugue O, Segrestin B, Sautière K, Elkohen M, et al. Left ventricular remodeling after anterior wall acute myocardial infarction in modern clinical practice (from the REmodelage VEntriculaire [REVE] study group). Am J Cardiol. 2006 Nov 1;98(9):1144-9.
29. Sutton JM, Ellis SG, Roubin GS, Pinkerton CA, King SB 3rd, Raizner AE, Holmes DR, et al. Major clinical events after coronary stenting. The multicenter registry of acute and elective Gianturco-Roubin stent placement. The Gianturco-Roubin Intracoronary Stent Investigator Group. Circulation. 1994 Mar;89(3):1126-37.
30. Torrent-Guasp F, Kocica MJ, Corno AF, Komeda M, Carreras-Costa F, Flotats A, Cosin-Aguillar J, et al. Towards new understanding of the heart structure and function. Eur J Cardiothorac Surg. 2005 Feb;27(2):191-201.

31. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, Galderisi M, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. J Am Soc Echocardiogr. 2011 Mar;24(3):277-313.
32. Reant P, Labrousse L, Lafitte S, Bordachar P, Pillois X, Tariosse L, Bonoron-Adele S, et al.Experimental validation of circumferential, longitudinal, and radial 2-dimensional strain during dobutamine stress echocardiography in ischemic conditions. J Am Coll Cardiol. 2008 Jan 15;51(2):149-57.
33. Zhang Y, Chan AK, Yu CM, Yip GW, Fung JW, Lam WW, So NM, W et al. Strain rate imaging differentiates transmural from non-transmural myocardial infarction: a validation study using delayed-enhancement magnetic resonance imaging. J Am Coll Cardiol. 2005 Sep 6;46(5):864-71.
34. Chan J, Hanekom L, Wong C, Leano R, Cho GY, Marwick TH. Differentiation of subendocardial and transmural infarction using two-dimensional strain rate imaging to assess short-axis and long-axis myocardial function. Sep 6;46(5):864-71. J Am Coll Cardiol. 2006 Nov 21;48(10):2026-33.
35. Park YH, Kang SJ, Song JK, Lee EY, Song JM, Kang DH, Kim YH, et al. Prognostic value of longitudinal strain after primary reperfusion therapy in patients with anterior-wall acute myocardial infarction. J Am Soc Echocardiogr. 2008 Mar;21(3):262-7. Epub 2007 Sep 29.
36. Antoni ML, Mollerna SA, Delgado V, Atary JZ, Borleffs CJW, Boersma E, Holman ER, et al. Prognostic importance of strain and strain rate after acute myocardial infarction. Euro Heart J. 2010 July;31(13):1640-47.
37. Mollema SA, Delgado V, Bertini M, Antoni ML, Boersma E, Holman ER, Stokkel MP, et al. Viability assessment with global left ventricular longitudinal strain predicts recovery of left ventricular function after acute myocardial infarction. Circ Cardiovasc Imaging. 2010 Jan; 3 (1):15-23.
38. Grabka M, Wita K, Tabor Z, Paraniak-Gieszczyk B, Chmurawa J, Elżbieciak M, Bochenek T, et al. Prediction of infarct size by speckle tracking echocardiography in patients with anterior myocardial infarction. Coron Artery Dis. 2013 Mar;24(2):127-34.
39. Cimino S, Canali E, Petronilli V, Cicogna F, De Luca L, Francone M, Sardella G,et al. Global and regional longitudinal strain assessed by two-dimensional speckle tracking echocardiography identifies early myocardial dysfunction and transmural extent of myocardial scar in patients with acute ST elevation myocardial infarction and relatively preserved LV function. Eur Heart J Cardiovasc Imaging. 2013 Aug;14(8):805-11. doi: 10.1093/ehjci/jes295. Epub 2012 Dec 20.
40. Munk K, Andersen NH, Schmidt MR, Nielsen SS, Terkelsen CJ, Sloth E, Bøtker HE, et al. Remote ischemic conditioning in patients With myocardial infarction treated with primary angioplasty: impact on left ventricular function assessed by comprehensive echocardiography and gated single-photon emission CT. Circ Cardiovasc Imaging. 2010 Nov;3(6):656-62.
41. Vartdal T, Brunvand H, Pettersen E, Smith HJ, Lyseggen E, Helle-Valle T, Skulstad H, et al. Early prediction of infarct size by strain Doppler echocardiography after coronary reperfusion. J Am Coll Cardiol. 2007 Apr 24; 49(16):1715-21.
42. Hung CL, Verma A, Uno H, Shin SH, Bourgoun M, Hassanein AH, McMurray JJ, et al. Longitudinal and circumferential strain rate, left ventricular remodeling, and prognosis after myocardial infarction. J Am Coll Cardiol. 2010 Nov 23;56(22):1812-22.
43. Weinberg EO. ST2 protein in heart disease: from discovery to mechanisms and prognostic value. Biomark Med. 2009 Oct;3(5):495-511.
44. Liew FY, Pitman NI, McInnes IB. Disease-associated functions of IL-33: the new kid in the IL-1 family. Nat Rev Immunol. 2010 Feb;10(2):103-10.
45. Miller AM, Liew FY. The IL-33/ST2 pathway--A new therapeutic target in cardiovascular disease. Pharmacol Ther. 2011 Aug;131(2):179-86.
46. Mueller T, Dieplinger B. The Presage(®) ST2 Assay: analytical considerations and clinical applications for a high-sensitivity assay for measurement of soluble ST2. Expert Rev Mol Diagn. 2013 Jan;13(1):13-30.
47. Mueller T, Jaffe AS. Soluble ST2--analytical considerations. Am J Cardiol. 2015 Apr 2;115(7 Suppl):8B-21B.
48. Demyanets S, Kaun C, Pentz R, Krychtiuk KA, Rauscher S, Pfaffenberger S, Zuckermann A, et al. Components of the interleukin-33/ST2 system are differentially expressed and regulated in human cardiac cells and in cells of the cardiac vasculature. J Mol Cell Cardiol. 2013 Jul;60:16-26.
49. Bartunek J, Delrue L, Van Durme F, Muller O, Casselman F, De Wiest B, Croes R, et al. Nonmyocardial production of ST2 protein in human hypertrophy and failure is related to diastolic load. J Am Coll Cardiol. 2008 Dec 16;52(25):2166-74.
50. Mildner M, Storka A, Lichtenauer M, Mlitz V, Ghannadan M, Hoetzenecker K, Nickl S, et al. Primary sources and immunological prerequisites for sST2 secretion in humans. Cardiovasc Res. 2010 Sep 1;87(4):769-77.

# Validation of the HEART Score System in the Emergency Department Patients with Chest Pain and Possible Acute Coronary Syndrome

Jericho C. De Leon, MD; Chito C. Permejo, MD

***Background*** --- Chest pain is one of the most common complaints of patients seeking consult in the Emergency Room (ER). The HEART score is a novel scoring system that utilizes the history, ECG, age of the patient, risk factors and troponin levels that may aid clinicians in the stratification of patients with chest pain in the ER. This study aims to determine the validity of the HEART score in predicting outcome in patients with chest pain seen in our emergency room.

***Methods*** --- Patients who presented with chest pain in the Emergency Department of the Philippine Heart Center were included in the study and their HEART scores were determined prospectively. Patients were followed up for 30 days and the occurrence of acute myocardial infarction, revascularization and/or death were noted. The sensitivity, specificity, positive and negative predictive values were then calculated in each HEART score.

***Results*** --- A total of 328 patients were included. One hundred seventy-six patients or 53.7% reached at least one endpoint. HEART scores of 0 to 3 yielded excellent sensitivity and negative predictive values. a score of 7 and above on the other hand showed high specificity and positive predictive values. The measured C-statistic for the HEART score was 0.951.

***Conclusion*** --- The HEART score is an easy, reliable and convenient scoring system for stratifying patients with chest pain in the emergency room. It can be applied in our local setting and it has an excellent ability to predict the occurrence of adverse cardiac events. ***Phil Heart Center J 2017;22(1):20-25.***

**Key Words: HEART Score System ■ vascular malformations ■ Myocardial Infarction ■ chest pain ■ scoring system**

Chest pain is one of the most common presentation of patients seen in the Emergency Room (ER). A lot of it however does not necessarily point to a cardiac cause. Acute coronary syndromes (ACS) should be quickly differentiated from these non-cardiac entities, as management for each of these conditions vary substantially and a delay in the treatmenf of ACS cases may be detrimental. Likewise, aside from differentiating cardiac and non-cardiac causes of chest pain, another problem that physicians in the emergency room face is stratifying patients with chest pain as to their severity and risk of developing a more serious or fatal condition. Dilemmas commonly arise as there are no definite criteria on whether to discharge or admit patients with chest pain in the ER.

Several scoring systems were developed to address this problem. Scoring systems such as the Thrombolysis In Myocardial Infarction (TIMI), platelet glycoprotein IIb/IIIa in unstable angina: Receptor Suppression Using Integrilin (PURSUIT) score, and Global Registry of Acute Coronary Events (GRACE) score, predict the short term prognosis of patients with ACS and were proved to aid the management decisions in these patients.[1,2] However, even though these scoring systems were validated and are backed-up by large clinical trials, none of them is widely used in clinical practice as they do not give much information in the differentiation of chest pain patients who are at low to moderate risk for an adverse outcome, or are too cumbersome and not ideal in an ER setting.

*Finalist*, Poster-Original Paper Presentation - Original Paper. 24th PHC Annual Research Paper Competition and Poster Presentation held on February 26, 2016 at Philippine Heart Center. Correspondence *to Dr. Jericho C. de Leon.* Department of Adult Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication**  2017 ISSN 0018-9034

A new scoring system has been proposed by A.J. Six and colleagues that consider the history, ECG findings, age of the patient, risk factors for cardiovascular disease, and Troponin levels.[3] The HEART scoring system considers these five factors and each can be scored with zero, one or two points, depending on the extent of the abnormality and the sum of these five considerations. It has been proved by observational and retrospective studies to predict outcomes in patients presenting with chest pain in the emergency room. However, no local study had been done yet to validate or test its applicability.

Once validated, the HEART score system will be of use in the decision making and might facilitate accurate diagnostic and therapeutic choices. This study aims to determine the validity of HEART score in predicting outcome in patients with chest pain seen in our emergency room.

## METHODS

This study was conducted with the approval of the Institutional Ethics Review Board (lERB) of the Philippine Heart Center. Informed consent were obtained on each participant prior to their inclusion in the study.

A prospective cohort study design was used. Adult patients aged 19 years and above who presented with chest pain in the emergency department of the Philippine Heart Center from January 2014 to October 2015 were included in the study. Patients were excluded if: 1) a clear traumatic etiology of pain was evident, 2) the patient had a terminal non-cardiac illness, 3) the troponin level was not requested or measured, or 4) there was a prior enrollment within 30 days.

*Sample size.* In the study of Six et al[3], a HEART score of 0-3 points holds a risk of 2.5% for an endpoint, while a score of 4-6 points carries a 20.3% risk, and for a score of 27 points implies a 72.7% risk of developing outcomes. Using a 95% confidence interval, a relative error of 5%, and a risk of 72.7% the sample size was targeted at 328 subjects.

*Study maneuver.* A standardized form was constructed for the collection of data on demographics, cardiac risk factors, cardiovascular history, and laboratory results including the ECG findings and troponin levels.

On patient arrival, initial evaluation was done, necessary diagnostic investigations were requested, and essential management interventions were administered to the patient. After stabilization, consent from the patient or nearest relative was procured for the participation in the study. The history part of the HEART score was completed first prior to the other components of the score in order to eliminate bias. Laboratory results were then reviewed for the completion of the score.

**The HEART Score**. A history of chest pain was deemed "slightly suspicious" for a cardiac origin if there was absence of specific elements in terms of pattern of the chest pain, onset and duration, relation with activity, cold or stress, localization, associated symptoms, and reaction to sublingual nitrates. This history was classified as "nonspecific" and was granted a score of O. If the patient history contained both nonspecific and suspicious elements, the history was classified as "moderately suspicious" and was granted one point. If the history contained primarily specific elements, the history was classified as "highly suspicious" and was given two points.

For the ECG, repolarization abnormalities without significant ST-segment depression received one point. One point was also granted for bundle branch block and typical abnormalities indicative of left ventricular hypertrophy. For significant ST-segment depressions or elevations in the absence of a bundle branch block, two points were given. In a normal ECG or in absence of the above findings, a score of zero was given. ECG findings were confirmed with the official readings of the tracings.

Two points were given for patients aged 65 years and above during the ER consult, one point if the patient was between 45 to 65 years, and no point if they were younger than 45 years old.

The following risk factors were considered in this study: diabetes mellitus, current or previous smoker, hypertension, dyslipidemia, family history of coronary artery disease and obesity. If

the patient had no risk factors at all, a zero point was given. For one or two risk factors, one point was given. For three or more risk factors, two points were given. Two points was also given for a history of coronary revascularization, myocardial infarction, stroke or peripheral arterial disease.

Troponin levels were measured using Istat and Pathfast troponin assays. If the troponin I level was normal or below the threshold value for positivity (troponin 1 ≤0.019) zero points were given. If the level was between 1-2x the threshold value for positivity, one point was given. If the level was more than twice the threshold value for positivity, two points were given.

The sum of the points for history, ECG, age, risk factors and troponin was noted as the HEART score.

*Outcomes.* Outcomes in this study were acute myocardial infarction, death of cardiac or unknown cause, or revascularization within 30 days of the emergency room visit. Revascularization may be in the form of fibrinolysis, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG). Patients with any of these outcomes were considered to have experienced an adverse cardiac event. Outcomes that occurred after patient assessment, whether in the emergency room, in the hospital, or after ER discharge, were included.

Follow-up was done by reviewing the medical records of patients and thru phone calls to note for any subsequent cardiac events.

*Statistical Analysis*. The sensitivity, specificity, positive predictive value and negative predictive value of each HEART score was computed. The C-statistic of the HEART score was also determined. All statistical computations were done using the software Stata.

## RESULT

A total of 328 patients were included in the study with only one patient lost to followup. Patients were 58.2 ± 14.4 years of age. Majority were males (n=218), comprising 66.5% of the population. Hypertension was the most prevalent risk factor (n=219, 66.8%), followed by smoking history (n=116, 35.4%) and diabetes mellitus (n=98, 29.9%). Previous myocardial infarction was present in 16 subjects (4.9%), and 54 patients had a known history of coronary artery disease (16.5%). Non-specific repolarization abnormalities were seen in the ECGs of 95 patients (29.0%), while 66 patients had normal ECG (20.1 %). Table 1 shows the demographic profile, risk factors and ECG findings of the included subjects.

A total of 176 patients reached at least one endpoint (53.7%) after a 30-day follow-up *(Table 2)*. Half or 164 patients were diagnosed with myocardial infarction and was managed as such (50.0%). A total of 73 patients (22.3%) underwent revascularization primarily in the form of PCI. Nineteen patients died constituting 5.8% of the subjects.

The HEART score can correctly place patients into low-, intermediate and high-risk groups. A score of 0-3 was considered to be low-risk, intermediate-risk for scores 4-6, and high risk for scores 7 and above. Table 3 shows the number of patients within ranges of HEART score with or without the combined endpoints.

The number of patients with and without endpoints in each HEART score with its corresponding sensitivity, specificity, positive predictive value and negative predictive value is shown in Table 4. A HEART score of 6 has a sensitivity of 96.0%, specificity of 79.6%, and with a positive and negative predictive values of 84.5% and 94.5% respectively. The area under the ROC curve was 95.1 %, as shown in Figure 1.

**Table 1.** Baseline Characteristics, Risk Profile and ECG Findings of Patients

| Characteristics n = 328 | Mean ± SD n = % |
|---|---|
| *Demographics* | |
| Mean Age | 58.2 ± 14.4 |
| Male | 218 (66.5) |
| Admitted to the hospital | |
| Hypertension | 219 (66.8) |
| Diabetes Mellitus | 98 (29.9) |
| Hypercholesterolemia | 14 (4.3) |
| Family history of cardiac disease | 31 (9.5) |
| History of smoking | 116 (35.4) |
| BMI | 24.8 ± 4.0 |
| Known coronary artery disease | 54 (16.5) |
| Previous myocardial infarction | 16 (4.9) |
| Congestive heart failure | 11 (3.4) |
| Atrial Fibrillation | 12 (3.7) |
| Normal | 66 (20.1) |
| Nonspecific ST-segment changes | 95 (29.0) |
| ST-segment depression >0.5 cm | 98 (29.9) |
| T-wave inversion | 56 (17.1) |
| Left Bundle Branch Block | 4 (1.2) |
| Right Bundle Branch Block | 12 (3.7) |
| Q-waves | 51 (15.5) |

**Table 2.** Incidence of 30-day Major Adverse Cardiac Event in Patients Presenting with Chest Pain Seen at the ER

| | n = % |
|---|---|
| **Any major adverse cardiac event** | 176 (53.7) |
| Acute Myocardial Infarction | 164 (50.0) |
| Revascularization | 73 (22.3) |
| Death from cardiac/unknown case | 19 (5.8) |

**Table 3.** Incidence of Major Adverse Cardiac Event Within the Ranges of HEART Score

| | Major Adverse Cardiac Event | | |
|---|---|---|---|
| **HEART Score** | One or more endpoients reached n=328 (%) | No endpoint reached n=328 (%) | Total |
| 0-3 | 1 (0.3) | 54 (16.5) | 55 |
| 4-6 | 28 (8.5) | 86 (26.2) | 114 |
| ≥7 | 147 (44.8) | 12 (3.7) | 159 |
| Total | 176 (53.7) | 152 (46.3) | 328 |

**Table 4.** Sensitivity, Specificity, Positive and Negative Predictive Values of Each HEART Score

| | **Major Adverse Cardiac Events** | | | | | |
|---|---|---|---|---|---|---|
| **HEART Score** | One or more endpoints reached (n=176) | No endpoint reached (n=152) | Sensitivity (%) | Specificity (%) | Positive Predictive Value (PPV, %) | Negative Predictive Value (NPV, %) |
| 0 | 0 | 1 | 100 | 0.2 | 50.6 | 100 |
| 1 | 0 | 10 | 100 | 0.7 | 53.8 | 100 |
| 2 | 0 | 17 | 100 | 7.2 | 55.5 | 100 |
| 3 | 1 | 26 | 100 | 18.4 | 58.7 | 100 |
| 4 | 0 | 31 | 99.4 | 35.5 | 64.1 | 98.2 |
| 5 | 6 | 36 | 99.4 | 55.9 | 72.3 | 98.8 |
| 6 | 22 | 19 | 96.0 | 79.6 | 84.5 | 94.5 |
| 7 | 40 | 9 | 83.5 | 92.1 | 92.5 | 82.8 |
| 8 | 63 | 2 | 60.8 | 98.0 | 97.3 | 68.4 |
| 9 | 37 | 1 | 25.0 | 99.3 | 97.8 | 53.4 |
| 10 | 7 | 0 | 4.0 | 100 | 100 | 47.4 |

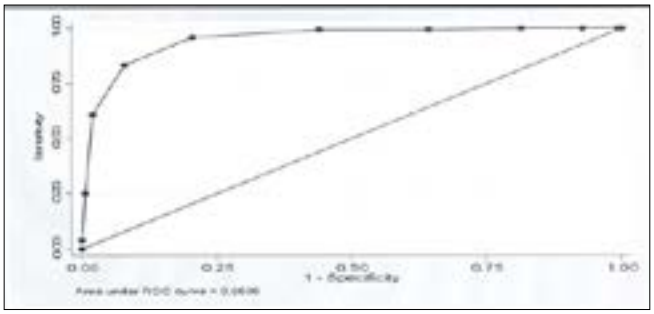

**Figure 1.** ROC Curve of the HEART score

## RESULTS

Majority of the patients included in the study are hypertensive, and it was the most common risk factor present. This was followed by smoking and diabetes mellitus. Only a minority of patients were previously diagnosed with hypercholesterolemia, a finding contrary to studies done by Six et al.[3,4] where hypercholesterolemia ranked second to hypertension in prevalence. This may be due to the under diagnosis of dyslipidemia since not all patients had a previous lipid profile done.

A total of 176 patients reached at least one endpoint. Most of them were diagnosed with myocardial infarction, with repeat determination of troponin levels showing increasing trend. Majority were managed medically, given antiplatelets, beta-blockers, anticoagulants. One-fifth of patients however underwent revascularization, mostly in the form of PCI, with only one patient receiving fibrinolytic agents and the rest underwent CABG.

The HEART scores were arbitrarily categorized into low, intermediate and high-risk categories in order to be more informative and useful in stratifying patients.[3] A score of 0-3 is considered low-risk, a score of 4-6 as intermediate risk, and high-risk for scores 7 and above. As seen in Table 4, a score of 0-3 (low-risk) has a good sensitivity and negative predictive value for adverse cardiac events. This is similar to the findings of Six and Cullen et al.[4] where the HEART score was validated in the Asia-Pacific population. Clinicians can be confident to discharge such low risk patients and minimize further diagnostic examinations, thus minimizing hospitalization costs. On the other hand, a high-risk score (7-10) has a high specificity and positive predictive value for adverse cardiac events, ranging 92.1-100% and 92.5-100% respectively.

In this study, the C-statistic was computed to be 0.9506, indicating that the HEART score has an excellent ability to discriminate patients with chest pain with higher risk of adverse cardiac event. This value exceeds with that of other studies. In comparing the HEART score and TIMI score, Six and Cullen et al[4] found that the HEART score and TIMI score have C-statistics of 0.83 and 0.75 respectively. In their study however, patients with ST-elevation myocardial infarction were excluded in the sample, which could have resulted into a lower C-statistic. Nevertheless, this study further strengthened the validity of the HEART score as a predictor of cardiac events. It also validates its use in our local setting.

Currently, several scoring systems are used for stratifying patients in the ER with ACS. However, each has its own drawbacks. The TIMI and PURSUIT scores were developed with the databases coming from large clinical trials of non ST-elevation ACS patients. These scores were designed to identify patients with high risks, who are most likely to benefit from aggressive therapy. They however do not give much information in the differentiation of chest pain patients who are at low to moderate risk for an adverse outcome.[1,3,5] The TIMI score is simple to calculate, but it is quite rough in a sense that it allows only binary choices, thus not considering the fact that many variables have a middle value or a 'grey area'. The PURSUIT score is outdated as it was designed before the introduction of troponin assays for clinical use. On the other hand, the major disadvantage of the GRACE score is that it can only be calculated with the use of the internet, which is not readily available in most of the emergency rooms in our country.

One important application of the HEART score is that it will aid clinicians in the judicious use of diagnostic examinations and ancillary procedures. In the study of Mahler et al[6], they compared patients with low and high HEART scores and found out that, with the use of this scoring system, cardiac testing could

have been reduced by 84.5%. They concluded that the HEART score could substantially reduce cardiac testing in a patient population with a low pretest probability of ACS if used to guide in the decision whether to do stress testing and cardiac imaging or not. These conclusions were further supported by another study of Mahler et al[7], where the HEART score combined with a 0 and 3-hour serial troponin determination after ER presentation identified 20% of patients for early discharge with 99% sensitivity for ACS. The HEART score improved stratification of patients with a net improvement of 10% versus unstructured assessment and 19% versus the North American Chest Pain Rule.[7,9]

Furthermore, HEART scores falling in the moderate risk group (score of 4-6) may warrant further noninvasive investigations such as repeated troponin, stress testing, and possible coronary angiography. Patients in this category may need admission for further clinical observation as this study indicates a higher risk of adverse cardiac events for such patients. Similarly, a score of 7 and above implies aggressive treatment with invasive procedures and may even deter unnecessary procedures that would delay institution of treatment. Further studies however are needed in order to validate such arbitrary cut-off points for the HEART score.

This study has several limitations. As mentioned previously, further studies are needed in order to provide the optimal cut-off points that would discriminate low, intermediate and high risk HEART scores. Also, since this study was done in only a single institution that specializes in cardiac patients, the author recommends additional studies that incorporates several medical centers with diverse patient population.

## CONCLUSION

The HEART score is an easy, reliable and convenient scoring system for stratifying patients with chest pain in the emergency room. It has an excellent ability to predict adverse cardiac events and is applicable in our local setting. It has an advantage over the present scoring systems in that it is simpler, easily calculated without the need of internet access, and may possibly stratify patients into low, moderate and high risk groups.

## REFERENCES


1. de Araújo Gonçalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. Eur Heart J. 2005 May; 26 (9):865-72.
2. Hess EP, Perry JJ, Calder LA, Thiruganasambandamoorthy V, Body R, Jaffe A, et al. Prospective validation of a modified thrombolysis in myocardial infarction risk score in emergency department patients with chest pain and possible acute coronary syndrome. Acad Emerg Med. 2010 Apr;17(4):368-75.
3. Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the HEART score. Neth Heart J. 2008 Jun; 16(6): 191–196.
4. Six AJ, Cullen L, Backus BE, Greenslade J, Parsonage W, Aldous S, et al. The HEART score for the assessment of patients with chest pain in the emergency department: a multinational validation study. Crit Pathw Cardiol. 2013 Sep;12(3):121-6.
5. Backus BE, Six AJ, Kelder JC, Mast TP, van den Akker F, Mast EG, et al. Chest pain in the emergency room: a multicenter validation of the HEART Score. Crit Pathw Cardiol. 2010 Sep;9(3):164-9.
6. Mahler SA, Hiestand BC, Goff DC Jr, Hoekstra JW, Miller CD. Can the HEART score safely reduce stress testing and cardiac imaging in patients at low risk for major adverse cardiac events? Crit Pathw Cardiol. 2011 Sep;10(3):128-33.
7. Mahler SA, Miller CD, Hollander JE, Nagurney JT, Birkhahn R, Singer AJ, et al. Identifying patients for early discharge: performance of decision rules among patients with acute chest pain. Int J Cardiol. 2013 Sep 30;168(2):795-802.
8. Hess EP, Jaffe AS. Evaluation of patients with possible cardiac chest pain: a way out of the jungle. J Am Coll Cardiol. 2012 Jun 5;59(23):2099-100.
9. Hess EP, Brison RJ, Perry JJ, Calder LA, Thiruganasambandamoorthy V, Agarwal D, et al. Development of a clinical prediction rule for 30-day cardiac events in emergency department patients with chest pain and possible acute coronary syndrome. Ann Emerg Med. 2012 Feb;59(2):115-25.e1.

# Comparison of Angiographic Characteristics of Coronary Artery Disease in Patients With Chronic Kidney Disease Versus Patients Without Chronic Kidney Disease

Anna Cristina M. Adora, MD

***Background*** --- Although patients with chronic kidney disease belong to a population which is at a higher risk to develop cardiovascular events, the management of coronary artery disease in this subset of patients is challenging. The purpose of the study is to determine if there is a difference in the angiographic characteristics of coronary artery disease in patients with chronic kidney disease and those without chronic kidney disease.
***Method*** --- This is a cross-sectional study done at the Philippine Heart Center from January 2014 to July 2015. Included in the study were 253 patients ages 19 and above undergoing diagnostic coronary angiography. The most recent creatinine measurement prior to coronary angiography was used to compute eGFR by Modification on Diet in Renal Disease. Coronary angiography results were read by at least two invasive cardiologists. The definitions of the angiographic characteristics described in this study were based on the definitions used in the SYNTAX Score.
***Results*** --- Upon comparison of the coronary artery anatomy of the patients with chronic kidney disease, the latter population had a higher of incidence of triple vessel disease (44% vs. 25%, p = 0.001), a higher incidence of multiple diseased segments (>4, 39% vs. 21%, p = 0.002, a higher incidence of diffuse or small vessel disease (14% vs. 2% p = 0.003) and a higher incidence of lesions longer than 20 mm (42% vs. 25%, p = 0.001).
***Conclusion*** --- Chronic kidney disease is an independent risk factor for coronary artery disease and patients with chronic kidney disease develop more complex and severe coronary artery lesions than patients without chronic kidney disease, specifically higher occurence of multi-vessel disease, multiple diseased segments, diffuse or small vessel disease and long segment lesions. ***Phil Heart Center J 2017;22(1):26-32.***

**Key Words: Coronary Artery Disease ■ Chronic Kidney Disease ■ Angiographic characteristics**

The prevalence of chronic kidney disease (CKD) continues to rise.[1] Over the years, investigators have shown that many patients with CKD die prematurely from cardiovascular disease instead of surviving long enough to undergo dialysis or transplantation.[2] In fact cardiac disease is directly responsible for the extremely high morbidity and mortality in patients with CKD, and it is now established as the leading cause of death for renal failure patients.[1]

The connections between CKD and cardiocardiovascular disease are numerous. People with CKD usually have risk factors for cardiovascular disease, such as hypertension, diabetes, and dyslipidemia. Renal disease also engenders an environment that promotes cardiovascular injury.[3]

Renal failure patients have a disturbance in calcium and phosphorus metabolism with secondary increase in parathyroid hormone levels. This leads to smooth muscle proliferation, vascular and myocardial calcification and coronary atherosclerosis. Chronic inflammation is also a factor in CKD. As renal function deteriorates, levels of toxins and proinflammatory

*Finalist*, Oral Presentation - Original Paper. 24th PHC Annual Research Paper Competition and Poster Presentation held on February 26, 2016 at Philippine Heart Center. Correspondence *to Dr. Anna Cristina M. Adora.* Department of Adult Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication**  2017 ISSN 0018-9034

cytokines increase, which promotes intramyocardial arteriolar thickening and myocardial fibrosis. There is sympathetic overactivity in patients with CKD due to the dysregulation of the renin-angiotensin-aldosterone system. This contributes to further increase in blood pressure and heart rate accelerating cardiac hypertrophy.[4] There is also chronic anemia, which increases the incidence of ischemic heart disease and accelerate cell death, ventricular dilatation, and decrease in systolic function. All of these create a metabolic condition with morphologic features such as cardiac hypertrophy, myocardial fibrosis and apoptosis, coronary atherosclerosis, and a reduction of capillary length density thereby reducing the ratio of perfusing capillaries to the myocardium supplied.[5]

Few studies have examined the association of CKD with coronary anatomy. Hong Liu, et al. investigated the prevalence of CKD and the relation of CKD and number of stenosed coronary vessels in patients who had undergone coronary angiography. They concluded that patients with CAD had a significantly higher prevalence of chronic kidney disease compared with patients without CAD, and that CKD was a strong risk factor for CAD.[6] In another study by Chonchol et al., they have concluded that patients with CKD were more likely than those without CKD to have at least one significant coronary obstruction and patients with CKD were more likely to have three-vessel and/or left main disease than those without CKD.[7]

Although patients with chronic kidney disease belong to a population which is at a higher risk to develop cardiovascular events, the management of coronary artery disease in this subset of patients is challenging. Optimal medical treatment is difficult as many of the medications used for coronary artery disease are metabolized or excreted by the kidney, thus placing these patients at risk to develop adverse effects. Also, there is a scarcity of knowledge and experience regarding revascularization in patients with chronic kidney disease. This paper aims to provide more insight to the complexity of coronary artery disease in patients with chronic kidney disease. Information yielded from this study could contribute to recommendations for management in patients with coronary artery disease and chronic kidney disease.

The purpose of the study is to determine if there is a difference in the angiographic characteristics of coronary artery disease in patients with chronic kidney disease and those without chronic kidney disease.

It also aimed to determine if there is a difference in the angiographic characteristics of coronary artery disease in patients with normal renal function (eGFR >90 mL/minute/1.73m2), mild renal dysfunction (59< eGFR <90 mL/minute/1.73m2), and moderate – severe renal dysfunction (eGFR <60 mL/minute/1.73m2) and to determine if there is a difference in the angiographic characteristics of coronary artery disease in patients with chronic kidney disease with concomitant diabetes mellitus and patients with chronic kidney disease without concomitant diabetes mellitus.

## METHODS

This is a cross-sectional study done at the Philippine Heart Center from January 2014 to July 2015. Included in the study were 253 patients age 19 and above undergoing diagnostic coronary angiography during the aforementioned time period were included. While excluded were patients who have concomitant acute kidney injury during the time of coronary angiography and those with concomitant valvular heart disease, cardiomyopathy and congenital heart disease.

*Sample Size Calculation.* Using the sample size calculation for comparing proportions by Hansheng Wang and Shein Chung Chow,[8] when wanting to prove a difference in proportions between two groups, assuming equal sample size allocation and a 0.05 level of significance and 80% power, with an equivalence margin of 15% the sample size needed is then given by the following equation:

$$n_1 = n_2 = \frac{(2_\alpha+2_\beta)^2(p_1(1-p1)+p_2(1-p_2)}{(e-8)^2}$$

$$= \frac{(1.64+0.84)^2(0.50(1.00-0.50)+0.55(1-0.55)}{(0.15+0.05)^2} \approx 77$$

Hence, the sample size are 77 subjects or each group.

*Study Maneuver*. The most recent creatinine measurement prior to coronary angiography was used. eGFR was calculated by the simplified Modification of Diet in Renal Disease equation: eGFR (mL per minute/1.73 m2) = 186.3 x serum creatinine $^{-1.154}$ (mg/dL) x age $^{-0.203}$ x 0.742 (if female). Patients were classified into two groups: normal renal function (eGFR > 90 mL per minute/1.73m2) and chronic kidney disease (eGFR < 90 mL per minute/1.73m2). For further analysis, those with chronic kidney disease were classified into sub-groups: mild renal dysfunction (59 < eGFR < 90 mL/minute/1.73m2) and moderate – severe renal dysfunction (eGFR < 60 mL/minute/1.73m2) and those with chronic kidney disease and concomitant diabetes mellitus versus those with chronic kidney disease without concomitant diabetes mellitus.

The patients underwent coronary angiography and all coronary angiography results were read by at least two invasive cardiologists. In case of disagreement, the final reading of the primary operator was the final decision. The definitions of the angiographic characteristics described in this study were based on the definitions used in the SYNTAX Score.[9-10,13]

*Statistical Analysis.* Descriptive statistics such as mean, standard deviation and range were presented for quantitative data. Intergroup differences of continuous variables were analyzed using *T*-test, while categorical variables were compared using chi-square test.

*Ethical Consideration.* The study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki. The study protocol was reviewed and approved by the Philippine Heart Center Institutional Ethics Review Board (PHC-IERB) and informed consent was waived by the board.

## RESULTS

A total of 253 patients who underwent diagnostic coronary angiography from January 2014 to July 2015 were included in the study. Of these patients, 88 of them had normal renal function and 165 had chronic kidney disease. There were no significant differences in age, gender, incidence of diabetes and hypertension, significant smoking history and history of acute coronary syndrome. *(Table 1)*

Upon comparison of the coronary artery anatomy of the patients with normal renal function and the patients with chronic kidney disease, the latter population had a higher incidence of triple vessel disease (44% vs 25%, p = 0. 001), a higher incidence of multiple diseased segments (>4, 39% vs 21%, p = 0.002), a higher incidence of diffuse or small vessel disease (14% vs 2%, p = 0.003) and a higher incidence of lesions longer than 20 mm (42% vs 25%, p = 0.001), which were all statistically significant. Other characteristics of the coronary artery anatomy such as presence of calcifications, total occlusions, bifurcation or trifurcation lesions and aorto-ostial lesions did not have any significant differences between patients with normal renal function and those with chronic kidney disease. *(Table 2)*

**Table 1.** Baseline Characteristics of Patients with normal renal function and patients with Chronic Kidney Disease

| | Normal Renal Function (n=88) | Chronic Kidney Disease (n=165) | p value |
|---|---|---|---|
| Age, years | 58.53 ± 8.85 | 60.35 ± 9.18 | 0.13 |
| Male (%) | 51 (58%) | 105 (64%) | 0.41 |
| Diabetes Mellitus (%) | 30 (34%) | 62 (38%) | 0.68 |
| Hypertension (%) | 60 (68%) | 125 (76%) | 0.23 |
| Significant smoking history (%) | 32 (36%) | 73 (44%) | 0.23 |
| History of Acute Coronary Syndrome (%) | 28 (32%) | 71 (43%) | 0.10 |

**Table 2.** Severity of coronary artery disease in patients with normal renal function versus patients with chronic kidney disease

| | Normal Renal Function (n=88) | Chronic Kidney Disease (n=165) | p value |
|---|---|---|---|
| **Number of Diseased Vessels** | | | **0.001** |
| No significant diseased vessels | 44 (50%) | 48 (29%) | |
| Single vessel disease | 7 (8%) | 25 (15%) | |
| Double vessel disease | 15 (17%) | 19 (12%) | |
| Triple vessel disease | 22 (25%) | 74 44%) | |
| **Number of Diseased Segments** | | | |
| 0 | 44 (50%) | 45 (27%) | **0.002** |
| 1 - 2 | 13 (15%) | 29 (18%) | |
| 3 - 4 | 12 (14%) | 27 (16%) | |
| More than 4 | 19 (21%) | 64 (39%) | |
| Presence of diffuse disease | 2 (2%) | 23 (14%) | **0.003** |
| Presence of calcifications | 29 (33%) | 73 (44%) | 0.10 |
| Presence of total occlusions | 18 (20%) | 52 (32%) | 0.07 |
| Presence of bifurcation or trifurcation lesions | 62 (70%) | 111 (67%) | 0.67 |
| Presence of aorto-ostial lesions | 1 (17%) | 6 (4%) | 0.42 |
| Presence of lesions longer than 20mm | 22 (25%) | 86 (42%) | **0.0001** |

**Table 3.** Severity of coronary artery disease in patients with normal renal function versus patients with mild renal dysfunction and moderate to severe renal dysfunction

| | Normal Renal Function (n=88) | Mild Renal Dysfunction (n=83) | Moderate-severe Renal Dysfunction (n=82) | p value |
|---|---|---|---|---|
| **Number of Diseased Vessels** | | | | **0.002** |
| No significantly diseased vessels | 44 (50%) | 26 (31%)) | 22 (26%) | |
| Single vessel disease | 7 (8%) | 26 (31%) | 10 (12%) | |
| Double vessel disease | 15 (17%) | 12 (15%) | 7 (9%) | |
| Triple vessel disease | 22 (15%) | 31 (37%) | 43 (52%) | |
| **Number of Diseased Segments** | | | | |
| 0 | 44 (50%) | 6 (7%) | 21 (26%) | **0.002** |
| 1 - 2 | 13 (15%) | 15 (18%) | 14 (17%) | |
| 3 - 4 | 12 (14%) | 18 (22%) | 9 (12%) | |
| > 4 | 19 (21%) | 26 (31%) | 38 (47%) | |
| Presence of diffuse disease | 2 (2%) | 6 (7%) | 17 (21%) | **0.0002** |
| Presence of calcifications | 29 (33%) | 29 (35%) | 49 (54%) | **0.01** |
| Presence of total occlusions | 18 (20%) | 20 (23%) | 32 (39%) | **0.02** |
| Presence of bifurcation or trifurcation lesions | 62 (70%) | 57 (69%) | 54 (66%) | 0.81 |
| Presence of aorto-ostial lesions | 1 (17%) | 1 (1%) | 5 (6%) | 0.08 |
| Presence of lesions longer than 20mm | 22 (25%) | 40 (48%) | 46 (56%) | **0.0002** |

The patients with chronic kidney disease were divided into two subgroups based on estimated glomerular filtration rate into those with mild renal dysfunction and those with moderate – severe renal dysfunction. The coronary artery anatomic characteristics among those with normal renal function and the two previously mentioned groups were compared and the subset of patients with moderate to severe renal dysfunction had higher incidences of triple vessel disease (52% vs 37% vs 15%, p = 0.002), four or more diseased segments (37% vs 31% vs 21%, p = 0.002), diffuse or small vessel disease (21% vs 7% vs 2%, p = 0.0002), calcifications (54% vs 35% vs 33%, p = 0.001), total occlusions (66% vs 23% vs 20%, p = 0.02), and lesions longer than 20 mm (56% vs 48% vs 25%, p = 0.0002) and these differences were statistically significant. Only the presence of bifurcation or trifurcation lesions and aorto-ostial lesions had no significant difference among the three groups. *(Table 3)*

**Table 4.** Severity of Coronary Artery Disease in patients with chronic kidney disease and concomitant diabetes mellitus versus patients with chronic kidney disease without concomitant diabetes mellitus

| | Chronic Kidney Disease and Diabetes Mellitus (n=62) | Chronic Kidney Disease without Diabetes Mellitus (n=103 | p value |
|---|---|---|---|
| **Number of Diseased Vessels** | | | **0.008** |
| No significantly diseased vessels | 11 (18%) | 37 (36%) | |
| Single vessel disease | 8 (13%) | 16 (15%) | |
| Double vessel disease | 5 (8%) | 14 (14%) | |
| Triple vessel disease | 38 (61%) | 36 (35%) | |
| **Number of Diseased Segments** | | | |
| 0 | 10 (16%) | 35 (34%) | 0.052 |
| 1 - 2 | 11 (18%) | 18 (17%) | |
| 3 - 4 | 10 (10%) | 17 (17%) | |
| More than 4 | 31 (50%) | 33 (32%) | |
| Presence of diffuse disease | 14 (23%) | 9 (9%) | **0.02** |
| Presence of calcifications | 38 (61%) | 35 (35%) | **0.0007** |
| Presence of total occlusions | 25 (40%) | 27 (26%) | 0.08 |
| Presence of bifurcation or trifurcation lesions | 26 (42%) | 28 (37%) | 0.06 |
| Presence of aorto-ostial lesions | 2 (3%) | 4 (4%) | 1.0 |
| Presence of lesions longer than 20mm | 40 (65%) | 46 (45%) | **0.02** |

Of the 165 patients with chronic kidney disease, 62 patients had concomitant diabetes mellitus and 103 patients did not have concomitant diabetes mellitus. The coronary artery anatomy of these subgroups were compared and there was a significantly statistically higher occurrence of triple vessel disease, diffuse or small vessel disease, calcifications and lesions longer than 20 mm in those with chronic kidney disease and concomitant diabetes mellitus. *(Table 4)*

## DISCUSSION

The results of this study affirm that chronic kidney disease is a risk factor for coronary artery disease and that patients with chronic kidney disease have more severe coronary artery disease as evidenced by the higher occurrence of triple vessel disease, multiple diseased segments,[12] diffuse or small vessel disease and long segment lesions, when compared to those with normal renal function *(Table 2)*. The result of this study also illustrate that as the renal dysfunction progresses, the severity of coronary artery disease worsens as seen by a higher occurrence of triple vessel disease, multiple diseased segments, presence of diffuse or small vessel disease, calcifications, total occlusions and long segment lesions in patients with moderate to severe renal dysfunction as compared to those with normal renal function and mild renal dysfunction. *(Table 3)*

This is consistent with a study by Hong Liu et al. which concluded that patients with chronic kidney disease succumb to a cardiovascular related mortality before they develop end stage renal insufficiency.[6] Studies by Hong Liu and Chonchol have demonstrated that the level of kidney dysfunction is associated with increased severity of demonstrable angiographic coronary artery disease.[6,7] According to Sarnak et al,[13] patients with chronic kidney disease usually have the traditional risk factors for cardiovascular disease which includes diabetes, low HDL cholesterol, hypertension, older age and left

ventricular hypertrophy.[14] However, aside from these risk factors, there are several other non-traditional risk factors that are associated with atherosclerosis which are distinctive to patients with kidney disease such as oxidant stress, elevated inflammatory markers and hyperhomocysteinemia. Renal replacement therapies may lead to even more oxidant stress, production of complement fragments and cytokines, and other proinflammatory factors. Aside from this, the altered metabolism of calcium and phosphorus in patients with renal dysfunction accelerates vascular calcification.[15] All of these create an environment which is conducive for the development of accelerated atherosclerosis and endothelial dysfunction.

Diabetes mellitus is also a separate risk factor for coronary artery disease and patients with chronic kidney disease and concomitant diabetes mellitus may promote further atherosclerosis by worsening the metabolic abnormalities that can be found in chronic kidney disease. The results of this study affirm this concept by showing that there was a higher occurrence of triple vessel disease, diffuse or small vessel disease, calcifications and long segment lesions in patients with chronic kidney disease and concomitant diabetes mellitus compared to patients with chronic kidney disease and no concomitant diabetes, suggesting that the presence of diabetes mellitus may lead to small vessel disease, longer stenoses and increased calcifications due to the altered metabolism of calcium.

*Limitations of the Study*. This study has several limitations. First, the patients were grouped according to renal function which was determined through estimated glomerular filtration rate derived from serum creatinine rather than the direct measurement of renal function such as inulin clearance. Also, a recent definition of chronic kidney disease includes the presence of proteinuria even with a normal glomerular filtration rate which was not considered for this study since urinalysis was not done on all patients. Second, although the target sample size was obtained for each major group (normal renal function, mild renal dysfunction and moderate to severe renal dysfunction), only 62 patients had chronic kidney disease and concomitant diabetes mellitus, which may have affected the comparison to the patients without concomitant diabetes mellitus.

## CONCLUSION

Chronic kidney disease is an independent risk factor for coronary artery disease and patients with chronic kidney disease develop more complex and severe coronary artery lesions than patients without chronic kidney disease, specifically higher occurrence of multi-vessel disease, multiple diseased segments, diffuse or small vessel disease and long segment lesions. The progression of renal dysfunction is associated with increased severity of the coronary artery lesions, in addition to the characteristics mentioned in the previous sentence, higher occurrence of total occlusions and calcifications as well. Patients with concomitant diabetes mellitus may be expected to have more multi-vessel disease, diffuse or small vessel disease, calcifications and long segment lesions. With this in mind, patients with chronic kidney disease and coronary artery disease should be considered as very high risk for major adverse cardiovascular events and should be treated aggressively, especially in patients with mild renal dysfunction and normal renal function but at risk to develop kidney disease in order to avoid accelerated progression of the coronary artery disease which is associated with moderate to severe renal dysfunction.

## RECOMMENDATION

Given this evidence, it is prudent to highly recommend screening of all patients with chronic kidney disease for cardiovascular risk factors and manage these patients aggressively, before the renal and cardiovascular diseases progress. For future studies, other methods such as intravascular ultrasound or coronary CT angiography may be considered to give more information about the vessel wall aside from quantifying the lesion complexity, as done in conventional coronary angiography.

## REFERENCES


1. Herzog CA, Asinger RW, Berger AK, Charytan DM, Díez J, Hart RG, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2011 Sep;80(6):572-86.
2. Tiu E. Kidney month 2012: awareness and prevention. [Internet]. Quezon City, Philippines. Philippine Informa tion Agency [Internet]. 2012 June 5. Available from: http://pia.gov.ph/news/index.php?article=11433879-0357.
3. Hostetter TH. Chronic kidney disease predicts cardiovascular disease. N Engl J Med. 2004 Sep 23; 351 (13):1344-6.
4. Middleton RJ, Parfrey PS, Foley RN. Left ventricular hypertrophy in the renal patient. J Am Soc Nephrol. 2001 May;12(5):1079-84.
5. Dilsizian V, Fink JC. Deleterious effect of altered myocardial fatty acid metabolism in kidney disease. J Am Coll Cardiol. 2008 Jan 15;51(2):146-8.
6. Liu H, Yan L, Ma GS, Zhang LP, Gao M, Wang YL, et al. Association of chronic kidney disease and coronary artery disease in 1,010 consecutive patients under going coronary angiography. J Nephrol. 2012 Mar-Apr;25(2):219-24.
7. Chonchol M, Whittle J, Desbien A, Orner MB, Petersen LA, Kressin NR. Chronic kidney disease is associated with angiographic coronary artery disease. Am J Nephrol. 2008;28(2):354-60.
8. Shein-Chung Chow, Hansheng Wang, Jun Shao. Sample size calculations in clinical research. New York: Marcel Dekker, Inc. c2003.
9. Tanaka T, Seto S, Yamamoto K, Kondo M, Otomo T. An assessment of risk factors for the complexity of coronary artery disease using the SYNTAX score. Cardiovasc Interv Ther. 2013 Jan;28(1):16-21.
10. Yan LQ, Guo LJ, Zhang FC, Gao W. The relationship between kidney function and angiographically-derived SYNTAX score. Can J Cardiol. 2011 Nov-Dec; 27 (6): 768-72.
11. Coskun U, Orta Kilickesmez K, Abaci O, Kocas C, Bostan C, Yildiz A, et al. The relationship between chronic kidney disease and SYNTAX score. Angiology. 2011 Aug;62(6):504-8.
12. Kramer H, Toto R, Peshock R, Cooper R, Victor R. Association between chronic kidney disease and coronary artery calcification: the Dallas Heart Study. J Am Soc Nephrol. 2005 Feb;16(2):507-13.
13. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension. 2003 Nov; 42 (5):1050-65.
14. Cerasola G, Nardi E, Palermo A, Mulè G, Cottone S.Epidemiology and pathophysiology of left ventricular abnormalities in chronic kidney disease: a review. J Nephrol. 2011 Jan-Feb;24(1):1-10.
15. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, et al. Assessment of the SYNTAX score in the Syntax study. EuroIntervention. 2009 May;5(1):50-6.

# The Prognostic Value of the FIT Treadmill Score in Patients with Coronary Artery Disease Undergoing Cardiac Rehabilitation

Lucky R. Cuenza, MD; Edgardo Ebba, MD; Leandro Bongosia, MD

***Background*** --- There are currently no available quantitative risk prediction tools for stratifying patients with established cardiovascular disease who undergo cardiac rehabilitation. The study aimed to determine the utility of a novel clinical treadmill score in determining the prognosis of patients with coronary artery disease after cardiac rehabilitation.

***Method*** --- Demographic, clinical and exercise data of 262 patients with coronary artery disease (mean age 55.8±10.1 years, 84% males) who completed an outpatient cardiac rehabilitation (CR) program were analyzed. The FIT treadmill score (% peak maximal heart rate + 12 (METs achieved) - 4 (age) + 43 if female) was determined prior to initiating the program and after completion. Patients were classified according to risk category using the FIT scores after exit from Phase 2 cardiac rehabilitation and were prospectively followed up for the occurrence of 10 year all cause mortality.

***Result*** --- On completion of the CR program, 3 (1.2%) patients were classified as very low risk (FIT score >100), 89 (34%) in the low risk group (FIT score 1-100), 130 (50%) patients were intermediate risk (FIT score: ≤ to -100) and 40 (15.3%) were classified as high risk (FIT score ≤100 to -200). There was a mean improvement of 26.1±16.2 points in the FIT score after completion of cardiac rehabilitation. On median follow up of 10.3 years, all cause mortality rate was 19.8%. On sensitivity and specificity analysis an improvement of the FIT score by 18.2 points has a 74.6% sensitivity (CI 67.6-79.8) and 67.3% specificity (CI 53.30-80.5) in predicting 10-year survival. Kaplan Meier survival curves showed increased occurrence of mortality in the high-risk group (48% survival in 5 years, <10% in 10 years) and in patients who did not have significant improvement in the FIT score (77% survival in 5 years, 59% in 10 years). A high-risk FIT score category on exit (HR 23.7,p=0.000) and failure to improve the FIT score (HR 4.8,p=0.000) were strongly associated with mortality. Receiver operator characteristics showed that improvement in the FIT score (AUC=0.81, CI 0.73-0.88) and the FIT score on exit (AUC=0.92, CI 0.89-0.95) both have excellent discrimination in predicting mortality.

***Conclusion*** --- The FIT treadmill score is predictive of mortality for patients with coronary artery disease undergoing cardiac rehabilitation. An improvement in the FIT score after participation in cardiac rehabilitation is associated with increased survival. The FIT score can be utilized as a simple tool to risk stratify patients that can be used as a measure of overall cardiovascular fitness and a marker of successful outcome for patients who participate in a cardiac rehabilitation program. ***Phil Heart Center J 2017;22(1):33-39.***

**Key Words: FIT treadmill score ■ cardiac rehabilitation**

Risk stratification is an integral part of determining the management and prognosis of patients with cardiovascular disease. For primary prevention, validated scoring systems such as the Framingham Risk Score and the new pooled cohort risk score, enable the clinician to calculate and predict the risk of an event to give the patient important information as well as make decisions on adjustment and aggressiveness of therapy. However, after the patient has already suffered a cardiovascular event such as myocardial infarction, the focus shifts from primary prevention to the development of effective secondary prevention, which includes coronary intervention, guideline directed medical therapy, lifestyle modification and cardiac rehabilitation.

*3rd Place*, Oral Presentation - Original Paper. 24th PHC Annual Research Paper Competition and Poster Presentation held on February 26, 2016 at Philippine Heart Center. Correspondence *to Dr. Lucky R. Cuenza.* Department of Adult Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication**  ISSN 0018-9034

While there is overwhelming evidence that comprehensive cardiac rehabilitation (CR) and its multidisciplinary components of exercise, behavioral and lifestyle interventions are associated with a reduction in both cardiac mortality (26-36%) and total mortality (13-26%)[1] there is a lack of studies that focus on the risk stratification of these patients. Available risk stratification models such as that of the American Association of Cardiovascular and Pulmonary Rehabilitation and the American Heart Association are used to determine risks involved in the initiation and exercise participation in the rehabilitation program.[2] Other studies focused on singular markers predictive of risk such as ejection fraction, exercise capacity and heart rate recovery.[3] While no doubt helpful, they are more of qualitative variables as indicated on hazard ratios indicating the presence or absence of risk. Similar to the risk scoring systems for primary prevention it would be ideal to have a risk stratification system for patients who underwent cardiac rehabilitation to be able to quantify their residual risk after an event and after participation with the program.

Cardiologists from John Hopkins Hospital developed the FIT treadmill score and the results were recently published.[4] The researchers were able to derived a formula using variables derive from a standard stress test that enables the clinician to predict a patient's ten-year risk of dying. The score has not been validated for use in different patient populations hence there is a need to study its accuracy and applicability. It could potentially be a useful tool for illustrating the spectrum of risk in patients undergoing cardiac rehabilitation.

## METHODS

*Study of Population.* Included were both male and female who underwent coronary artery bypass graft (CABG) post percutaneous catheter intervention (PCI) or patients with stable coronary artery disease who were enrolled and completed Phase II Cardiac Rehabilitation at the Philippine Heart Center. Excluded in the study were patients who were unable to complete the cardiac rehabilitation; patients who were enrolled in the cardiac rehabilitation program after undergoing a procedure other than coronary artery bypass or PCI and those patients whose follow-up status are not verified.

*Study Procedure.* This ambidirectional cohort study is based on patients seen at the Philippine Heart Center who underwent the outpatient Phase 2 comprehensive cardiac rehabilitation program. Relevant information was derived through review of department records from 2001 to 2005 along with electronic data (Medtrak). Using this data patients were prospectively followed up through clinic or telephone calls from the time of completion of the program for a minimum of five and up to ten years for all cause mortality (cardiovascular and non-cardiovascular cause). Follow-up was done by an individual who was blinded to the study objectives and outcomes.

*FIT Treadmill Score.* Treadmill score is a risk score that was derived to predict a person's ten year risk of mortality. The formula uses a patient's age, gender, fitness level (measured via metabolic equivalents or METs achieved in an exercise test), and peak maximal heart rate (PMHR) reached during exercise and their estimated risk is calculated. (*Figure 1*). For men, the FIT Treadmill Score is as follows:

$$\text{PMHR} + 12 \times \text{METs} - 4 \times \text{Age}$$

For women, the FIT Treadmill Score is as follows:

$$\text{PMHR} + 12 \times \text{MET} - 4 \times \text{Age} + 43$$

Patient scores were calculated at the start of the program and on completion and the exit scores were used to determine risk stratification. In the original study from which the equation was logistically derived, a score of greater than or equal to 100 means a patient has 2% risk of death in ten years. On the other end of the spectrum, a score of -100 to -200 entails a risk of 38%.[4] For the purposes of our study patients were classified in quartiles of risk based on the FIT treadmill score after completion of Phase 2 cardiac rehabilitation and we reclassified risk assessment based on the FIT treadmill score as follows:

1. (2:100)= very low risk
2. (1-100)= low risk
3. (≤ 0 to -100)= intermediate risk
4. ( ≤ -100 to -200)= high risk

*Data Analysis.* Data analysis was done using STATA SE version 13. Quantitative variables were summarized and presented as mean and standard deviation, while qualitative variables were tabulated and presented as frequency and percent distribution. The association between the change in FIT score and mortality was determined and tested using logistic regression analysis. The cut off value of the change in FIT score in predicting mortality was determined based on the graph of its sensitivity and specificity via area under the curve analysis. Survival curves were estimated by Kaplan-Meier method. Discrimatory ability of the FIT treadmill score was determined with reciever operator characteristics (ROC) curve analysis. The level of significance was set at <0.05.

*Sample Size.* Using STATA SE version 13 software, the minimum sample size requirement is estimated to be at least 92 based on the following parameters: alpha = 0.05, power = 80%, and mortality of 11% in the ≤ 0 to -100 FIT score category and 38% for the ≤-100 to -200 FIT score category. The minimum sample size requirement was increased to 115 accounting for 20% drop out rate.

FIT Treadmill Score = %MPHR + 12 (METS) - 4 (age) + 43 if female

**Figure 1.** Computation of the FIT treadmill score

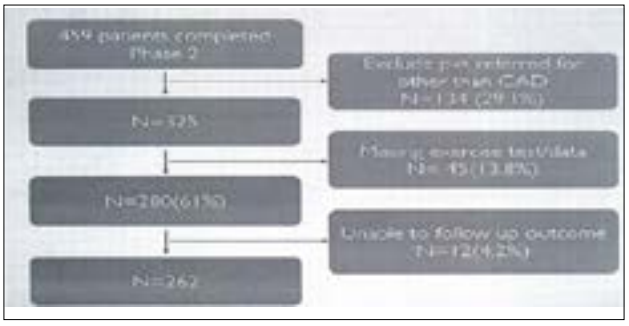


**Figure 2.** Study flowchart and process of patient exclusion

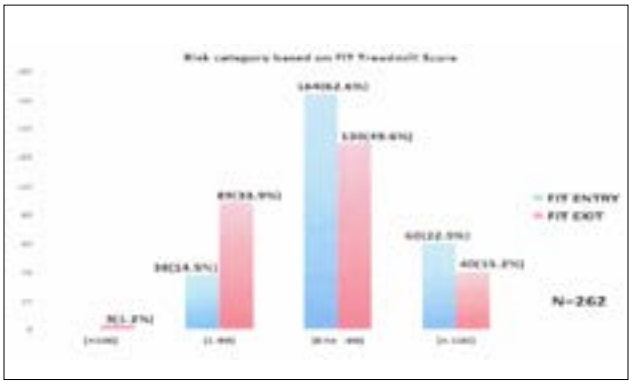


**Figure 3.** Classification of patients by FIT treadmill score

## RESULTS

There were 459 patients in our original cohort. We excluded 134 (29.1%) patients because they were referred for cardiac rehabilitation for reasons other than CAD such as valvular and congenital heart disease. We then excluded 45(13.8%) as they did not have all the variables needed to calculate the FIT score due to missing exercise stress test and data. Another 12 (4.2%) patients were excluded as we could not ascertain their 10 year outcome status by 2015. Thus, a total of 262 patients were eligible for analysis. (*Figure 2*) The different baseline characteristics of the patients are listed in Table 1. The patients' mean age were 55.8 ± 10.1, most were male and hypertensive (84% and 73% respectively) 231 (88.2%) underwent coronary artery bypass graft, 21 (8%) had PCI and 17 (6.5%) were referred for stable coronary artery disease. The mean ejection fraction was 58.2 ± 12.5. On entry patients' mean METs achieved was 6.2±2 prior to initiation of cardiac rehabilitation and 8.3 ±2.2 after Phase 2 with a mean improvement of 2.1 ±1.2. The mean FIT score was -56.9±59.5 on entry and -30.9±63.3 on exit, respectively, with a mean improvement of 26.1±16.2 points.

With regards to risk category, there were 38 (14.5%) who had an entry FIT score of 1-99 (low risk), 164 (62.6%) had an entry FIT score in the 0 to -99 range (moderate risk) and 60 (22.9%) were classified as high risk. As expected, participation in cardiac rehabilitation resulted in improvement of risk stratification based on the FIT score, with 3 patients achieving very low risk status (exit FIT score > 100), and a

**Table 1.** Baseline clinical characteristics

| | Total N (%) or ± SD |
|---|---|
| Age | 55.8 ± 10.1 |
| Sex (Male) | 221 (84.4) |
| Body Mass Index | 25.1 ± 3.5 |
| Hypertension | 191 (73) |
| Diabetes | 79 (30) |
| Smoking | 138 (52.7) |
| Dyslipidemia | 161 (61.5) |
| Hx of previous CABG | 231 (88.2) |
| Hx of previous PCI | 21 (8) |
| Stable CAD | 17 (6.5) |
| Aspirin/Clopidogrel | 252 (96.2) |
| Beta blocker | 200 (76.3) |
| Calcium channel blocker | 80 (30.5) |
| Diuretic | 55 (20.9) |
| Digoxin | 68 (25.9) |
| ACEI/ARB | 162 (61.8) |
| Ejection fraction | 58.2 ± 12.5 |
| Double product | 23679 ± 5049 |
| Abnormal double product | 51 (19.5) |
| Double product reserve | 14340 ± 5088 |
| Abnormal double product reserve | 40 (15.3) |
| Abnormal heart rate recovery | 75 (28) |
| Peak Maximal Heart Rate (PMHR) | 141.2 ± 18.7 |
| % PMHR | 86.1 ± 9.3 |
| METS on entry | 6.2 ± 2.0 |
| METS on completion | 8.3 ± 2.2 |
| FIT score at entry | -56.9 ± 59.5 |
| FIT score on completion | -30.9 ± 63.3 |
| Improvement in FIT score | 26.1 ± 16.2 |

**Table 2.** Distribution of patients and events based on improvement of the FIT score

| Degree of FIT improvement | Deaths (%) |
|---|---|
| Improvement of FIT Score >18.2 (n=167) | 17 (10.2) |
| FIT category after completion <18.1 (n = 95) | 35 (36.8) |

**Table 3.** Cox proportional hazards analysis of Improvement in the FIT SCore and FIT category on completion

| Variable | Hazards ratio (95% CI) | P Value |
|---|---|---|
| Improvement of FIT Score | 4.8 (2.7-8.5) | 0.000 |
| FIT category after completion | 23.7 (12.7-44.4) | 0.000 |

decrease in the number of patients belonging in the moderate risk (49.6%) and high risk (15.2%) compared to previous classification, respectively *(Figure 3*). There were 14 deaths (5%) in the moderate risk group and 38 (14.5%) in the high risk group.

Sensitivity and specificity analysis curves (*Figure 4*) show that improvement of the FIT score with a cutoff of 18.21 points has a 74.6% sensitivity (CI 67.6% - 79.8%) and 67.3% specificity (CI 53.30% - 80,51%) in predicting 10-year survival. In patients who exhibited an improvement of >18.2 points there were 17 deaths (10.2%) compared with 35 events (36.8%) for those who achieved an improvement of <18.2 points (*Table 2*). Using the same cut-off value, Kaplan Meier survival curves (mean follow-up of 10.3 years) showed that patients whose FIT treadmill score did not improve had a 5 year survival rate of 77% and 10 year survival rate of around 59% respectively. In contrast to those whose FIT treadmill score improved by at least 18.2 points had a 5 and 10 year survival rate of 94% and 90%, respectively (*Figure 5*). Survival estimates were also analyzed using the FIT score category on exit (*Figure 6*). Patients belonging to the intermediate risk group (FIT score ≤0 to -100) after Phase 2 cardiac rehabilitation showed a 88% 10 year survival rate. In contrast, patients belonging to the high-risk group (FIT score ≤-100 to -200) had a 48% survival rate in 5 years, which progressively decreased to around <10% survival in 10 years. Cox proportional hazards analysis (*Table 3*) showed that failure to improve the FIT score (HR 4.78, 95% CI 2.7-8.6) using the specified cut-off value is associated with increased mortality (p=0.000). A high-risk FIT score category on exit (HR 23.7,95% CI 12.7-44.4) is also strongly associated with mortality (p=0.000).

The receiver operator curves for predicting mortality is shown in Figure 7. The improvement in FIT score (AUC 0.81, Cl 0.73-0.88) and the FIT score on Exit (AUC 0.92, Cl 0.89-0.95) both have excellent predictive ability, with the Exit FIT score having a better discriminatory ability than the improvement in FIT Score (p=0.000).

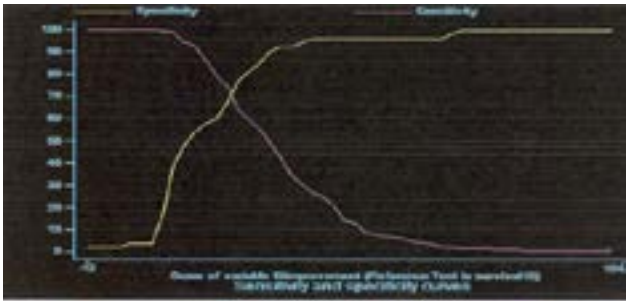

**Figure 4.** Sensitivity and specificity curves of the FIT treadmill score in predicting mortality

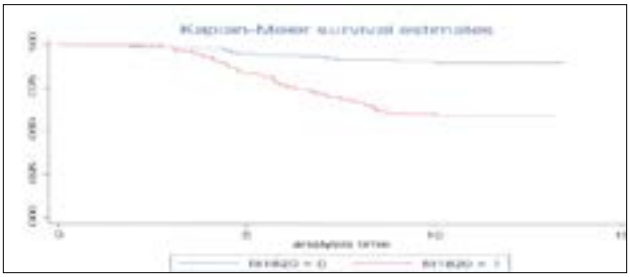

**Figure 5.** Kaplan Meier survival curves according to improvement of the FIT score on Exit. The cut off of 18.2 points in improvement in the FIT score was used. (improved by >18.2=blue line, improved by <18.2= red line)

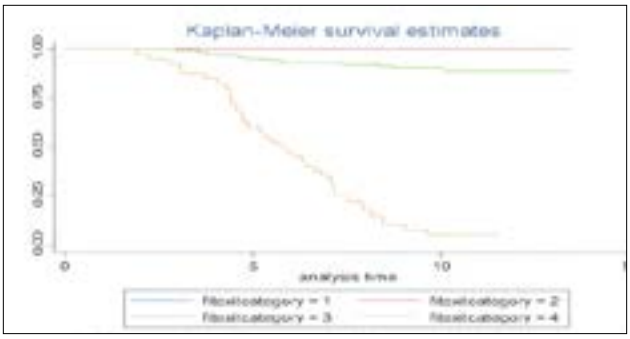


**Figure 6.** Category 1=FIT score >100. FIT category 2= FIT score 0-99. FIT exit category = FIT score = FIT score ≤0 to -100. FIT exit category 4=FIT score ≤-100 to -200

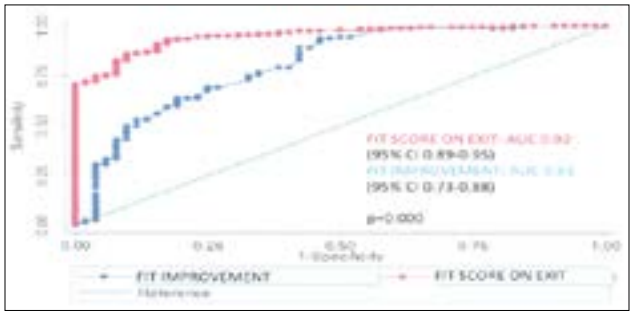


**Figure 7.** Comparison of Area Under the Curve (AUC) of FIT Score on EXIT and Improvement in the FIT Score in predicting mortality (CI=confidence interval)

## DISCUSSION

There are two notable findings in this study. First, a high risk category (<-100 to -200) was predictive for the occurrence of all cause mortality. This emphasizes the importance of cardiovascular fitness in predicting outcomes.[5] Kavanagh et al. reported in patients referred for cardiac rehabilitation that a higher exercise capacity was associated with decreased mortality even when controlling for traditional cardiovascular risk factors.[6] In patients with acute myocardial infarction who underwent percutaneous catheter intervention, exercise capacity was shown to be an independent and better predictor of 2 and 5 year mortality than left ventricular ejection fraction.[7] The FIT score which makes use of important exercise variables provides a measure of cardiorespiratory fitness with strong prognostic significance. Secondly, the degree of improvement in the FIT score is also strongly associated with improved survival. When using the cut-off in our sensitivity analysis of 18.21 points increase in the FIT score, analysis showed a statistically significant hazard risk of 4.8 likelihood of mortality for patients who failed to reach this cut-off. Tabet et al. noted that a lack of improvement in exercise capacity after an exercise training program has a strong association between increase in fitness and decreased mortality with a 30% reduction in mortality per metabolic equivalents increase in cardiorespiratory fitness during CR especially in patients with low fitness levels.[9]

Cardiac rehabilitation is a multidisciplinary approach that involves risk factor modification, behavioral education, and nutritional counseling in addition to exercise training. It is expected that participation in exercise based cardiac rehabilitation has favorable effects on cardiovascular risk factors, including smoking, blood pressure, body weight, and lipid profile along with significant reductions in mortality and adverse events.[10] Improvements in cardiopulmonary fitness are tightly coupled to the exercise training component of cardiac rehabilitation and it has been suggested that improvements in cardiorespiratory fitness will have the most prognostic value and a potential quantifiable biomarker in assessing response to cardiac rehabilitation. [11]

There have been numerous proposed outcome measures in assessing outcomes in cardiac rehabilitation.[12] Most studies have individually analyzed qualitative components of the exercise test such as improvement in functional capacity, peak maximal heart rate, heart rate recovery and improvement of metabolic profiles.[13] Among these it has been consistently shown that fitness level is not only the most powerful predictor of mortality.[14,15] but it also has prognostic power that is independent of age, gender, ejection fraction and all other traditional cardiovascular risk factors.[16]

The novelty of the FIT treadmill score is that it provides a quantitative measure of cardiovascular fitness. Compared to the Duke Treadmill Score (DTS), it is easier to compute and determine. Although traditionally used as a prognostic marker in risk stratifying patients, the DTS has been shown to have limited prognostic value in those with already established coronary artery disease, the elderly[17] as well as asymptomatic women.[18] Pending comparative studies, it would appear that among the advantages of the FIT treadmill score is the fact that it does not rely on symptoms, is not confounded by electrocardio graphic changes and it factors in gender and age to the equation for prediction of risk. Finally, the FIT treadmill score emphasizes fitness and exercise performance to predict long-term survival rather than risk during exercise participation or predicting obstructive coronary artery disease. In the original FIT study patients in the intermediate and high risk category had a mortality rate of 11% and 38% respectively. Participation in the cardiac rehabilitation program can lead to improvement of the FIT score, which presumably led to a lower mortality rate in our study (5% and 14.5% for intermediate and high risk groups, respectively). Cardiac rehabilitation also promotes better adherence to medications, exercise and lifestyle modification and this will be expected to reflect in the FIT score as well. Patients with a high risk FIT score category undergoing cardiac rehabilitation can be targeted to improve their FIT score with a goal to increase exercise capacity and improve their outcomes.

There are some limitations to this study that need to be pointed out. First, this was a single center study that uses a historical cohort in nature and inherent to potential biases. Nevertheless, the applied methodology is comparable to other prospective validation and population studies. An ambidirectional cohort method for retrospective data collection and prospective follow-up was done to overcome this limitation. The authors took into account all follow up status with blinded prospective follow up and excluded all missing data to get the most accurate representation of the sample. Secondly, the study was limited to patients with coronary artery disease who underwent cardiac rehabilitation. We did not include patients with other forms of heart disease (congenital, valvular). Further studies will be needed to confirm our findings externally although there is ample evidence to suggest that cardiac rehabilitation will equally benefit these patients[19] and this may be expected to reflect in the FIT score. Lastly, the FIT score was calculated using METs derived from the Neptet protocol that has less incremental increases in speed and grade compared to the Bruce protocol. The original investigators of the FIT study used the Bruce protocol which may have differential effects on different exercise parameters. However many of our patients are elderly and previously have undergone coronary artery bypass or percutaneous catheter interventions and may have been likely unable to perform the Bruce protocol. The Neptet protocol is a submaximal test which primary measures exercise capacity making it suitable for less fit patients.

To the best of our knowledge since its derivation, this is the first study that explored the potential prognostic utility of the FIT treadmill score in patients who underwent cardiac rehabilitation. The FIT treadmill score is quickly calculated, easily attainable from a standard exercise test and has excellent discriminative ability for long term mortality. It has been shown that poor physical fitness is a modifiable risk factor, and improvements in fitness over time have been demonstrated to improve prognosis.[20] The FIT treadmill score can be used as a reliable metric in assessing response to cardiac rehabilitation to improve cardiovascular fitness and prognosis.

## CONCLUSION

The FIT treadmill score predicts long term mortality in patients undergoing cardiac rehabilitation. Perhaps equally important is that improvement in the FIT treadmill score is associated with significantly improved survival. It is a simple tool for risk stratification of patients that may be used as gauge of overall cardiovascular fitness and a marker of a successful outcome of patients participating in a cardiac rehabilitation program.

## REFERENCES


1. Mampuya WM. Cardiac rehabilitation past, present and future: an overview. Cardiovasc Diagn Ther. 2012 Mar; 2(1):38-49.
2. Silva, Anne Kastelianne Franca da, Barbosa, Marianne Penachini da Costa de Rezende, Bemardo, Aline Femanda Barbosa, Vanderlei, Franciele Marques, Pacagnelli, Francis Lopes, & Vanderlei, Luiz Carlos Marques. (2014). Cardiac risk stratification in cardiac rehabilitation programs: a review of protocols. Revista Brasileira de Cirurgia Cardiovascular, 29(2), 255-265.
3. Adams BJ, Carr JG, Ozonoff A, Lauer MS, Balady GJ. Effect of exercise training in supervised cardiac rehabilitation programs on prognostic variables from the exercise tolerance test. Am J Cardiol. 2008 May 15; 101(10):1403-7.
4. Ahmed HM, Al-Mallah MH, McEvoy JW, Nasir K, Blumenthal RS, Jones SR, et al. Maximal exercise testing variables and 10-year survival: fitness risk score derivation from the FIT Project. Mayo Clin Proc. 2015 Mar;90(3):346-55.
5. Franklin BA, McCullough PA. Cardiorespiratory fitness: an independent and additive marker of risk stratification and health outcomes. Mayo Clin Proc. 2009 Sep; 84(9):776-9.
6. Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P, et al. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. Circulation. 2002 Aug 6;106(6):666-71.
7. Dutcher JR, Kahn J, Grines C, Franklin B. Comparison of left ventricular ejection fraction and exercise capacity as predictors of two- and five-year mortality following acute myocardial infarction. Am J Cardiol. 2007 Feb 15;99(4):436-41.
8. Tabet JY, Meurin P, Beauvais F, Weber H, Renaud N, Thabut G, et al. Absence of exercise capacity improvement after exercise training program: a strong prognostic factor in patients with chronic heart failure. Circ Heart Fail. 2008 Nov;1(4):220-6.
9. Martin BJ, Arena R, Haykowsky M, Hauer T, Austford LD, APPROACH Investigators. Cardiovascular fitness and mortality after contemporary cardiac rehabilitation. Mayo Clin Proc. 2013 May;88(5):455-63.
10. Lawler PR, Filion KB, Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. Am Heart J. 2011 Oct; 162(4):571-584.
11. Shenoy C, Patel MJ. Improved fitness as a measure of success of cardiac rehabilitation: do those who get fitter live longer? Int J Cardiol. 2013 Aug 10;167(3):903-4.
12. Sanderson BK, Southard D, Oldridge N; Writing Group. AACVPR consensus statement. Outcomes evaluation in cardiac rehabilitation/secondary prevention programs: improving patient care and program effectiveness. J Cardiopulm Rehabil. 2004 Mar-Apr; 24 (2):68-79.
13. Rodrigues P, Santos M, Sousa MJ, Brochado B, Anjo D, Barreira A, et al. Cardiac rehabilitation after an acute coronary syndrome: the impact in elderly patients. Cardiology. 2015;131(3):177-85.
14. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med. 2002 Mar 14;346(11):793-801.
15. Gulati M, Pandey DK, Arnsdorf MF, Lauderdale DS, Thisted RA, Wicklund RH, et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. Circulation. 2003 Sep 30;108(13):1554-9.
16. Myers J. Physical activity: the forgotten prescription, Eur J Cardiovasc Prev Rehabil. 2005 Apr; 12(2):85-6.
17. Kwok JM, Miller TD, Hodge DO, Gibbons RJ. Prognostic value of the Duke treadmill score in the elderly. J Am Coll Cardiol. 2002 May 1;39(9):1475-81.
18. Gulati M, Arnsdorf MF, Shaw LJ, Pandey DK, Thisted RA, Lauderdale DS, et al. Prognostic value of the duke treadmill score in asymptomatic women. Am J Cardiol. 2005 Aug 1;96(3):369-75.
19. Savage PD, Rengo JL, Menzies KE, Ades PA. Cardiac Rehabilitation After Heart Valve Surgery: comparison with coronary artery bypass graft patients. J Cardiopulm Rehabil Prev. 2015 Jul-Aug;35(4):231-7.
20. Blair SN, Kohl HW 3rd, Barlow CE, Paffenbarger RS Jr, Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. JAMA. 1995 Apr 12;273(14):1093-8.

# Factors Associated with Embolization in Patients with Atrial Myxoma

Jenny-Lynn V. Juhuri, MD; Liberty O. Yaneza, MD

***Background*** --- The treatment of cardiac myxoma is prompt surgical resection of the tumor and this aggressive approach is due to the constant threat of embolization from fragmentation or complete tumor detachment. There have been no studies appropriately designed and powered to develop a risk prediction model of tumor characteristics, as well as clinical factors, that may predispose to embolization.

***Method*** --- We retrospectively examined the demographics, diagnostic and tumor variables of patients with atrial myxoma admitted at the Philippine Heart Center from 2005 to 2014. Cases included those with embolic phenomenon documented by any imaging/ancillary study. Those without embolic event were defined as controls. Initial analysis used descriptive statistics and univariate analyses to compare epidemiological, diagnostic and tumor variables between the case and control groups. Subsequently, candidate risk factors were entered into a logistic regression model to find out significant factors between the two groups. Statistical significance was considered at $p<0.05$.

***Result*** --- A total of 112 patients were identified during the 10-year study period. Approximately 20.5% percent of these patients (n=23) were under the case group and 79.5% (n=89) were under the control group. The mean age is 52.4 years with predominance of females (67.9%). Majority presented with a functional capacity of class I (52.7%). Only 14.6% of the total population had atrial fibrillation. Masses were mostly located in the left atrium (88.2%) and, upon operation, most were attached to the interatrial septum without a stalk (49.6%). Among the comorbidities present, hypertension was significantly greater in those with embolic events compared to those without embolization (52.2% versus 20.2%, p=0.003). Those who had decreased sensorium during hospitalization was noted to be significant in the cases compared to the controls (39.1% versus 7.7%, p=0.001). However, significantly greater patients with pre-operative anticoagulation were noted in the case group compared to the control group (13% versus 1.1%, p=0.001), although only a minority of the total population had anticoagulation pre-operatively (3.6%). Among the laboratory tests, creatinine level was higher in those with embolic events but was found to be non significant compared to those without embolic events (0.14 ± 0.19 versus 0.09 ± 0.05, p=0.143). Multivariate analysis revealed that patients with hypertension have greater risk of tumor embolization (p=0.001), as well as those who presented with decreased sensorium (p=0.000). Pre-operative anticoagulation conferred greater risk for embolization (p=0.012). On the contrary, atrial fibrillation did not confer a higher risk for embolic events compared to patients who are in sinus rhythm (OR=0.47, p=0.044).

***Conclusion*** --- Patients with atrial myxoma who had embolic events were mostly hypertensive. Those who had decreased sensorium during admission were likely to have embolic phenomenon. Atrial fibrillation, compared to sinus rhythm, did not confer a higher risk for embolization. Surprisingly, pre-operative anticoagulation was noted to be higher in those with embolic events. This may be due to inadequate target levels of anticoagulation. Identifying possible factors like these, contributing to embolization in patients with atrial myxomas could help in the management and probably in prevention of mortality and morbidity from atrial myxomas. ***Phil Heart Center J 2017;22(1):40-46.***

**Key Words: Atrial Myxoma ■ cardiac tumors ■ embolization ■ emboli**

Primary tumors of the heart are rare. They have a frequency of approximately 0.3% in postmortem studies.[1] But despite the rarity, there are multiple histologic types found. Seventy-five percent of all primary cardiac tumors are benign and at least half of them are cardiac myxomas, which are also the most common type of primary cardiac tumor, accounting to 30 to

*Finalist*, Poster-Original Paper Presentation - Original Paper. 24th PHC Annual Research Paper Competition and Poster Presentation held on February 26, 2016 at Philippine Heart Center. Correspondence *to Dr. Jenny-Lynn V. Juhuri.* Department of Adult Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication**  2017 ISSN 0018-9034

50%.[2] In a local data by Regino-Ribo, et.al., based on the Philippine Heart Center Tumor Registry from 1976-2006, there were noted 17 cases of primary malignant cardiac tumors. Although the encounter with benign tumors were not mentioned based on the said tumor registry, the majority of primary cardiac tumors are benign.[3] Cardiac myxomas have an annual incidence of 0.5 per million population and most commonly presents in adults 30 to 50 years of age, 65% of which are noted in women.[2] They arise most commonly from the interatrial septum, usually on the left side.[4] They are histologically benign but due to their location and size, they can cause significant morbidity and mortality.[4] They have the potential to cause obstruction of intracardiac flow, arrhythmias secondary to myocardial invasion, constitutional symptoms or embolization of tumor fragments.[5] Hence, the treatment of symptomatic cardiac myxoma is prompt surgical resection of the tumor and that complete excision is the goal.[2] This aggressive approach is due to the constant threat of pulmonary or systemic embolization and occlusion of the valve orifices.[6]

The most common initial manifestations of myxoma include dyspnea, palpitation, chest pain, signs of embolism, symptoms of congestive heart failure because of cardiac obstruction, and systemic rheumatism depending on the localization, size, and humoral activity of the tumor.[7] In a study by Namazee et. al., systemic embolization occurred in ten patients (63%) before surgery and in five patients, embolic events were the first manifestation of the tumor. Embolic phenomenon observed included cerebral infarction, transient ischemic attacks (TIAs), myocardial infarction (MI), limb ischemia and multiple infarctions. They also cited a study conducted from 1980 through 1992 by Mattle et al, which followed 12 patients with cardiac myxomas for an average of 4.4 years. Reviewing the reports showed that this tumor is more frequent in women but gender has no effect on the rate of embolic events.[7]

Embolization resulting from fragmentation or complete tumor detachment occurs in up to 30% of cases and most of these tumors embolize to the central nervous system, resulting in cerebrovascular accidents (CVAs).[8] Atrial myxomas have been estimated to cause up to 0.5% of ischemic stroke.[9] In a local study by Ribu et. al., they reviewed 104 patients who underwent cardiac myxoma excision at Philippine Heart Center from February 1975 to December 1998 and revealed that 0.92% had CVA preoperatively. CVA was noted only in left atrial myxomas and this was secondary to fragmentation and systemic embolization of the tumor.[10] Two patients had CABG but they could not determine whether this is atherosclerotic or due to tumor embolization to coronary vessels. Embolization to the lungs, coronary arteries, kidneys, spleen, intestines, and lower extremities also occurs.[8] Coley and colleagues presented an unusual case of complete embolization of a left atrial myxoma resulting in acute peripheral artery occlusion and sudden lower extremity ischemia. The patient had no previous medical conditions, constitutional symptoms, or obstructive symptoms before the embolic event, which should serve as a reminder that the diagnosis of embolic myxoma should be suspected in younger, previously healthy patients presenting with acute arterial ischemia.[8] In the study of Vogel and colleagues, arterial embolism is a common complication of left atrial myxomas, caused either by thrombus formation at the surface of the tumor or by fragmentation of villous myxomas with particularly fragile extensions.[11]

Oliveira and colleagues set out a study to relate the predominant clinical features, divided into constitutional, embolic or obstructive, with tumor location and characteristics using transesophageal echocardiography (TEE) data. The predominant clinical features were due to the obstruction caused by the tumor in more than two thirds, followed by constitutional symptoms in one third and embolic events in 30% involving the brain, kidneys and lower limbs.[12] Embolic phenomena were more frequent in small tumors and in those with a villous appearance.[12] Zheng et.al. observed that cardiac myxoma specimens were soft, crunchy, and had the jelly-like appearance with the uneven surface, thus, tumor debris and tumor thrombus emboli can easily fall off to cause embolism. Due to hemodynamic factors, the right atrial myxoma mainly caused pulmonary embolism, while the left atrial myxoma can cause systemic embolism, of which the most common is cerebral embolism, from their

citation of the study by Salcedo et al. (1992).[13] Namazee et. al. mentioned two different types of myxoma. First was round with a nonmobile surface and second was polypoid that is soft and irregular in shape with a mobile surface. The chance for emboli formation in the second·type is more common.[7]

It is now well established that microembolic signals (MES) is a frequent phenomenon in patients with ischemic stroke and that the amount of MES is related to stroke onset, with the peak occurring in the first hours and days after stroke. In cardiology, transcranial Doppler (TCD) is a reliable technique for the detection of MES from cardiac embolic sources, such as prosthetic cardiac valves, aortic plaques and atrial fibrillation (AF). So, Telman et. al. made the first reported attempt to examine the emboliogenic potential of cardiac myxoma in patients with acute stroke through the monitoring of MES by TCD. Their findings showed the absence of MES on two consecutive TCD examinations, suggesting a spontaneous occurrence, rather than the permanent presence, of embolization, even in the most acute phase of stroke. These data are compatible with literature sources pointing to the simultaneous appearance of multiple emboli at different target sites in patients presenting with cardiac myxomas.[9]

There have been no studies appropriately designed and powered to develop a risk prediction model of tumor, as well as clinical factors that may predispose to embolization.[5] ElBardissi and colleagues revealed that tumor location, specifically left atrial and aortic valve tumors, and smaller tumor burden were the most significant factors in the occurrence of embolism.[5] Also, smaller tumors, minimal symptomatology and no evidence of mitral regurgitation have a high risk of embolism.[5] Nevertheless, they concluded that short and long-term outcomes after surgical resection of benign primary cardiac tumors are excellent with a low incidence of tumor recurrence and embolic events in the follow-up period.[5] In our local setting, due to the rarity of cardiac myxomas, more so of studies evaluating the factors contributing to embolization in patients with atrial myxomas, the purpose of this study is to find out these factors, which could help in the management and probably in prevention of mortality and morbidity from atrial myxomas.

## METHODS

The medical records of all patients with atrial myxoma who were admitted at the Philippine Heart Center from 2005 to 2014 were reviewed. Subject inclusion criteria included all patients, 10 years old and above, who were diagnosed with atrial myxoma by standard 2D echocardiogram. Subject exclusion criteria included patients with atrial myxoma but with concomitant hypercoagulable states (medical history of cancer, anti-phospholid antibody syndrome, protein S or C deficiency and pregnancy), female patients with regular intake of oral contraceptive pills for at least 4 weeks, within the year of diagnosis of atrial myxoma and cardiac myxoma cases with embolization but were not documented by any imaging/ancillary study. Case group was defined as those who had any embolic phenomenon documented by any imaging/ancillary study, e.g. cranial CT/MRI study, coronary angiogram, arterial/venous duplex scan, etc. Those with no history of an embolic event were defined as control group.

The study made a retrospective review of medical records of these patients, using a combination of two diagnostic categories namely, atrial myxoma. Embolization or embolic phenomenon is defined as an embolic event believed to be secondary to tumor debris or tumor thrombus emboli, which fall off to cause embolism. This will include cerebral infarction, TIA, MI, limb ischemia and other organ infarction. Patient's demographics, medical history, clinical presentation and diagnostic data were collected from the patient's records. Laboratory tests, such as the following: hemoglobin, hematocrit, leukocyte count (WBC), platelet count, protime (PT) INR, lipid profile, potassium (K), creatinine, and imaging studies like chest x-ray and transthoracic or transesophageal echocardiogram (TTE/TEE) were also noted. Presence of decreased sensorium or impaired mental status, acute respiratory failure, systemic inflammatory response syndrome (SIRS) and acute renal failure were analyzed. Operative procedure and histopathology were reviewed as well. The outcomes, e.g.

morbidity and mortality, were recorded.

The results were analyzed initially using descriptive statistics and univariate analyses to compare epidemiological, diagnostic and tumor variables between the case and control groups. Continuous variables are expressed as mean ± standard deviation (SD). On the second part of the analysis, candidate risk factors that included epidemiological, diagnostic and tumor variables were entered into a logistic regression model to find out significant factors between the case and control groups. Prediction scores were developed based on the odds ratios (ORs) derived from the logistic regression model. Statistical significance was considered at $p<0.05$. The Institutional Review Board (IRB) approved this study. Since data gathering was through medical records and did not involve any patient interaction, with confidentiality of the study data maintained, informed consent was not required. Using Epi Info version 7, the minimum sample size requirement is estimated to be at 146 (47 cases and 93 controls) based on the % exposed among cases = 19% and % exposed among controls = 9% (ElBardissi et al, 2009) with alpha level of 5%, power of 80% and ratio of controls to ratio which is 2.

## RESULTS

Of the 112 patients with atrial myxoma admitted at our institution, 23 (20.5%) presented with an embolic event and were categorized as cases while the remaining 89 (79.5%) were categorized as controls. Within the general sample population, the mean age is 52.4 years with predominance of females. Only 3.6% (n=4) are maintained on oral anticoagulation prior to admission, with a mean PT inr of 1.3 (0.9 - 2.2). Most had stable vital signs on admission. Majority of them showed sinus rhythm on electrocardiogram (ECG), while only a minority showed atrial fibrillation (AF). Based on 2D echocardiogram, locations of the tumor were mostly on the left atrium (LA) followed by the right atrium (RA) and lastly, on either of the two ventricles. Upon operation, majority of these tumors were attached directly to the interatrial septum (IAS) without a stalk. The histopathological findings of most of the tumors revealed myxoma. *(Table 1)*

**Table 1.** Baseline Characteristics of Patients with Atrial Myxoma

| Variables (n = 112) | Mean ± SD n = % |
|---|---|
| Age | 52.4 ± 17 |
| Male | 36 (32.1) |
| Female | 76 (67.9) |
| Smoker | 23 (20.5) |
| Alcoholic drinker | 27 (24.1) |
| Comorbidities: | |
| CAD | 8 (7.1) |
| CHD | 1 (0.9) |
| DCMP | 3 (2.7) |
| DCMP | 2 (1.8) |
| HPN | 30 (26.8) |
| DM | 13 (11.6) |
| Dyslipidemia | 2 (1.8) |
| CVD | 15 (13.4) |
| Renal disease | 1 (0.9) |
| Thyroid diseases | 5 (4.5) |
| Pulmonary diseases | 7 (6.3) |
| Gynecological diseases | 5 (4.5) |
| Gastrointestinal diseases | 2 (1.8) |
| Breast cancer | 1 (0.9) |
| Acute Respiratory Failuire | 9 (8) |
| SIRS | 12 (10.7) |
| Acute Kidney Injury | 10 (8.9) |
| Decreased sensorium | 16 (14.3) |
| Functional status: | |
| NYHA Class I | 59 (52.7) |
| NYHA Class II | 30 (26.8) |
| NYHA Class III | 13 (11.6) |
| NYHA Class IV | 2 (1.8) |
| Embolic phenomenon | 23 (20.5) |
| Preoperative anticoagulation | 4 (3.6) |
| SBP (mmHg) | 111.7 ± 16.3 |
| HR (bpm) | 83 ± 17 |
| RR (cpm) | 20 (16-35) |
| Temperature (C) | 36.2 ± 0.4 |
| Height (cm) | 158.5 ± 7.3 |
| Weight (kg) | 57.2 (34-90) |
| BMI | 22.7 (14.6-37.6) |
| Hemoglobin | 125.2 ± 17.6 |
| Hematocrit | 0.38 ± 0.05 |
| WBC Count | 10.7 (4.4 - 25.1) |
| Platelet | 283.9 (63 - 355.6) |
| PTR inr | 1.3 (0.9 - 2.2) |
| Potassium | 3.9 ± 0.6 |
| Creatinine | 0.09 (0.04 - 0.99) |
| ECG: | |
| SR | 71 (64.6) |
| SR with LAA | 21 (19.1) |
| AF | 16 (14.6) |
| Other rhythm | 2 (1.8) |

| | |
|---|---|
| 2D Echocardiogram: | |
| LA mass | 97 (88.2) |
| RA mass | 21 (19.1) |
| LV mass | 16 (14.6) |
| RV mass | 2 (1.8) |
| Tumor size: | |
| <13 cm | 24 (28.2) |
| ≥13 cm | 61 (71.8) |
| Operative findings: | |
| Mass directly attached to IAS | 55 (49.6) |
| Mass directly attached to other structures | 13 (11.7) |
| Stalk attached to IAS | 24 (21.6) |
| Stalk attached to other structures | 2 (1.8) |
| Histopath findings: | |
| Other type | 2 (1.9) |
| Myxoma | 77 (72.6) |
| Myxoma with thrombus | 10 (9.4) |

CAD: coronary artery disease; CHD: congenital heart disease; VHD: valvular heart disease; CHF: congestive heart failure; HPN: hypertension; DM: diabetes mellitus; CVD: cerebrovascular disease; SIRS: systemic inflammatory response syndrome; NYHA: New York Heart Association; SBP: systolic blood pressure; HR: heart rate; BMI: body mass index; WBC: white blood cell; PT inr: protime international normalized ratio; SR: sinus rhythm; LAA: left atrial abnormality; AF: atrial fibrillation; LA: left atrium; RA: right atrium; LV: left ventricle; RV: right ventricle; IAS: interatrial septum

**Table 2.** Characteristics of Atrial Myxoma Cases With or Without Embolic Events

| Variables (n = 112) | With Embolization n = 23 (%) | Without Embolization n = 89 (%) | Odds Ratio | P Value |
|---|---|---|---|---|
| Age | 53.7 ± 17.3 | 52.1 ± 16.5 | 1.00 | 0.682 |
| Gender | | | | |
| Male | 8 (34.8) | 28 (31.5) | | |
| Female | 15 (65.2) | 61 (68.5) | 0.86 | 0.761 |
| BMI | 22 ± 3.3 | 22.9 ± 3.7 | 0.92 | 0.256 |
| Smoker | 5 (21.7) | 18 (20.2) | 1.1 | 0.873 |
| Comorbidities | | | | |
| CAD | 2 (8.7) | 6 (6.7) | 1.32 | 0.746 |
| CHD | 0 | 1 (1.1) | - | - |
| VHD | 1 (4.4) | 2 (2.3) | 1.98 | 0.585 |
| DCMP | 1 (4.4) | 1 (4.4) | 4 | 0.334 |
| HPN | 12 (52.2) | 18 (20.2) | 4.3 | 0.003 |
| DM | 5 (21.7) | 8 (9) | 2.81 | 0.099 |
| Dyslipidemia | 0 | 2 (2.3) | - | - |
| CVD | 3 (13) | 12 (13.5) | 0.96 | 0.956 |
| Renal disease | 0 | 1 (1.1) | - | - |
| Thyroid diseases | 1 (4.4) | 4 (4.5) | 0.97 | 0.976 |
| Pulmonary diseases | 1 (4.4) | 6 (6.7) | 0.63 | 0.675 |
| Gynecological diseases | 0 | 5 (5.6) | - | - |
| Gastrointestinal diseases | 1 (4.4) | 1 (1.1) | 4 | 0.334 |
| Breast cancer | 0 | 1 (1.1) | - | - |
| Functional status | | | | |
| NYHA Class I | 13 (59.1) | 46 (56.1) | | |
| NYHA Class II | 6 (27.3) | 24 (29.3) | 0.88 | 0.825 |
| NYHA Class III | 2 (9.1) | 11 (13.4) | 0.64 | 0.595 |
| NYHA Class IV | 1 (4.6) | 1 (1.2) | 3.54 | 0.383 |
| Decreased sensorium | 9 (39.1) | 7 (7.7) | 7.53 | 0.001 |
| Preoperative anticoagulation | 3 (13) | 1 (1.1) | 13.2 | 0.029 |

BMI: body mass index; CAD: coronary artery disease; CHD: congenital heart disease; VHD: valvular heart disease; CHF: congestive heart failure; HPN: hypertension; DM: diabetes mellitus; CVD: cerebrovascular disease; GI: gastrointestinal

**Table 3.** Preoperative Laboratory Tests, ECG, and Echocardiographic Findings in Atrial Myxoma Cases With or Without Embolic Events

| Variables (n = 112) | With Embolization n = 23 (%) | Without Embolization n = 89 (%) | Odds Ratio | P Value |
|---|---|---|---|---|
| Laboratory Tests | | | | |
| Hemoglobin | 123 ± 19.8 | 125.8 ± 17.1 | 0.99 | 0.496 |
| Hematocrit | 0.37 ± 0.06 | 0.38 ± 0.05 | 0.01 | 0.271 |
| WBC | 11.5 ± 4.9 | 10.5 ± 4.6 | 1.05 | 0.358 |
| Platelet | 254.6 ± 95.8 | 291.3 ± 365.3 | 0.10 | 0.669 |
| PT inr | 1.2 ± 0.3 | 1.3 ± 0.2 | 0.29 | 0.294 |
| Potassium | 3.9 ± 0.6 | 3.9 ± 0.6 | 1.01 | 0.982 |
| Creatinine | 0.14 ± 0.19 | 0.09 ± 0.05 | 49.8 | 0.143 |
| ECG | | | | |
| SR | 15 (65.2) | 56 (64.4) | | |
| SR with LAA | 4 (17.4) | 17 (19.5) | 0.88 | 0.836 |
| AF | 3 (13) | 13 (14.9) | 0.86 | 0.832 |
| Other rhythm | 1 (4.4) | 1 (1.2) | 3.73 | 0.362 |
| 2D Echocardiogram: | | | | |
| LA mass | 20 (90.9) | 77 (87.5) | | |
| RA mass | 2 (9.1) | 8 (9.1) | 0.96 | 0.963 |
| LV mass | 0 | 0 | - | - |
| RV mass | 0 | 0 | - | - |
| Tumor size: | | | | |
| <13 cm | 6 (35.3) | 18 (26.5) | 1.52 | 0.472 |
| ≥13 cm | 11 (64.7) | 50 (73.5) | | |

WBC: white blood cell; PT: protime international normalized ratro; SR: sinus rhythm; LAA: left atnal abnormality; AF: atrial fibrillation; LA: left atrium; RA: right atrium; LV: left ventricle; RV: right ventricle

**Table 4.** Operative and Histopathological Findings of Atrial Myxoma Cases With or Without Embolic Events

| Variables (n = 112) | With Embolization n = 23 (%) | Without Embolization n = 89 (%) | Odds Ratio | P Value |
|---|---|---|---|---|
| Operative findings: | | | | |
| Mass directly attached to IAS | 9 (40.9) | 46 (51.7) | | |
| Mass directly attached to other structures | 4 (18.2) | 9 (10.1) | 0.73 | 0.243 |
| Stalk attached to IAS | 3 (13.6) | 21 (23.6) | 2.79 | 0.661 |
| Stalk attached to other structure | 0 | 2 (2.3) | - | - |
| Histopathology findings | | | | |
| Myxoma | 16. (72.7) | 61 (72.6) | | 0.989 |
| Myxoma with thrombus | 0 | 10 (11.9) | | - |
| Other type | 0 | 2 (2.4) | | - |

IAS: interatrial septum

**Table 5.** Multivariate Analysis for Risk of Tumor Embolism

| Variables | OR | CI | P Value |
|---|---|---|---|
| HPN | 20.61 | 3.39 - 125.33 | 0.001 |
| Decreased sensorium | 178.16 | 11.85 - 2677.49 | 0.000 |
| Preoperative anticoagulation | 161.29 | 3.05-8519.96 | 0.012 |
| AF | 0.47 | 0.00 - 0.93 | 0.044 |

HPN: hypertension; PT: protune international normalized ratio; AF: atrial fibrillation

## DISCUSSION

The study showed that the age of presentation of patients with atrial myxoma is 52.4 ± 17 years. This is consistent with the text by McManus, wherein atrial myxoma presents at the age of 30 to 50 years of age. Also, our study showed that there is a predominance of atrial myxoma in females, which is also consistent with the text by McManus, wherein 65% of atrial myxoma cases are noted in women. Most of our subjects had comorbidities identified. In the study by Coley et al, they presented a case of embolization of a left atrial myxoma and noted that the patient had no previous medical condition. Majority of our subjects showed sinus rhythm, with atrial fibrillation noted as the least. Several articles stated that atrial myxomas are usually on the left side, hence, we could have presumed that the left atrium will enlarge and might predispose to arrhythmia, however this is not the case in our study. Likewise, in the study done by ElBardissi and his colleagues, they mentioned that atrial myxomas have the potential to cause arrhythmias secondary to myocardial invasion, but in our study, arrhythmia was the least documented on ECG of our subjects. Based on 2D echocardiogram, our study revealed that most of the tumors were located in the LA, which is consistent with the article by Ho and Hirsch.[4] The histopathological findings of the tumors in our study revealed mostly pure myxoma. Zheng et.al mentioned that tumor debris and tumor thrombus emboli can easily fall off to cause embolism, but our subjects showed only a few having myxoma with thrombus. Even if such, Vogel and colleagues mentioned in their case report that embolism is a common complication of left atrial myxomas, caused either by thrombus formation at the surface of the tumor or by fragmentation of villous myxomas with particularly fragile extensions.

Patients with atrial myxoma who had embolic events compared to those without embolic events had no significant difference on age and gender proportion. Reviewing previous reports on this tumors, it was mentioned that this tumor is frequent in women but gender per se has no effect on the rate of embolic events.[7] Our study also showed that hypertension was significantly prevalent in the case group compared to the control group. A minority was maintained on oral anticoagulation prior to admission and there was a significant difference between the cases and the controls. However, despite the cases showing higher incidence of pre-operative anticoagulation, anticoagulation was inadequate based on the INR levels, hence embolic phenomenon was not prevented. Patients in AF were less likely to have embolic events compared to those who are in sinus rhythm. Electrocardiograms are performed but are frequently nonspecific.[4] Even in the case control study of Elbardissi et al, there was no significant difference in the incidence of AF or use of preoperative anticoagulation between the case and control groups. Small LA tumors are unlikely to warrant investigation because patients rarely have concomitant cardiovascular or hemodynamic alterations, and consequently appear to be asymptomatic.[5] Thus, LA and aortic valve tumors that do not reach anatomic dimensions great enough to alter cardiovascular function may lie dormant for long periods of time, thereby increasing the probability of embolization, whereas larger tumors may undergo diagnosis and resection early in the tumor life cycle.[5] This early diagnosis of larger tumors might prevent further embolization. Larger tumors pose an increased risk of irreversible cardiac and hemodynamic deterioration, whereas smaller, deceptively "innocent" tumors are at high risk of systemic embolization.[5] Supposedly, larger tumors which would cause enlargement of the LA and concomitant AF, are diagnosed earlier and resected earlier, hence a decreased probability of embolization, compared to patients in sinus rhythm, with probable smaller LA tumors having high risk of embolization. This was also evident in the study of Oliveira et al, wherein embolic phenomena were more frequent in small tumors and in those with

a villous appearance. Even in a case report by Matana et al,[14] the patient presented with a spherical, solid, smooth-surfaced myxoma not prone to embolization, as compared to polypoid prolapsing tumors. In a local study by Ribu et al, it was also evident that cerebrovascular accidents were noted only in left atrial myxomas. Another study also reported that RA myxoma mainly caused pulmonary embolism, while LA myxoma can cause systemic embolism.[13] Despite the findings of our study, showing predominance of myxoma in the LA, consistent with mentioned previous studies, location of the tumor did not show significant difference between the two groups.

The major limitation of this study might be due to low sample size, as well as inadequate information gathered from the medical records.

## CONCLUSION

Our study demonstrated that patients with atrial myxoma who had embolic events were mostly hypertensive. This study also revealed that those who had decreased sensorium during admission were likely to have embolic phenomenon. Atrial fibrillation, compared to sinus rhythm, did not confer a higher risk for embolization. And, although most of those with embolization were anticoagulated pre-operatively, anticoagulation was found to be inadequate. Identifying these possible factors contributing to embolization in patients with atrial myxomas could help in the management and probably in prevention of mortality and morbidity from atrial myxomas.

## REFERENCES


1. Tas demir K, Emirogullari N, Ceyran H, Asik R, Yasim A. Case study: Intracardiac masses. Asian CV Thorac Ann. [Internet] 2000 8: 378. [Accessed on 2013 July 13] Available from: DOI: 10.1177/021849230000800421.
2. McManus B. Braunwald's Heart Disease: a textbook of cardiovasuclar medicine. 9th Ed. PA: Saunders, Elsevier Inc. 2012. Chapter 74, Primary cardiac tumors;1638-1650.
3. Regino-Ribo M, de Luna A, Asuncion B, Orillaza M. Left atrial primary cardiac leiomyosarcoma in a 36-year-old male. Philippine Journal of Cardiology. [Internet] 2008; 36 (1): 16-22. Available from: http://www.philheart.org/documents/PJC2008voll.pdf [Accessed 21st January 2014].
4. Ho V, Hirsch M. Left atrial myxoma. Military Medicine. [Internet] 2006; 171 (9:iv-vi). Available from: rad.usuhs.mil/amsus/4 c Left Atrial Myxoma _Sept_2006.pdf [Accessed on 2013 July 13].
5. ElBardissi A, Dearani J, Daly R, Mullany C, Orszulak T, Puga F, et. al. Embolic potential of cardiac tumors and outcome after resection: a case-control study. Stroke. [Internet] 2009;40: 156-162. Available from: doi: 10.11611STROKEAHA.108.525709 [Accessed on 2013 July 13]
6. Bortolotti U, Maraglino G, Rubino M, Santini F, Mazzucco A, Milano A, et. al. Surgical excision of intracardiac myxomas: a 20-year follow-up. Ann Thorac Surg. [Internet] 1990; 49: 449-453. Available from: DOI: 10.1016/0003-4975(90)90253-3. [Accessed on 2013 July 13].
7. Narnazee M, Rohani-Sarvestani H, Serati A. The early presentation of atrial myxoma with acute myocardial infarction. Arch Iranian Med [Internet] 2008; 11 (1): 98 - 102. Available from: www.ncbi.nlm.gov/pubmedI 181 5 4429 [Accessed on 2013 August 2].
8. Coley C, Lee KR, Steiner M, Thompson CS. Complete embolization of a left atrial myxoma resulting in acute lower extremity ischemia. Tex Heart Inst J. 2005; 32 (2):238-40.
9. Telman G, Mesica O, Kouperberg E, Cohen O, Bolotin G, Agmon Y. Microemboli monitoring by transcranial doppler in patient with acute cardioembolio-genic stroke due to atrial myxoma. Neurol Int. 2010 Jun 21; 2(1): e5.
10. Ribu R, Catalan G, Centeno W, Rico A, Aventura A. Cardiac myxoma: a clinicopathologic profile. Phil Heart Center J 2001 Jan-Dec;8:81-84.
11. Vogel B, Thomas D, Mereles D, Rottbauer W, Hugo AK. Systemic embolization and myocardial infarction due to clinically unrecognized left atrial myxoma. Case Rep Med. 2011: 159024. doi: 10.1155/2011/159024.
12. Oliveira R, Branco L, Galrinho A, Abreu A, Abreu J, Fiarresga A, et al. Cardiac myxoma: a 13-year experience in echocardiographic diagnosis. Rev Port Cardiol. 2010 Jul-Aug;29(7-8):1087-100. [Article in English, Portuguese].
13. Zheng JJ, Geng XG, Wang HC, Yan Y, Wang HY. Clinical and histopathological analysis of 66 cases with cardiac myxoma. Asian Pac J Cancer Prev. 2013; 14 (3):1743-6.
14. Matana A, Zaputović L, Simić O, Kastelan ZM. The protective effect of mitral stenosis on the embolization of a free-floating left atrial myxoma. Eur J Echocardiogr. 2006 Aug;7(4):322-5.

# Correlation of Right Ventricular Strain Imaging Parameters with Cardiac Magnetic Resonance Imaging Parameters in the Assessment of Right Ventricular Function Among Repaired Tetralogy of Fallot Patients

Lorielyn Garcia-Mandigma, MD; Ma. Bernadette A. Azcueta, MD;
Roy C. Sasil, MD; Regina Christina Q. Mangada, MD

***Background*** --- Strain imaging offers an alternative non-invasive method to quantify right ventricular (RV) function.This study aims to utilize strain imaging in the assessment of RV function among repaired tetralogy of fallot patients in order to determine subclinical RV dysfunction and thereby aid the clinician in the follow-up and management of post-operative patients.

***Method*** --- This is a prospective cross sectional study done at the Philippine Heart Center. Cardiac magnetic resonance imaging and echocardiographic strain imaging were done on all subjects during the same day. Statistical comparison was performed using mean standard deviation and percent distribution for quantitative variables. Sensitivity and specificity curves using cardiac magnetic resonance imaging (MRI) derived right ventricular ejection fraction (RVEF) as the reference test was used to determine optimal cut-off values for global and regional longitudinal systolic strain and strain rate. Paired t-test was used for the assessment of intra-observer variability for 2D strain measurements.

***Result*** --- Twenty-two subjects were included, with a mean age of 16.7 $\pm$ 5.3 years old and a postoperative year interval of 8.95 ± 4.3 years. There was significant inverse, moderate correlation between cardiac MRI derived RVEF and right ventricular free wall mid segment strain (r=-0.42; p value =-0.05) and global longitudinal strain (r=-0.62, p value = 0.002). The determined cut-off for RV dysfunction tor right ventricular global longitudinal strain was -20.66% which showed a sensitivity of 88.83% and a specificity of 100%, PPV of 100%, NPV of 88.83%; right ventricular free wall mid segment strain determined cut-off was -16.19 which showed sensitivity of 88.33% and a specificity of 100%, PPV of 100%, NPV of 88.33%.

***Conclusion*** --- Strain imaging is an easy, feasible and reproducible parameter in two dimensional echocardiography that can be used as a good screening tool with high sensitivity and specificity for detecting right ventricular dysfunction among repaired TOF patients. ***Phil Heart Center J 2017;22(1):47-57.***

**Key Words: global longitudinal strain and strain rate ■ regional longitudinal strain and strain rate ■ Tetralogy of Fallot ■ right ventricular dysfunction ■ strain imaging**

Tetralogy of Fallot (TOF) is a cyanotic congenital heart disease that share the following anatomic abnormalities. A large mal-aligned ventricular septal defect (VSD), overriding of the aorta, right ventricular outflow tract obstruction (RVOT) and right ventricular hypertrophy (RVH).[1] TOF constitutes the most common cause of cyanotic heart disease with an incidence of approximately 0.5/1000 live births (5% to 7% of congenital heart lesions).[2] It is almost uniformly amenable to surgical repair and good long term outcomes.[1] With the advent of intracardiac repair, survival of patients with TOF into adulthood has become routine with a good long-term prognosis.[3] However, many patients have significant pulmonary regurgitation that can lead to right ventricular (RV) dilatation and dysfunction, right heart failure, arrhythmias and sudden cardiac death.[1] Pulmonary regurgitation worsens gradually and progressively deteriorates RV function, resulting in exercise intolerance, ventricular arrhythmia and death.[5]

*2nd Place*, Oral Presentation - Original Paper. 24th PHC Annual Research Paper Competition and Poster Presentation held on February 26, 2016 at Philippine Heart Center. Correspondence *to Dr. Loreilyn G. Mandigma.* Department of Pediatric Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication**  2017 ISSN 0018-9034

There is uniform agreement that patients with significant pulmonary regurgitation have mild to moderate impairment in exercise capacity with large individual variations.[6] Hence, assessment of RV function is crucial in the treatment of these patients as those with significant RV dilatation and symptoms may improve after pulmonary valve replacement.[7]

Right ventricular function has been shown to be a major determinant of clinical outcome in congenital heart disease patients. Accurate assessment of right ventricular function might be important for optimal timing of RV outflow re-evaluation.[8] RV function assessment should provide useful guidelines for more appropriate pulmonary valve replacement timing. However, measurement of RV function is not always easy to perform, especially when tricuspid regurgitation and pulmonary regurgitation are present.[5] RV dysfunction is a significant problem in patients with post-operative TOF.[6] Currently, magnetic resonance imaging remains to be the gold standard and reference method to evaluate volume and ventricular function but it is not often available, time consuming and costly.

Strain imaging offers an alternative non-invasive method to quantify RV function.[8] It does not rely on geometric assumptions and is based on the measurement of myocardial velocities caused by myocardial motion. This technique allows detection of delicate regional myocardial deformational abnormalities and has been validated for the assessment of regional function of the ventricles.[9,10] RV strain (Ɛ), corresponds to the extent of regional shortening/thickening and strain rate (SR) to the rate at which the deformation takes place.[8] These new and promising indices of ventricular function are independent of geometric constraints making them potentially useful for evaluation of the RV.[11]

This study aims to utilize strain imaging in the assessment of right ventricular function among post-operative TOF patients in order to determine subclinical right ventricular dysfunc tion and thereby aid the clinician in the follow-up and management of post-operative patients.

In the study by Nair et al., showed that subclinical RV dysfunction occurs in surgically repaired TOF patients as shown by decreased myocardial velocities and increased myocardial performance index.[12]

Wall motion abnormalities are relatively common in patients with congenital heart disease. Strain and strain rate seem to be useful in detecting motion abnormalities. These two indices can be calculated non-invasively in both the LV and RV to provide information on regional myocardial dysfunction.

A study by Haghighi et al., showed that although routine echocardiography derived indeces are not accurate to evaluate RV function in repaired TOF patients, systolic strain of the RV free wall can be used as a reliable tool to estimate RV function and functional capacity.[5]

Solarz et al., showed that in patients with postoperative TOF, systolic and diastolic strain rate and strain were impaired in the right ventricular free wall (RVFW) but preserved in the interventricular septum. Their speculation is that interventricular septum (IVS) myocardial function is preserved as a compensatory mechanism for RVFW function.[11] The significant findings of this study are that, for patients with repaired TOF, RV dysfunction exists in the face of normal RVEF and that RVFW function is depressed; however, IVS function is preserved. These findings are significant because they suggest that RV dysfunction may be unrecognized in the absence of strain rate (SR) and strain (Ɛ) analysis and that preserving IVS function is a potential compensatory mechanism in patients with postoperative TOF.[11]

Almost similarly, a study by Weidmann also showed abnormalities in regional RV (RVFW and IVS) and LV systolic myocardial function in asymptomatic postoperative TOF patients as quantified by the deformation parameters strain rate and strain.[10]

In a study by Li et al., they found a significant association between RV strain indices and CMR-derived RVEF, whereas conventional RV function parameters such as TAPSE and Sm are not associated with CMR-based RVEF. In addition, although RVEF levels were normal or near normal in the majority of patients in this study, RV longitudinal strain, and strain rate were reduced in patients compared with control

subjects. Therefore, they conclude that STE-derived strain and strain rate may be more sensitive for detecting changes in biventricular performance and that STE may be a useful follow-up tool in the early detection of myocardial impairment. Based on their findings that RV GLS and GLSR were correlated with CMR-derived RVEF ($r_1$ = 0.64, <0.05; r2 = 0.60, P <0.05, they have concluded that STE indeces may be a more accurate echocardiographic measurements of RV systolic performance than conventional echocardiographic parameters of RV function.[13]

## METHODS

The study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki. Prior to the study initiation, a review and approval of the study protocol and informed consent and subsequent amendments by the Philippine Heart Center-Institutional Ethics Review Board (PHC-IERB) was done.

Before a subject's participation, a written informed consent was obtained by the investigator after adequate explanation of the aims, methods, anticipated benefits and potential risks of the study. The informed consent was signed and personally dated by the subject or her legally authorized representative and the person who conducted the informed consent discussion. One copy of the informed consent was given to the subject.

The investigator preserved the confidentiality of all subjects who took part in the study. The investigator ensured that the subject's anonymity was maintained.

This is a prospective cross-sectional study conducted at the Philippine Heart Center for the calendar year 2015 for a period of 6 months. The study included patients who underwent tetralogy of fallot correction and who have pulmonary regurgitation.

*Study Maneuver.* Repaired TOF subjects who followed up at the OPD and met the inclusion and exclusion criteria were enrolled. The base line characteristics of the subjects in terms of sex, age, age at the time of operation, heart rate, blood pressure, QRS duration on ECG, degree of pulmonary regurgitation; degree of residual pulmonary stenosis and functional class were determined. Functional class was determined using the NYHA classification for heart failure. An informed consent was obtained from the parents, assent for children 7 to 18 years of age and consent for ≥19 years old.

*Echocardiography.* A complete 2D-echocardiogram with color flow doppler studies (2D-CFDS) using the Acuson SC200 machine with the 4V1c transducer depending on the patients weight was on the same day that cardiac MRI was done.

The presence of a residual RVOT gradient was determined and graded using the parasternal short axis view.

The degree of pulmonary regurgitation was also determined using the same view and was graded by determining its pressure half time and the presence of flow reversal at the level of the main pulmonary artery and branch pulmonary arteries.

Strain imaging (ventricular strain rate and strain analysis) was measured by automatic frame-by-frame tissue tracking by offline analysis using all RV images that were obtained in the apical four chamber view. The strain and strain rate indices were measured along the right ventricular free wall and interventricular septum at the basal (tricuspic annulus level), mid and apical segments. Peak systolic strain and strain rate were measured in three segments of RV free wall and three segments of IVS; in each segment, the strain and strain rate were measured for three consecutive heart beats and then averaged.[1]

Global longitudinal strain and strain rate were also measured for three consecutive heart beats and then averaged.

In order to allow an evaluation of the inter-observer reproducibility, a second echocardiographer blinded to other results reviewed the images. Another offline assessment of global RV strains and strain rates using the same method of analysis was done.

*Cardiac MRI.* All subjects underwent cardiac MRI during the same day that the strain imaging by 2D echocardiography was done. During the cardiac MRI procedure, the subjects were given breathing instructions prior to the capture of quality images in MRI. The right ventricle structure and function of cardiac MRI examination protocol, which does not require the use of a contrast medium, was used in the evaluation of the heart of the subject. The RV ejection function, pulmonary regurgitation fraction, and RV end diastolic and end systolic volume were determined and compared with the RV myocardial strain parameters. **Outcome variables:** presence of right ventricular dysfunction.

*Sample Size.* Using NCSS-PASS version 13, the minimum sample size was estimated to be at least 21 based on alpha of 5%, power of 90% and correlation of -0.64 based on the study of Li et al.[13] A total of 22 subjects were included in the study.

*Plan for analysis.* Data analysis was done using STATA SE version 13. Quantitative variables were summarized and presented as mean and standard deviation, while qualitative variables were tabulated and presented as frequency and percent distribution. The inter-observer reproducibility of the strain and strain rate assessment was tested using the paired t-test analysis. Correlational analysis of strain and strain rate imaging with cardiac magnetic resonance imaging was tested using Pearson correlation coefficient (r), P values <0.05 were considered statistically significant. Considering CMR as gold standard for the determination of the RV function with the cut-off for RV dysfunction at RVEF of <50%, the diagnostic accuracies of strain and SR was investigated by computing the area under the Receiver Operative Characteristics (ROC) curve (AUC). Specificities (Sp), sensitivities (Se), positive predictive value, negative predictive value were computed for the strain and strain rate parameters using their optimum values as well as the standard cut-off values whenever available.

**Table 1.** Demographic and clinical features

| Variables (N=22) | Mean ± SD |
|---|---|
| Sex | |
| Female | 12 (54.5%) |
| Male | 10 (45.5%) |
| Age (years) | 16.7 ± 5.3 |
| Age at repair (years) | 7.7 ± 4.3 |
| Post-operative years | 8.95 ± 4.3 |
| Heart rate (bpm) | 72 ± 9.9 |
| BP systolic (mmHg) | 100.9 ±9.2 |
| BP diastolic (mmHg) | 67.3 ± 7.7 |
| QRS duration (msecs) | 131 ± 28 |
| Severity of PR | |
| Mild | 9 (40.9%) |
| Moderate | 11 (505) |
| Severe | 2 (9.1%) |
| Severity of PS | |
| None | 9 (40.9%) |
| Mild | 9 (40.9%) |
| Moderate | 2 (9.1%) |
| Severe | 2 (9.1%) |
| NYHA Functional Class | |
| I | 21 (95.5%) |
| II | 1 (4.5%) |
| III | 0 (0%) |
| IV | 0 (0%) |

**Table 2.** Right ventricular strain rate and strain indeces

| | Mean ± SD |
|---|---|
| Peak strain rate (s1) | |
| RVFW Base | -1.36 ± 0.34 |
| RVFW Mid | -1.24 ± 0.22 |
| RVFW Apex | -1.63 ± 0.43 |
| Peak strain rate (s1) | |
| IVS Base | -2.99 ± 0.95 |
| IVS Mid | -1.28 ± 0.51 |
| IVS Apex | -1.28 ± 0.39 |
| Global longitudinal strain rate | -1.12 ± 0.51 |
| Strain (%) | |
| RVFW Base | -18.48 ± 4.15 |
| RVFW Mid | -17.12 ± 3.39 |
| RVFW Apex | -20.88 ± 5.46 |
| IVS Base | -33.69 ± 9.39 |
| IVS Mid | -20.79 ± 6.09 |
| IVS Apex | -17.65 ± 6.45 |
| Global longitudinal strain | -20.15 ± 3.3 |

**Table 3.** Inter-observer reproducibility of strain and strain rate assessment

| | Observer I | Observer 2 | P Value |
|---|---|---|---|
| Peak strain rate (s1) | | | |
| RVFW Base | -1.38 | -1.28 | 0.29 |
| RVFW Mid | -1.27 | -1.19 | 0.24 |
| RVFW Apex | -1.68 | -1.33 | 0.02 |
| Peak strain rate (s1) | | | |
| IVS Base | -3.0 | -1.94 | 0.004 |
| IVS Mid | -1.55 | -1.32 | 0.20 |
| IVS Apex | | | |
| Global longitudinal strain rate | -1.13 | -1.02 | 0.46 |
| Strain (%) | | | |
| RVFW Base | -18.69 | -16.5 | 0.28 |
| RVFW Mid | -17.78 | -16.87 | 0.4 |
| RVFW Apex | -20.9 | -18.5 | 0.27 |
| IVS Base | -31.95 | -25.24 | 0.08 |
| IVS Mid | -21.62 | -19.15 | 0.14 |
| IVS Apex | -18.18 | -16.34 | 0.5 |
| Global longitudinal strain | -20.48 | -18.64 | 0.08 |

**Table 4.** Cardiac Magnetic Resonance Imaging Data

| | Mean ± SD |
|---|---|
| RVEF (%) | 47.65 ± 7.6 |
| PRF (%) | 35.25 ± 18.2 |
| RVEDV (ml) | 160.8 ± 56.8 |
| RVEDV index (ml/m2) | 118.36 ± 26.3 |
| RVESV (ml/m2) | 87.5 ± 33.9 |
| RVESV index (ml/m2) | 62.6 ± 18.75 |

**Table 5.** Correlations between right ventricular function assessed by cardiac magnetic resonance imaging and strain imaging parameters

| | r4 | P Value |
|---|---|---|
| Peak strain rate (s1) | | |
| RVFW Base | 0.05 | 0.82 |
| RVFW Mid | 0.01 | 0.95 |
| RVFW Apex | -0.34 | 0.11 |
| Peak strain rate (s1) | | |
| IVS Base | -0.08 | 0.72 |
| IVS Mid | 0.05 | 0.83 |
| IVS Apex | 0.05 | 0.83 |
| Global longitudinal strain rate | -0.04 | 0.88 |
| Strain (%) | | |
| RVFW Base | -0.33 | 0.13 |
| RVFW Mid | -0.42 | 0.05 |
| RVFW Apex | -0.33 | 0.14 |
| IVS Base | -0.15 | 0.5 |
| IVS Mid | -0.10 | 0.65 |
| IVS Apex | -0.62 | 0.49 |
| Global longitudinal strain | -0.62 | 0.002 |

Table 1 shows the demographic characteristics and clinical data of the subjects (n=22) that were included in the study. The mean age of the subjects was 16.7 ± 5.3 years and there was an almost equal distribution of gender (54.5% vs. 45.5%) in our population. The mean postoperative interval was 8.95 ± 4.3 years. Majority of the subjects had none to mild residual pulmonary stenosis and are in functional class 1.

Table 2 shows the mean values for global and regional stain imaging indices at the right ventricular free wall, interventricular septum.

Table 3 shows that the overall inter-observer variabilty in the right ventricle strain imaging measurements was not significant. There were only 2 segments at the strain rate imaging that yielded a significant inter-observer variability (p value <0.(5).

Table 4 shows the cardiac magnetic resonance imaging data. The mean right ventricle ejection fraction (RVEF) was 47.65 ± 7.6% which was below the normal value (50%)[14] and was almost at the threshold level for the recommendation of pulmonary valve replacement (<47%).[15] There was also significant pulmonary regurgitation fraction with a mean 35.24 ± 18.2% based on the indication guidelines for pulmonary valve replacement after tetralogy of fallot correction (>25%). The right ventricle end diastolic volume (RVEDV) index and the right ventricle end systolic volume (RVESV) were 117.63 ± 26.3 ml/m$^2$ and 61.96 ± 19 ml/m$^2$ respectively, which was still within normal limits based on the indication guidelines for pulmonary valve replacement after tetralogy of fallot correction (RVEDV = > 160 ml/m$^2$ and RVESV = > 80 ml/m$^2$).

Table 5 shows the correlation analysis between cardiac MRI (CMRI) derived RVEF and RV strain imaging parameters. Among the strain imaging parameters that were determined, the right ventricle free wall mid segment strain and the global longitudinal strain were the only index that significantly correlated with RVEF with a correlation coefficient (r) of -0.42 at a p value of 0.05 and (r) of -0.62 and a p value of 0.002, respectively. There was also a weak correlation that was noted on strain analysis of the right ventricular free wall base and apical

**Table 6.** Sensitivity, specificity and positive predictive value of right ventricular strain and strain rate indices in the assessment of right ventricular systolic dysfunction

| Echocardiographic Parameter | Cut-off | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|
| Peak strain rate (s1) | | | | | |
| RVFW Base | -1.3 | 41.67 | 50 | 50 | 41.67 |
| RVFW Mid | -1.24 | 50 | 40 | 50 | 40 |
| RVFW Apex | -1.56 | 50 | 40 | 50 | 40 |
| Peak strain rate (s1) | | | | | |
| IVS Base | -3.14 | 50 | 50 | 54.55 | 45.45 |
| IVS Mid | -1.45 | 58.33 | 50 | 58.33 | 50 |
| IVS Apex | -1.27 | 41.67 | 30 | 41.67 | 30 |
| Global longitudinal strain rate | -1.29 | 75 | 30 | 56.25 | 50 |
| Strain (%) | | | | | |
| RVFW Base | -17.99 | 66.67 | 60 | 66.67 | 60 |
| RVFW Mid | -16.25 | 83.33 | 100 | 100 | 83.33 |
| RVFW Apex | -20.5 | 50 | 60 | 60 | 50 |
| Strain (%) | | | | | |
| IVS Base | -36.07 | 58.33 | 60 | 63.64 | 54.55 |
| IVS Mid | -21.36 | 50 | 50 | 54.55 | 45.45 |
| IVS Apex | -17.37 | 41.67 | 40 | 45.45 | 36.36 |
| Global longitudinal strain | -20.66 | 83.33 | 100 | 100 | 83.33 |

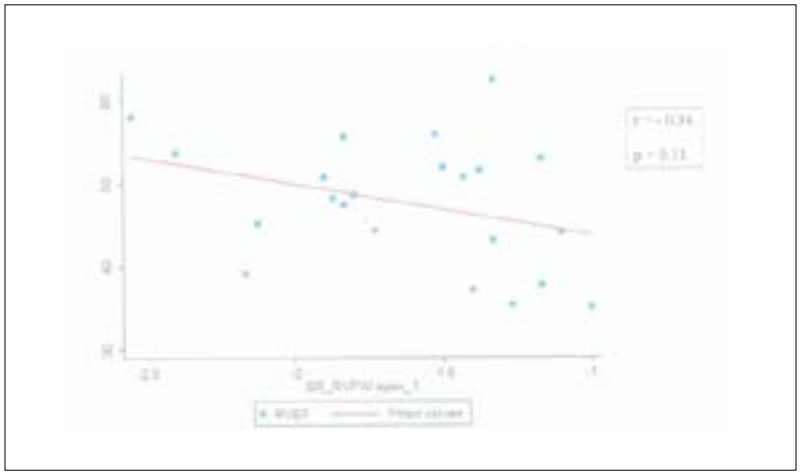

**Figure 1.** Relation between magnetic resonance imaiging derived right ventricular ejection fraction (RVEF) (vertical axis) and strain rate at the right ventricular free wall apical segment (horizontal axis)

segment, and on strain rate analysis of the right ventricular free wall apical segment, although it was not statistically significant.

Figure 1 showed that there was a weak and inverse correlation between cardiac derived RVEF and strain rate at the apical segment of the right ventricular free wall.

Figure 2 showed that there was a weak to moderate and inverse correlation between cardiac derived RVEF and strain rate at the right ventricular free wall segments.

Figure 3 showed that there was a good correlation between cardiac derived RVEF and global longitudinal strain with a Pearson's coefficient of -0.62 with a p value of -0.002.

The optimal cut-offs determined for global and regional longitudinal systolic strain and strain rate to determine RV dysfunction using the sensitivity and specificity curve with RV dysfunction as reference and the diagnostic accuracy of the strain imaging parameters were shown in Table 6. A RVEF threshold of <50% was used to detect RV dysfunction.

Figure 4 showed that the receiver operating characteristic curve analysis for global and regional longitudinal systolic strain and strain rate, showed that the right ventricular free wall mid-segment and the global longitudinal strain were the only parameters that had a high sensitivity and specificity to detect RV dysfunction. Both parameter were sensitive at 83.33% and specific at 100%

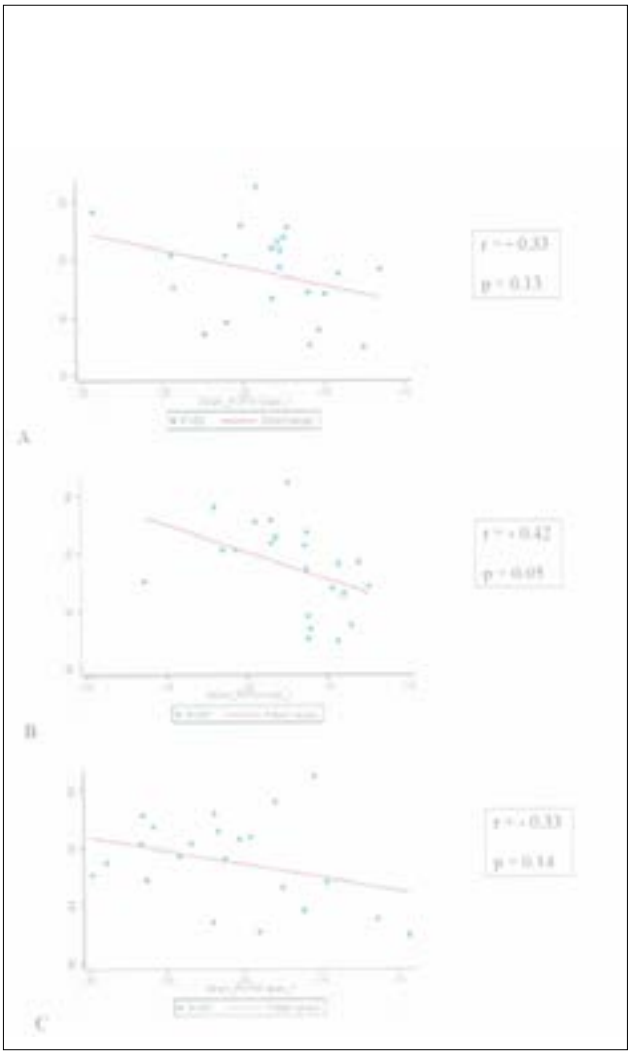

**Figure 2.** Relation between magnetic resonance imaiging derived right ventricular ejection fraction (RVEF) (vertical axis) and strain rate at the right ventricular free wall (horizontal axis) a) base, b) mid segment, c) apical segment

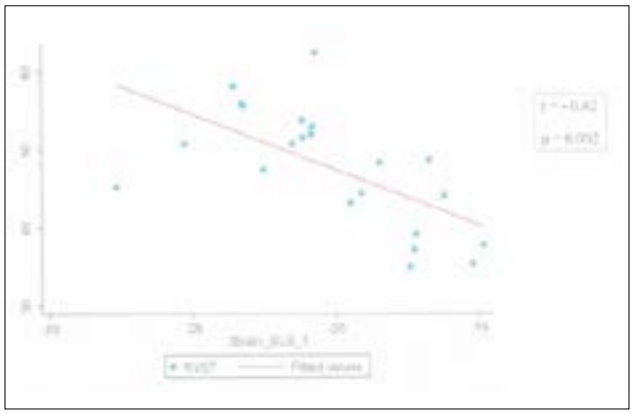

**Figure 3.** Relation between magnetic resonance imaiging derived right ventricular ejection fraction (RVEF) (vertical axis) and global longitudinal strain

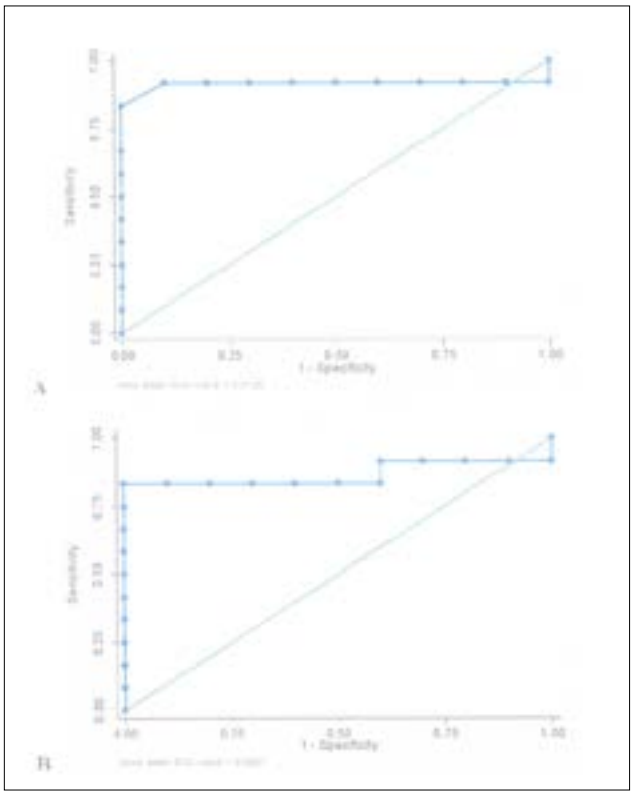

**Figure 4.** ROC curve illustrating the capacity of a) RV free wall mid segment; b) global longitudinal systolic strain to detect RV dysfunction

## DISCUSSION

Our study demonstrated the diagnostic potential of strain imaging in the detection of subclinical right ventricular dysfunction among corrected tetralogy of fallot patients. Significant findings of our study showed that RV systolic strain and strain rate parameters are decreased in repaired tetralogy of fallot patients compared to the established normal values.[16] We also found a significant correlation between global longitudinal strain and right ventricular free wall mid segment strain and cardiac MRI derived RVEF. A cut-off value of -20.54% for global longitudinal strain and -16.25% for right ventricular free wall mid segment strain were established to detect RV dysfunction by strain imaging. Both parameter were sensitive and highly specific.

Impaired RV regional and global function in patients with repaired TOF is not unique and has also been identified in other studies.[3,17,18] Previous studies of Li et al[13] and Scherptong et al[17] have shown that the RV longitudinal systolic regional and global strain and strain rate of majority of their postoperative tetralogy of fallot

population were significantly reduced compared to their control subjects, even if they were asymptomatic and have normal or near normal RVEF. Significant correlation between RV strain and RVEF was also seen in previous studies.[13,17,19] In a study by Solarz et al, they found out that in patients with repaired TOF, systolic RV myocardial strain rate and systolic strain were impaired in the right ventricular free wall but preserved in the interventricular septum.[11]

This finding of a decreased systolic strain and strain rate values is likely due to the combined effects of early pressure overload and hypoxia prior to the corrective surgery and volume overload due to pulmonary regurgitation in later life.[20] Other several unfavorable factors that may influence postoperative RV function are: (1) a non-contractile RVOT patch, (2) a chronic dilated free wall, and (3) septum dysfunction.[13,21] Changes in the myocardial architecture like the extensive presence of myocardial fibrosis among repaired tetralogy of fallot patients shown in a study by Babu-Nayaran et al. may also affect RV function.[13,22] These findings are therefore significant because they suggest the presence of early RV myocardial dysfunction even if the patient is asymptomatic and with preserved ejection fraction, thus warranting continued serial monitoring of these patients.[11,23]

Contrary to previous studies, our study showed that segmental longitudinal systolic strain and strain rate, as well as global longitudinal systolic strain rate, were not correlated to cardiac MRI derived RVEF. A similar finding of non-correlation of RV longitudinal systolic and strain rate indices with RVEF was also noted in a study of Bonnemains et al[24] and Rotes e al[25]. Results of Bonnemains et al showed that echocardiographic indices which includes strain parameters, failed to predict RVEF in repaired tetralogy of fallot patients.[24] They proposed that the reason for the lack of correlation between RVEF and longitudinal contraction indices was complicated and that several phenomena may be involved: (i) the RV longitudinal contraction in their post-operative population could have been impaired by the pericardicetomy and possible adhesions between the heart and sorrounding tissues (ii) 34% of their postoperative tetralogy of fallot patient have significant triscuspid regurgitation. Another reason that may have contributed to the lack of correlation in their study was the long time interval between cardiac MRI and 2D echocardiography (4 ± 1 month). They have acknowledged that the RV loading conditions may not be the same and this potential loading variation may have influenced the RVEF. Unlike in our study, cardiac MRI and strain imaging were performed on the same day.

Findings of a reduced systolic RV myocardial strain rate and systolic strain in the right ventricular free wall but preserved in the interventricular septum in the study of Solarz et al. was speculated to be because the interventricular septum functions to regulate right ventricle and left ventricle function.[11] This theory has been supported by previous studies that have concluded that the interventricular septum regulates ventricular stroke volumes to maintain proper balance between systemic and pulmonic circulation and is, thus, of critical importance to both right ventricle and left ventricle function.[11,28]

Myocardial deformation as measured by strain and strain rate imaging allows quantification of regional function. The interpretation of the myocardial deformation parameters is however complex because of the interaction between different physiologic parameters influencing strain measurements in postoperative patients with TOF. The increased stroke volume caused by pulmonary regurgitation should increase RV myocardial deformation, while RV dilatation has the opposite effect on myocardial deformation, as a larger ventricle needs to deform less to generate the same output. This probably explains why different studies performed in different study populations generated different results.[22]

RVEF has been proposed as a criterion influencing the timing of the surgery (with a threshold of 45%).[26,27] These criteria imply MRI acquisition, and the timing of which could be driven by an echocardiographic monitoring of the RVEF. It is therefore very important in the echocardiographic follow-up on repaired tetralogy of fallot patients to detect any RVEF alteration in order to plan the first pulmonary revalvulation surgery.

In a study by Geva et al.[26,27] they identified and elucidated the four phases in the ventricle dilatation: (i) Phase 1 is a compensated stage that may last for many years or even decades. During this phase, the slow but inevitable increase in PR will result in a progressive RV dilatation while the global systolic function and the mass-to-volume ratio remain normal (compensated hypertrophy). (ii) During Phase 2 the compensatory mechanisms fail. The ventricle dilatation progress with an inadequate hypertrophy (decreased mass-to-volume ratio) and a decreased EF while the intrinsic myocardial contractility remains normal. At this age, patients are still asymptomatic, however, this it is also in this moment where clinicians should closely monitor because the slope of the relation between pulmonary regurgitation and end diastolic volume will then follow a hyperbolic increase. (iii) During Phase 3, the myocardial contractility is impaired. This systolic dysfunction may still be reversible if valve replacement or repair is done promptly. (iv) Phase 4 implies irreversible myocardial injury with fibrosis. Clearly, intervention should be done before or at the beginning of Phase 3 sets in because when RVEF starts decrease, the RV dilatation rate increases further.

After repair of TOF, left and right ventricular ejection fractions are important markers of clinical status and outcome. Therefore, it is deem important to detect subclinical RV dysfunction among asymptomatic repaired TOF, before irreversible right ventricular dilatation and progressive RV dysfunction sets in. Our study showed that strain is a sensitive and specific marker of right ventricular dysfunction and it may yield incremental prognostic value.

## RECOMMENDATION

Regional and global longitudinal strain and strain rate analysis is an easy, feasible and reproducible echocardiographic parameter that can be used with good sensitivity and specificity. The utility of this parameter especially in the field of pediatric cardiology is highly recommended, and it should be routinely used along with our established cut-offs to determine RV dysfunction among repaired tetralogy of fallot patients.

Cardiac MRI remains to be the reference method to accurately measure the right ventricular ejection fraction although there are quantitative echocardiographic measurements that are recommended and are comparable with cardiac MRI. These parameters are however unable to detect regional myocardial dysfunction unlike strain imaging.

Strain and strain rate analysis is a very promising tool that can be utilized in the field of pediatric cardiology especially in the monitoring of repaired tetralogy of fallot patients.

## LIMITATION OF THE STUDY

Our population have included 4 patients with moderate to severe pulmonary stenosis which could have an effect on the value of strain and strain rate. A homogenous population would have been more ideal and reflective of the relationship between cardiac MRI derived RVEF and strain imaging parameters.

The role of vendor manufacturer and vendor-specific software variability was not addressed in our study. Compared to previous studies, our study utilized a non-GE ultrasound machine and software. GE ultrasound machine and software have heen well-utilized in researches in the field of strain imaging.

## CONCLUSION

Our subject population had a preserved right ventricular systolic function as determined by echocardiographic derived RVEF and were all asymptomatic. However, cardiac magnetic resonance imaging derived RVEF showed that almost 54.5% of them had a RVEF below 50%. These findings showed how asymptomatic repaired tetralogy of fallot patient with echocardiographic findings of preserved RVEF may go unnoticed until they become symptomatic, and by that time, reintervention may already be

too late for the right ventricle to adapt.

Findings of our study have shown that strain imaging is an easy, feasible and reproducible added parameter in two dimensional echocardiography that can be used as a good screening tool with good sensitivity and specificity for detecting RV dysfunction among repaired tetralogy of fallot.

RV strain imaging is not yet a surrogate for cardiac MRI in determining RVEF. However, utilizing with its determined cut off value for RV dysfunction, it can compliment our current echocardiographic assessment among repaired tetralogy of fallot and can accurately predict the presence of RV dysfunction. This will therefore aid the clinician to be able to timely recommend a cardiac MRI examination to define the patient's indication for reintervention.

In our study, we have determined a cut-off value for RV global longitudinal strain that was nearly similar to that of Bonnemains et al[9], and Urheim et al[24] (-20.54 vs. -19.2 vs. -20%). This cut off value had a high sensitivity to detect RV dysfunction.

## REFERENCES


1. Moss and Adams heart disease in infants and children. 7th ed. pp888.
2. Ho KW, Tan RS, Wong KY, Tan TH, Shankar S, Tan JL. Late complications following tetralogy of Fallot repair: the need for long-term follow-up. Ann Acad Med Singapore. 2007 Nov;36(11):947-53.
3. van Straten A, Vliegen HW, Hazekamp MG, de Roos A. Right ventricular function late after total repair of tetralogy of Fallot. Eur Radiol. 2005 Apr;15(4):702-7.
4. Giannopoulos NM, Chatzis AC, Bobos DP, Kirvassilis GV, Tsoutsinos A, Sarris GE. Tetralogy of Fallot: influence of right ventricular outflow tract reconstruction on late outcome. Int J Cardiol. 2004 Dec;97 Suppl 1:87-90.
5. Haghighi OS, Mahsid Z, Ahmad A, Feridoun N, Mahboobeh DF, Farid S, et al. Right ventricular strain predicts functional capacity in patients with repaired tetralogy of fallot. Iran Heart J 2011;12(3)17.36.
6. Gatzoulis MA, Elliott JT, Guru V, Siu SC, Warsi MA, Webb GD, et al. Right and left ventricular systolic function late after repair of tetralogy of Fallot. Am J Cardiol. 2000 Dec 15;86(12):1352-7.
7. Redington AN.Determinants of short- and long-term outcome in the surgical correction of tetralogy of Fallot. Curr Opin Pediatr. 1993 Oct;5(5):619-22.
8. Eyskens B, Brown SC, Claus P, Dymarkowski S, Gewillig M, Bogaert J, et al. The influence of pulmonary regurgitation on regional right ventricular function in children after surgical repair of tetralogy of Fallot. Eur J Echocardiogr. 2010 May;11(4):341-5.
9. Urheim S, Edvardsen T, Torp H, Angelsen B, Smiseth OA. Myocardial strain by Doppler echocardiography. Validation of a new method to quantify regional myocardial function. Circulation. 2000 Sep 5;102(10):1158-64.
10. Weidemann F, Eyskens B, Jamal F, Mertens L, Kowalski M, D'Hooge J, et al. Quantification of regional left and right ventricular radial and longitudinal function in healthy children using ultrasound-based strain rate and strain imaging. J Am Soc Echocardiogr. 2002 Jan;15(1):20-8.
11. Solarz DE, Witt SA, Glascock BJ, Jones FD, Khoury PR, Kimball TR. Right ventricular strain rate and strain analysis in patients with repaired tetralogy of fallot: possible interventricular septal compensation. J Am Soc Echocardiogr. 2004 Apr;17(4):338-44.
12. Nair KKM, Ganapathi S, Bijulal S, Thajudeen A, Pillai HS, Tharakan J, et al. Asymptomatic right ventricular dysfunction in surgically repaired adult tetralogy of fallot patients. Ann Pediatr Cardiol. 2013 Jan-Jun; 6(1): 24–28.
13. Li Y, Xie M, Wang X, Lu Q, Zhang L, Ren P. Impaired right and left ventricular function in asymptomatic children with repaired tetralogy of Fallot by two-dimensional speckle tracking echocardiography study. Echocardiography. 2015 Jan;32(1):135-43.

14. Sadeghpour A, Kyavar M, Madadi S, Ebrahimi L, Khajali Z, Sani ZA. Doppler-derived strain and strain rate imaging assessment of right ventricular systolic function in adults late after tetralogy of Fallot repair: an observational study. Anadolu Kardiyol Derg. 2013 Sep; 13(6):536-42.
15. Geva T. Indications for pulmonary valve replacement in repaired tetralogy of fallot: the quest continues. Circulation. 2013 Oct 22; 128(17): 1855–1857.
16. Levy PT, Sanchez A, Machefsky A, Fowler S, Holland MR, Singh GK. Normal ranges of right ventricular systolic and diastolic strain measures in children: a systematic review and meta-analysis. J Am Soc Echocardiogr. 2014 May; 27(5): 549–560.e3.
17. Scherptong RW, Mollema SA, Blom NA, Kroft LJ, de Roos A, Vliegen HW, et al. Right ventricular peak systolic longitudinal strain is a sensitive marker for right ventricular deterioration in adult patients with tetralogy of Fallot. Int J Cardiovasc Imaging. 2009 Oct;25(7):669-76.
18. Davlouros PA, Kilner PJ, Hornung TS, Li W, Francis JM, Moon JC, et al. Right ventricular function in adults with repaired tetralogy of Fallot assessed with cardiovascular magnetic resonance imaging: detrimental role of right ventricular outflow aneurysms or akinesia and adverse right-to-left ventricular interaction. J Am Coll Cardiol. 2002 Dec 4;40(11):2044-52.
19. Eyskens B, Brown SC, Claus P, Dymarkowski S, Gewilig, M, Bogaert, J, et al. The influence of pulmonary regurgitation on regional right ventricular function in children after surgical repair of tetralogy of Fallot. Euro J Echocardiog. 2010;11:341-345.
20. Hausdorf G, Hinrichs C, Nienaber CA, Schark C, Keck EW. Left ventricular contractile state after surgical correction of tetralogy of Fallot: risk factors for late left ventricular dysfunction. Pediatr Cardiol. 1990 Apr; 11 (2):61-8.
21. Dexter L. Atrial septal defect. Br Heart J. 1956 Apr;18 (2):209-25.
22. Babu-Narayan SV, Kilner PJ, Li W, Moon JC, Goktekin O, Davlouros PA, et al. Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of fallot and its relationship to adverse markers of clinical outcome. Circulation. 2006 Jan 24;113(3):405-13.
23. Friedberg MK, Mertens L. Deformation imaging in selected congenital heart disease: is it evolving to clinical use? J Am Soc Echocardiogr. 2012 Sep; 25 (9):919-31.
24. Bonnemains L, Stos B, Vaugrenard T, Marie PY, Odille F, Boudjemline Y. Echocardiographic right ventricle longitudinal contraction indices cannot predict ejection fraction in post-operative Fallot children. Eur Heart J Cardiovasc Imaging. 2012 Mar;13(3):235-42.
25. Rotes A, Bonnichsen C. Reese C, Connolly H, Burkart H, Dearani J. Long-term follow-up in repaired tetralogy of fallot: can deformation imaging help identify optimal timing of pulmonary valve replacement? J Am Soc Echocardiogr. 2014 Dec; 27(12):1305-1310.
26. Geva T. Indications and timing of pulmonary valve replacement after tetralogy of Fallot repair. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2006:11-22.
27. Knauth AL, Gauvreau K, Powell AJ, Landzberg MJ, Walsh EP, Lock JE, et al. Ventricular size and function assessed by cardiac MRI predict major adverse clinical outcomes late after tetralogy of fallot repair. Heart. 2008 Feb;94(2):211-6.
28. Stoylen A, Heimdal A, Bjornstad K, Torp HG, Skjaerpe T. Strain rate imaging by ultrasound in the diagnosis of regionaldysfunction of the left ventricle. Echocardiography. 1999 May;16(4):321-329.

# Accuracy of Rapid Shallow Breathing Index (RSBI) Rate During Spontaneous Breathing Trial as a Predictor of Weaning Outcome

Edgardo D.C. Tiglao, Jr., MD; William E. Del Poso, MD; Teresita S. De Guia, MD

***Background*** **---** Rapid shallow breathing index (RSBI) is commonly used clinically for predicting the outcome of weaning from mechanical ventilation. However, studies reported that a single RSBI determination is not reflective of the entire weaning process. Thus in this study, we evaluated the predictive value of RSBI rate in weaning outcome among mechanically ventilated patients.

***Method*** **---** This is a prospective cohort study done at the critical care units of the Philippine Heart Center from May to December 2015. Seventy-one adult patients mechanically ventilated over 48 hours were enrolled according to the weaning criterion and underwent spontaneous breathing trial (SBT) with T-piece. During SBT, respiratory rate (RR1), tidal volume of spontaneous breath (VT1), and rapid shallow breathing index (RSBI1) were determined at the first minute of SBT. Likewise RR2, VT2, and RSBh were measured at the 30th minute of SBT. RSBI rate was then calculated using the following formula: [(RSBh - RSBI1)] / RSBI] x 100%. Patients were observed and followed-up for their weaning outcome. Clinical data and respiratory indices during SBT were compared between patients in weaning success group and those in weaning failure group. Predictive accuracy of the RSBI rate in predicting weaning outcome was presented as sensitivity, specificity, PPV, NPV and AUROC.

***Results*** **---** Weaning was successful in 59 patients and failed in 12 patients. Among those with weaning failure, 4 patients required reinstitution of mechanical ventilation within 48 hours (extubation failure), 3 patients required noninvasive ventilation after extubation (extubation failure) and 5 patients could not be extubated after SBT (trial failure). Weaning failure group showed higher respiratory rate, tidal volume and RSBI compared with the weaning succesful group. The association of RSBI rate in predicting weaning outcome was statistically significant ( p= <0.001). The sensitivity, specificity, positive predictive value, negative predictive value and mean area under the receiver operating characteristic curve of RSBI rate on extubation outcome were 100%, 81.36%, 52.17% 100%, 0.94 respectively.

***Conclusion*** **---** Rapid shallow breathing index (RSBI) rate is a reliable parameter in predicting weaning outcome among mechanically ventilated patients. ***Phil Heart Center J 2017;22(1):58-64.***

**Key Words: Rapid Shallow Breathing Index (RSBI) rate ■ Weaning ■ Mechanical Ventilation**

Weaning from mechanical ventilation is a key element in the care of critically ill intubated patients. In fact, the liberation from the mechanical ventilatory support marks the milestone in the progression to patient recovery in the intensive care unit. However, this always pose a challenge to primary care physicians - a challenge whose outome leans on the physician's subjective judgement associated with patient's clinical status.

There are numerous advances in mechanical ventilation and respiratory support that can be used to determine weaning parameters. However, despite of these medical breakthrough the science of determining the patient's readiness for extubation is still very imprecise. Moreover, none of the available parameters was consistently able to predict weaning outcome.[1]

Of the various weaning parameters used, the rapid shallow breathing index (RSBI), defined as the ratio of respiratory rate (breaths/min) to tidal

*1st* place, Oral Presentation - Original Paper. 24th PHC Annual Research Paper Competition and Poster Presentation held on February 26, 2016 at Philippine Heart Center. Correspondence *to* ***Dr. Edgardo DC. Tiglao, Jr.*** Division of Pulmonary and Critical Care Medicine. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication**  ISSN 0018-9034

volume (VT), has been shown to be the best.[2,3] It was proven to be more powerful , accurate and reliable in predicting weaning outcome than other traditional parameters.[4] However, the utility of a single RSBI determination is not a representative of the whole weaning process since respiratory failure may develop in a progressive nature during spontaneous breathing trial.[5] Studies have demonstrated that rapid shallow breathing index (RSBI) rate or a measure of change of RSBI over time, may offer more predictive value than its RSBI predecessor.[6] The evolution of breathing pattern as assessed by the change in RSBI is a marker of the dynamic changes occurring during weaning, thus this may improve the ability to predict extubation outcome. It was shown that a RSBI rate of less than or equal to 20% was correlated to be 89% specific and sensitive in predicting successfullness of weaning from mechanical ventilation.[6]

The study aims to determine the predictive value of RSBI rate in weaning outcome during a spontaneous breathing trial among Filipino patients admitted at the critical care units of the Philippine Heart Center. Its value can be used in lessening delays in extubation thus decreasing complications brought by prolonged mechanical ventilatory support such as ventilator associated pneumonia, airway trauma and tracheostomy. It will also minimize patient's hospital expenditure and mortality.

## METHODS

The study was conducted in compliance of the ethical principles set forth by the Declaration of Helsinki. It was reviewed and approved by the Philippine Heart Center Institutional Ethics Review Board (PHC-IERB). A written informed consent was obtained after adequate explanation of the aims, methods, anticipated benefits and potential risks of the study. Since the subject was intubated, the informed consent was signed and personally dated by the legally authorized representative and the person who conducted the informed consent. One copy of the informed consent was given to the subject's legally authorized representative. Verbal assent was also given to a decisionaly-abled subject. A subject can withdraw their participation in the study at their request of their legally authorized representative at any time for any reason.

*Study Design, Setting, and Time Frame.* This was a prospective cohort study done at the Philippine Heart Center Critical Care Units (Medical Intensive Care Unit, Coronary Care Unit, Surgical Intensive Care Unit, Neurological Intensive Care Unit) from May 1, 2015 - December 31, 2015.

*Subject Selection.* All adult patients (19 to 70 years old) admitted at the intensive care units who have undergone controlled mechanical ventilation for more than 48 hours and are judged ready for weaning based on criteria (objective and clinical assessement) set by the Evidenced-Based Medicine Task Force of the American College Chest Physcicians[7,8] were included in the study. The following were the objective assessment criteria used: adequate oxygenation (P02 $\geq$60 mm Hg on Fi02 $\leq$ 0.4, PEEP $\leq$5-10 cm H2O, P02/Fi02 $\geq$ 150-300); stable cardiovascular system (HR $\leq$140, systolic BP 90-160 mmHg, no/or minimal pressors such as dopamine or dobutamine $\leq$5 ug/kg/min); afebrile (temperature $<$ 38°C); no significant respiratory acidosis; adequate hemoglobin (Hgb $\geq$ 8-10 g/dl.); adequate mentation (arousable, GCS $\geq$13, no continuous sedative infusions); stable metabolic status (acceptable electrolytes); absence of diaphoresis and signs of increased work of breathing (use of accessory respiratory muscles, and thoracoabdominal paradox); sedatives, hypnotics and narcotics withheld for 24 hours prior to weaning trial. The following were the subjective clinical assessment used: resolution of disease's acute phase for which the patient was intubated; physician believes discontinuation is possible; adequate cough; absence of excessive tracheobronchial secretion. Exclusion criteria included: patients with significant cardiac ischemia, arrhythmia, or left ventricular dysfunction; known upper airway obstruction; prior tracheostomy and with signed consent for "do not intubate or resuscitate" status.

*Study Maneuver.* Patients included were orally intubated (with tube size $\geq$ 7.0 mm) and mechanically ventilated for more than 48 hours. Assist-control ventilation (AC), Pressure Support Volume (PSV), Synchronized Intermittent Mechanical Ventilation with Pressure Support

(SIMV-PS), Adaptive Support Ventilation (ASV) were the preferred modes prior to initiation of the weaning trial. Study investigators did not provide any input regarding the primary or critical care physician's desicion to start a weaning trial, reconnect the subjects to mechanical ventilator or extubate or intubate the subject.

*Spontaneous Breathing Trial (SBT) Protocol*. SBT was performed in the morning after a night's rest of at least 6 hours under controlled mechanical ventilation. The patient was placed in a semi-seated position using a T-piece and supervised by the respiratory therapist on duty. The T-piece was connected to a corrugated large bore tubing where oxygen flow (Fractional Inspired 02) was set to the same value used during mechanical ventilation. Initial $RSBI_1$ and arterial blood gas was taken in the first one minute of T-piece weaning. $RSBI_2$ was measured after 30 minutes of T-piece weaning. Patients was then observe and follow-up for the outcome of their weaning trial.

*Measurement of rapid shallow breathing index (f/Vt)*. Rapid shallow breathing index was defined as the respiratory rate (expressed in breaths/minute) divided by the tidal volume (expressed in liters). The respiratory rate was measured in one minute via direct visualization using a handwatch. Tidal volume was measured by connecting the patient's endotracheal tube to the portable Wright respirometer (Model Mk 14 Ferraris Respirometer). The calculated mean of the tidal volume in three breaths was used. $RSBI_1$ was determined during one minute of SBT and $RSBI_2$ was measured after thirty minutes of SBT.

*Measurement of the rate of change of rapid shallow breathing index.* The RSBI rate was calculated by obtaining the difference between the initial $RSBI_1$ and the final $RSBI_2$, and then dividing the result by the initial $RSBI_1$. The resulting number was then multiplied by 100. RSBI rate of ≤20% was predictive of weaning success.[6]

*Classification and analysis of weaning outcome.* Weaning was classified as successful if patients was able to maintain spontaneous breathing for 48 hours after extubation. Failure of weaning was classifed as: (1) extubation after spontaneous breathing trial but requiring reinstitution of mechanical ventilatory support in the following 48 hours or patients who received non-invasive ventilation (NIV) after extubation but was not able to remove it after 48 hours of extubation *(extubation failure)*[1,6] (2) reinstitution of mechanical ventilator during the weaning process due to inability of the patient to tolerate or endure the weaning trial *(trial failure)*.[1] The decision to extubate or reintubate the patient was based on the assessment of the primary care or critical care physician.

*Sample Size Calculation.* Using Epi Info 7 software, the minimum sample size requirement was estimated to be at least 67 based on the following parameters: Alpha (α) = 5%; sensitivity of RSBI rate in detecting weaning outcome = 89% based on the study by Segal et al[6] ; maximum tolerable error (e) = 7.5%.

*Statistical Analysis.* Data analysis was done using Stata SE version 13. Quantitative variables were summarized and presented as mean and standard deviation, while qualitative variables were tabulated and presented as frequency and percent distribution. Comparison of the profile between patients with successful and failure of weaning were tested using independent t-test for quantitative variables and Fisher's exact test for qualitative variables. The accuracy of the RSBI rate in predicting weaning outcome among patient in spontaneous breathing trial was presented as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under receiver characteristic curve (AUROC). Association between RSBI rate and weaning outcome was determined and tested using Fisher's exact test. The level of significance was set at 0.05.

## RESULTS

A total of seventy-one patients were included in the study. Fifty-nine patients (89.10%) were weaned successfully and twelve patients (16.90%) failed weaning. Among those with weaning failure, four patients required reinstitution of mechanical ventilation after 48 hours of extubation, three patients received non-invasive ventilation after extubation but were unable to withdraw it after 48 hours, and five patients did not tolerate spontaneous breathing trial and were not extubated. Table 1 summarizes the clinical

characteristics of the patients. Fifty-four patients (76%) were males and 17 (24%) were females. The mean age of the study population was 48 years old. Majority of the patients were intubated after open heart surgeries such as coronary artery bypass graft and valvular heart surgeries. Some patients required mechanical ventilation support due to medical illnesses such of COPD in exacerbation, bronchial asthma in exacerbation and high-risk pneumonia. Most of the primary care physicians preferred Assist-Control mode and Pressure Support Ventilation mode prior to starting spontaneous breathing trial. There was a trend towards older age, higher BMI, higher APACHE II score, longer duration of mechanical ventilation in weaning failure group as compared with weaning success group. There were no significant differences between groups in the variables at baseline.

Table 2 summarizes the respiratory and ventilatory mechanics of patients during spontaneous breathing trial. Static and dynamic compliance of patients with successful weaning tends to be higher as compared with weaning failure group. Arterial blood gas values were comparable between the two groups. At the initiation of spontaneous breathing trial, the weaning failure group demonstrated higher respiratory rate, tidal volume and RSBI compared with the succesful weaning group. However, there was no significant difference in the initial mean values of the respiratory rate, tidal volume and RSBI. After 30 minutes of spontaneous breathing trial, the weaning failure group showed an increase in the RSBI (mean 67.08 ± 13.27). There was no significant difference in the mean values for respiratory rate, tidal volume and RSBI between the two groups.

Table 3 summarizes the association between RSBI rate and weaning outcome. From the 71 patients, 48 patients (68%) have RSBI ≤20% and 23 patients (32%) have RSBI >20%. All 48 patients with RSBI ≤20% were extubated succesfully. In the 23 patients with RSBI >20%, 11 patients (18.6%) succeeded with extubation while 12 patients (100%) failed from weaning. Based on these results, the association of RSBI rate in predicting weaning outcome was statistically significant. Thus the sensitivity and specificity of RSBI rate to predict weaning outcome were 100% and 81.36%, respectively. (*Table 5*). Likewise, the positive predictive value (PPV) and negative predicitve value (NPV) were 52.17% and 100%, respectively. (*Table 5*) The overall accuracy of RSBI rate in predicting weaning outcome was 94% as shown in Figure 2.

**Table 1.** Baseline characteristics of patients

| Variables | Weaning Success (n=59) | Weaning Failure (n=12) | p-value |
|---|---|---|---|
| Gender: | | | |
| Male | 45 (76.27%) | 9 (75%) | 1.00 |
| Female | 14 (23.73) | 3 (25%) | |
| Age (years) | 47 ± 15.07 | 49 ± 12.11 | 0.58 |
| Height (cm) | 159.93 ± 16.38 | 163.17 ± 6.59 | 0.50 |
| Weight (kg) | 57.21 ± 10.63 | 61.44 ± 12.32 | 0.22 |
| BMI (kg/m$^2$) | 21.91 ± 3.70 | 23.03 ± 4.15 | 0.35 |
| Medical History: | | | |
| Cardiac | | | |
| Hypertension | 30 (50.85%) | 5 (41.67%) | 0.75 |
| RHD | 13 (22.03%) | 2 (16.67%) | 1.00 |
| CHD | 3 (5.08%) | 1 (8.33%) | 0.53 |
| CHF | 1 (1.69%) | 0 (0) | 1.00 |
| COPD | 6 (10.17%) | 2 (16.67%) | 1.00 |
| Bronchial Asthma | 6 (10.17%) | 1 (8.33%) | 1.00 |
| Diabetes Mellitus | 19 (32.20%) | 4 (33.33%) | 1.00 |
| Hyperthyroidism | 1 (1.69%) | 1 (8.33%) | 0.31 |
| CKD | 4 (6.78%) | 2 (16.67%) | 0.27 |
| Smoking History: | | | |
| Non-smoker | 20 (33.90%) | 4 (33.33%) | 0.92 |
| Ex-smoker | 24 (40.67%) | 4 (33.33%) | |
| Current smoker | 15 (25.42%) | 4 (33.33%) | |
| APACHE II Score | 8.58 ± 3.23 | 10.08 ± 3.37 | 0.16 |
| Ventilator status before initiation of SBT: | | | |
| Duration of MV (hr) | 32 ± 30.80 | 38.92 ± 47.96 | 0.63 |
| Internal Diameter of ETT (mm) | 7 ± 1.50 | 7 ± 0.50 | 0.09 |
| Mode of Ventilation prior to SBT | | | |
| ACC Mode | 23 (38.98%) | 7 (58.33%) | 0.60 |
| SIMV-PS | 2 (3.39%) | 0 (0) | |
| ASV | 4 (6.78%) | 1 (8.33%) | |
| PSV | 30 (50.85%) | 4 (33.33%) | |
| Hemoglobin | 124.07 ± 16.33 | 117.43 ± 11.34 | 0.16 |
| Reason of MV: | | | |
| COPD in exacerbation | 3 (5.08%) | 1 (8.33%) | 0.92 |
| Bronchial Asthma | 1 (1.69) | 0 | |
| Exacerbation | 3 (5.08%0 | 0 | |
| Pnuemonia (↑risk) | 5 (8.47%) | 0 | |
| Heart Failure | 2 (3.39%) | 0 | |
| Neurologic Dse. | | | |
| Post-op | | | |
| CABG | 21 (35.59%) | 4 (33.33%) | |
| Valve | 20 (33.90%) | 6 (50.00%) | |
| Vascular | 3 (5.08%) | 1 (8.33%) | |
| VATS with Deloculation | 1 (1.69%) | 0 | |

RHD: Rheumatic heart disease; CHD: Congenital heart disease; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; APACHE II:Acute Physiological and Chronic Health Evaluation II score; SBT.·Spontaneous breathing trial; MV: Mechanical ventilation; ETT: Endotracheal tube; AC Mode: Assist-Control mode; SIMV-PS: Synchronized Intermittent Mechanical Ventilation with Pressure Support; ASV: Adaptive Support Ventilation; PSV: Pressure Support Ventilation; CABG: Coronary artery bypass grafting surgery; VATS: Video-assisted thoracoscopic surgery

Figure 3 illustrates ROC curves of initial RSBI, static compliance, dynamic compliance and RSBI rate of the patients. RSBI rate (area under the curve 0.94) tends to be better than static compliance (area under the curve 0.48), dynamic compliance (area under the curve 0.34), initial RSBI (area under the curve 0.37) in predicting weaning outcome.

**Table 2.** Respiratory and ventilatory parameters during spontaneous breathing trial

| Variables | Weaning Success (n=59) | Weaning Failure (n=12) | p-value |
|---|---|---|---|
| Cstat | 38.48 ± 12.52 | 29.97 ± 16.77 | 0.73 |
| Cdyn | 35.05 ± 7.86 | 32.96 ± 10.88 | 0.44 |
| ABG (pre-extubation) | | | |
| pH | 7.41 ± 0.07 | 7.42 ± 0.05 | 0.84 |
| pCO2 | 38.28 ± 5.31 | 40.93 ± 6.16 | 0.13 |
| pO2 | 117.13 ± 39.63 | 129.93 ± 38.01 | 0.31 |
| HCO3 | 24.01 ± 3.23 | 25.19 ± 4.18 | 0.28 |
| O2 Sat (%) | 96.21 ± 9.37 | 97.2 ± 3.23 | 0.72 |
| Ventilatory data during SBT: Initial data at 1min | | | |
| $RR_1$ | 18.03 ± 2.07 | 20.50 ± 2.78 | 0.45 |
| $VT_1$ | 457.97 ± 116.76 | 500.24 ± 115.83 | 0.26 |
| $RSBI_1$ | 41.51 ± 10.22 | 49.62 ± 19.14 | 0.62 |
| Data at 30 minutes | | | |
| $RR_{30}$ | 18.88 ± 2.17 | 19.42 ± 2.27 | 0.44 |
| $VT_{30}$ | 430.15 ± 114.78 | 433.29 ± 86.01 | 0.93 |
| $RSBI_{30}$ | 47.35 ± 12.91 | 67.08 ± 13.27 | 0.95 |

Cstat: static compliance; Cdyn: dynamic compliance; ABG: arterial blood gas; $RR_1$: respiratory rate at 1 minute of SBT; $VT_1$: average tidal volume at 1 minute of SBT; $RSBI_1$: rapid shallow breathing index at 1 minute of SBT; $RR_{30}$: respiratory rate at 30 minutes of SBT; $VT_{30}$: average tidal volume at 30 minutes of SBT; $RSBI_{30}$: rapid shallow breathing index at 30 minutes of SBT

**Table 3.** Association between RSBI Rate and weaning outcome

| RSBI Rate | Weaning Outcome: Success (n=59) | Weaning Outcome: Failure (n=12) | p-value |
|---|---|---|---|
| RSBI ≤ 20% | 48 (81.4) | 0 | <0.001 |
| RSBI ≥ 20% | 11 (18.6) | 12 (100) | |

RSBI: rapid shallow breathing index

**Table 4.** Accuracy of RSBI in predicting outcomes

| | Sensitivity | Specificity | Positive Predictive Value (PPV) | Negative Predictive Value (NPV) | Overall Accuracy |
|---|---|---|---|---|---|
| RSBI Rate | 100% | 81.36% | 52.17% | 100% | 94.21% |

**Figure 1.** Schematic diagram of the study manuever. SBT= Spontaneous breathing trial; RR= respiratory rate in breaths per minute; Vt = tidal volume in iiters; RSBI= respiratory shallow breathing index; BP= blood pressure

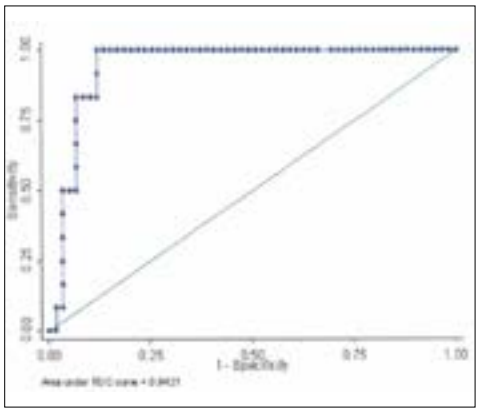

**Figure 2.** The ROC curve that illustrates the ability of RSBI rate to predict weaning outcome.

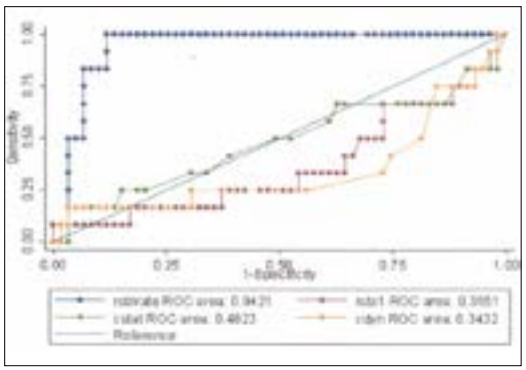

**Figure 3**. The ROC curves comparing the ability of initial RSBI, static compliance dynamic compliance and RSBI rate in predicting weaning outcome

## DISCUSSION

This study evaluated the accuracy of RSBI rate on weaning outcome among heterogenous group of subjects admitted at the intensive care units. The data demonstrated that measuring the rate of change of RSBI over time, may offer more predictive value in the extubation outcome of patients than to most physiologic and respiratory indices. This finding suggests that RSBI rate represents a useful addition to the prognostic armamentarium during initial attempts to discontinue mechanical ventilatory support among critically ill patients.

Rapid shallow breathing index (RSBI) is an accurate and powerful paramater in predicting weaning outcome. As shown in some studies[3,4] it is more reliable than other traditional pulmonary indices when initiating weaning. However, conflicting results regarding the usefulness of a single determination of RSBI have been reported. Prior studies[2,5] showed that a single RSBI measurement may not represent the entire weaning process since respiratory failure may develop in a progressive manner during spontaneous breathing trial. It was also reported that a RSBI taken only during first minute of spontaneous breathing trial is not long enough for a patient to develop respiratory drive thereby may not reflect respiratory muscle endurance.[9] Serial RSBI measurement have also been investigated but have shown minimal or no improvement in the ability to predict successful extubation.[10,11] In the present study, subjects with weaning failure had increased respiratory rate, tidal volume and RSBI during their initial spontaneous breathing trial, suggesting imbalance between the work of breathing and respiratory muscle capacity. Thus our results favored the notion that RSBI changes during spontaneous breathing trial, and a single RSBI determination may only afford limited accuracy in predicting extubation outcome.

While previous studies have evaluated individual values of RSBI as a predictor of weaning outcome, the current study extends prior observations by determining the dynamic changes of the patients breathing pattern as a guide for suceeding requirement for re-intubation. Change in breathing pattern may be an expression of the increased effort needed to overcome different elements of respiratory mechanics, or it may occur as end product of load-capacity imbalance.[12] Hence, the evolution of respiratory pattern, as assessed by the change in RSBI or RSBI rate, is a marker of the dynamic changes that occur during weaning that may improve the ability to predict extubation outcome.

RSBI rate was shown to have more predictive value in weaning outcome than a single RSBI determination. In this study, this parameter was measured by taking RSBI in two time periods: first, during l-minute period of stable spontaneous breathing, avoiding the times when subjects had increase secretions, cough and recent suctioning thereby avoiding transient changes of the initial RSBI value; second, after 30 minutes of spontaneous breathing trial. Studies reported that RSBI obtained at 30 minutes of spontaneous breathing trial has a high positive predictive value (96%) in predicting successful extubation.[2,6] Our results showed that RSBI rate of $\leq$20% has increase accuracy in predicting successful extubation among critically ill patients. This finding was consistent with the studies of Segal et al[6] (89% sensitivity and 89 specificity) and Susilo et al[13] (97% sensitivity and 75% specificity). Moreover, clinical data of patients in the weaning failure group such as older age, higher APACHE II score and longer duration of mechanical ventilation were also consistent with their results. The study also determined that RSBI rate was superior to other parameters tested (ctsat, cdyn, initial RSBI) in predicting weaning outcome in the overall study population.

Several factors may have influenced the results of the study. First, the study involved few subjects with clinical characteristics associated with increased rates of extubation failure (e.g. COPD, prolonged intubated patients and prior failed extubation or weaning trial) which may limit the applicability of the results to these high risk group of patients. Second, common to a prospective study, selection bias of subjects might have occurred. Lastly, the dynamic change in RSBI would not predict weaning outcome when changes in the respiratory status of patients occurs after extubation due to aspiration, mucus

plugging, upper airway obstruction, hemodynamic instability and alteration of mental status. Furthermore, the study determined that the maximum RSBI among the study population who develop rapid shallow breathing during their spontaneous breathing trial was only 80 (67.08 ± 13.27) in contrast to its theoretical value of > 105. Hence, we recommend a prospective determination of RSBI value specific for Filipino patients.

## CONCLUSION

In conclusion, in an ICU population eligible for weaning from mechanical ventilation, evaluation of the dynamic change of breathing pattern as assessed by the rapid shallow breathing index (RSBI) rate was proven to be a reliable parameter in predicting weaning outcome.

## REFERENCES


1. Ping-Hung K, Huey-Dong W., Been- Ying L., Mei-Tai C., Sow -Hsong K., Pan-Chyr Y. Predictive value of rapid shallow breathing index measured at initiation and termination of a 2-hour spontaneous breathing trial for weaning outcome in ICD patients. J Formos Med Assoc 2006; 105: 390-398.
2. Chatila W, Jacob B, Guaglionone D, Manthous CA. The unassisted respiratory rate-tidal volume ratio accurately predicts weaning outcome. Am J Med. 1996 Jul;101(1):61-7.
3. Jacob B, Chatila W, Manthous CA. The unassisted respiratory rate/tidal volume ratio accurately predicts weaning outcome in postoperative patients. Crit Care Med. 1997 Feb;25(2):253-7.
4. Yang KL, Tobin MJ. A prospective study of indices predicting the outcome of trials of weaning from mechanical ventilation. N Engl J Med. 1991 May 23; 324:1445-50.
5. Jubran A, Grant BJ, Laghi F, Parthasarathy S, Tobin MJ. Weaning prediction: esophageal pressure monitoring complements readiness testing. Am J Respir Crit Care Med. 2005 Jun 1;171(11):1252-9.
6. Segal LN, Oei E, Oppenheimer BW, Goldring RM, Bustami RT, Ruggiero S, Berger KI, et al. Evolution of pattern of breathing during a spontaneous breathing trial predicts successful extubation. Intensive Care Med. 2010 Mar;36(3):487-95.
7. MacIntyre NR, Cook DJ, Ely EW Jr, Epstein SK, Fink JB, Heffner JE, et al. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. Chest. 2001 Dec;120(6 Suppl):375S-95S.
8. Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, et al.Weaning from mechanical ventilation. Eur Respir J. 2007 May;29(5):1033-56.
9. Capdevila X, Perrigault PF, Ramonatxo M, Roustan JP, Peray P, d'Athis F, et al. Changes in breathing pattern and respiratory muscle performance parameters during difficult weaning. Crit Care Med. 1998 Jan; 26 (1):79-87.
10. Krieger BP, Isber J, Breitenbucher A, Throop G, Ershowsky P. Serial measurements of the rapid-shallow-breathing index as a predictor of weaning outcome in elderly medical patients. Chest. 1997 Oct; 112 (4):1029-34.
11. Teixeira C, Zimermann Teixeira PJ, Hohër JA, de Leon PP, Brodt SF, et al. Serial measurements of f/VT can predict extubation failure in patients with f/VT < or = 105? J Crit Care. 2008 Dec;23(4):572-6.
12. Jubran A, Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. Am J Respir Crit Care Med. 1997 Mar;155(3):906-15.
13. Susilo J. Rapid shallow breathing index rate (RSBI rate) as a predictor of weaning from mechanical venti lation.[Internet]. Universitas Gadjah Mada; 2010. [cited on 2018 Apr 17]. Available from: Etd.repository.ugm.

# Predictive Formula for Starting Pressure During CPAP Titration for Filipino Patients With Obstructive Sleep Apnea

Karen G. Sobere Yu, MD, Lily Y. Lao, MD, Aileen G. Banzon, MD, Maria Encarnita B. Limpin, MD

***Background*** --- Obstructive sleep apnea (OSA) is a form of sleep-disordered breathing, which can be diagnosed by clinical history, physical exam, and confirmatory test such as polysomnography. After a patient is diagnosed with OSA, the current standard of practice involves continuous positive airway pressure (CPAP) titration. This study aims to determine the factors related to starting CPAP level among Filipino patients with obstructive sleep apnea who achieved optimal CPAP titration during polysomnography and develop a predictive formula based on the determined factors that were not included in the existing calculation by Oliver and Hoffstein. This formula will be used as starting pressure during CPAP titration in order to hasten and allow the optimal CPAP to be reached sooner and minimize the risk of running out of time during titration.

***Method*** --- A retrospective, cross-sectional study was conducted among Filipino patients aged more than 19 years old who were diagnosed by polysomnography with OSA and underwent CPAP titration (therapeutic or split-night study) with starting pressure at 4 cm H2O at PHC Sleep Laboratory from January 1, 2012 to December 31, 2014. There were 2 phases in this study: (1) The PHC Sleep Questionnaire was retrieved to gather all the factors related to OSA and CPAP titration; and, (2) After the significant factors were identified, the coefficients of these factors were used to develop the predictive formula of starting CPAP for Filipino patients with OSA.

***Results*** --- A total of 108 patients were enrolled in the study with mean age of 51 years with male (71%) predominance, obese (BMI of 34.4 ± 12.6), and 76% were diagnosed with severe OSA. These patients had higher neck circumference with Mallampati score at 3.6 ± 0.7. Immediately prior to polysomnography, these patients complained of mild to moderate daytime sleepiness and comorbidities observed such as hypertension (n=72), diabetes mellitus (n=37), and coronary artery disease (n=28). Total cholesterol and LDL levels of the patients were unremarkable. FBS was elevated. Only mild hypoxemia was recorded as the lowest oxygen saturation achieved during diagnostic study. The patients slept for a total of7 to 8 hours, with approximately 4 hours allotment for titration study.

***Conclusion*** --- After multiple linear regression analysis, the factors related to starting CPAP level among Filipino patients with obstructive sleep apnea who achieved optimal CPAP titration during polysomnography were age, BMI, neck circumference, and AHI during diagnostic study. The coefficients of these factors were used to develop the predictive formula for starting pressure during CPAP titration as follows:

Starting CPAP level = (0.046 x Age) + (0.077 x BMI) + (0.119 x NC) +
(0.034 x AHI dx) - 5.3

***Phil Heart Center J 2017;22(1):65-71.***

**Key Words: ■ Obstructive Sleep Apnea (OSA) and risk factors ■ formula for starting pressure ■**

Obstructive sleep apnea (OSA) is a form of sleep-disordered breathing that is characterized by repetitive complete and/or partial collapse of the upper airways. The prevalence of patients at high risk for OSA ranges from 4.98% to 27.3%.[1] OSA is clinically defined by the occurrence of daytime sleepiness, loud snoring, witnessed breathing interruptions, or awakenings due to gasping or choking in the presence of at least 5 obstructive events (apneas, hypopneas, or respiratory event related arousals) per hour of sleep. The presence of equal to or greater than 15 respiratory events per hour of sleep in the absence of sleep-related symptoms is

*Winner*, Poster-Original Paper Presentation - Original Paper. 24th PHC Annual Research Paper Competition and Poster Presentation held on February 26, 2016 at Philippine Heart Center. Correspondence *to Karen G. Sobere Yu.* Division of Pulmonary and Critical Care Medicine. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication**  ISSN 0018-9034

also sufficient for the diagnosis of OSA.[2] After a patient is diagnosed with OSA, the current standard of practice involves continuous positive airway pressure (CPAP) titration to determine the optimal pressure for maintaining upper airway patency. The recommended minimum starting CPAP should be 4 cm $H_20$ in adult patients then with increments of ≥l-cm in ≥5-minute intervals and is continued according to the breathing events observed until ≥30 minutes without breathing events is achieved.[3]

Using the recommended CPAP titration protocol, there may not be enough time for proper titration. Sleep time spent at each pressure may be too short to sample all sleep stages and all positions. The optimal pressure determined during the CPAP titration study may sometimes be inadequate during a full night polysomnography (PSG). Hence, a calculation was proposed by Oliver and Hoffstein in 2000 which determines the starting pressure from the predictive formula utilizing body mass index (BMI), neck circumference (NC), and the AHI determined during diagnostic PSG as follows: Predicted pressure = (0.16 X BMI) + (0.13 X NC) + (0.04 X AHI) - 5.12. The study concluded that the said variables are important in calculating the starting pressure for initiating CPAP titration in the majority of patients with sleep apnea.[4]

However, other risk factors of OSA that could influence in the calculation for starting pressure should also be considered including ethnicity,[5] family history or genetics,[6] smoking,[7] increased age, and metabolic syndrome.[8]

This study aims to determine the factors related to starting CPAP level among Filipino patients with obstructive sleep apnea who achieved optimal CPAP titration during polysomnography and develop a predictive formula based on the determined factors that were not included in the existing calculation by Oliver and Hoffstein[4] such as hyperlipidemia, hypertriglyceridemia, fasting blood sugar, smoking history, and age among Filipino patients. This formula will be used as starting pressure during CPAP titration in order to hasten and allow the optimal CPAP to be reached sooner and minimize the risk of running out of time during titration.

## METHODS

The study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki. Prior to the study invitation the protocol was reviewed and approved by the Philippine Heart Center Institutional Ethics Review Board (PHC-IERB). The investigator requested for the waiver of informed consent for the following reasons: difficulty of obtaining individual authorization since the last contact with research subjects.

The risk to the subject's privacy was minimal and no sensitive information was obtained. The investigator will ensure that the subject's anonymity was maintained.

The study design was a retrospective, cross-sectional. Conducted at the Philippine Heart Center from January 1, 2012 to December 31, 2014. Included in the study were Filipino patients aged more than 19 years old who were diagnosed by polysomnography with obstructive sleep apnea and underwent CPAP titration (therapeutic or split-night study) with starting pressure at 4 cm $H_2O$ at Philippine Heart Center Sleep Laboratory were included in this study. While excluded were patients who underwent bilevel positive airway pressure (BPAP) instead of CPAP, those who have neuromuscular diseases such as acute cerebrovascular disease at the time of examination, intrinsic lung disease, taking sleeping medications, or with mental disorders.

Sample size calculation was done using NCSS-PASS 2013 software, the minimum sample size requirement was estimated to be at least 40 based on the following parameters: alpha = 5%, power of 80%, and correlation between optimal manual CPAP and Series equation = 0.435. Data analysis was done in Stata SE Version 13. Quantitative variables were summarized and presented as mean and standard deviation, while qualitative variables were tabulated and presented as frequency and percent distribution. Significant clinical factors associated with starting pressure with optimal CPAP titration were determined using multiple linear regression analysis. The coefficients of these

were used to develop the predictive formula of starting CPAP for Filipino patients with OSA. The level of significance was set at 0.05.

## RESULTS

There were 108 patients enrolled in the study, with 77 males and 31 females. As shown in Table 1, the majority of the patients included were middle-aged (50.8 ± 13.8), obese (BMI of 34.4 ± 12.6), and approximately 76% were diagnosed with severe obstructive sleep apnea. These patients had also higher neck circumference with Mallampati score at 3.6 ± 0.7.

The Epworth Sleepiness Scale (ESS) immediately prior to polysomnography was also notable at 12.1 ± 4.9 which is indicative of mild to moderate daytime sleepiness. Total cholesterol and LDL levels of the patients were below the borderline high values set in the laboratory. However, triglyceride level was within the borderline high range. Moreover, the fasting blood sugar was high at 6.0 ± 1.9 mmol/L, The comorbidities observed in these patients at the time of in-laboratory polysomnography included hypertension (n=72), diabetes mellitus (n=37), and coronary artery disease (n=28), which were controlled with maintenance medications and/or cardiac surgery. Only mild hypoxemia was recorded as the lowest oxygen saturation achieved during diagnostic study with mean at 93.7% ± 4.5%. The patients slept for a total of 7 to 8 hours, with approximately 4 hours allotment for titration study which was the recommended duration to achieve optimal CPAP titration as mentioned in the methodology.

After univariate analysis was done, the following anthropometric data and clinical factors were significant (*Table* 2): age (p=0.046), BMI (p=0.000), neck circumference (p=0.000, Mallampati score (p=0.008), ESS immediately prior to polysomnography (p=0.023), fasting blood sugar (p=0.013), AHI during diagnostic study (p=0.000), comorbidities such as hypertension (p=0.015), congestive heart failure (p=0.016), and malignancy (p=0.001). Since only one patient had malignancy (breast cancer), the data of such patient were withdrawn in the multivariate analysis.

The significant clinical factors associated with starting pressure with optimal CPAP titration were further determined using multiple linear regression analysis (*Table 3*) which were age (p=0.010), BMI (p=0.00l), neck circumference (p=0.048), and AHI during diagnostic study (p=0.000).

**Table 1.** Baseline Demographic Profile and Anthropometric Data of OSA Patients

| Variables | $\bar{X}$ ± SD/ f (%) N = 108 |
|---|---|
| Age (in years) | 50 ± 13.8 |
| Sex | |
| Male | 77 (71) |
| Female | 31 (29) |
| BMI (kg/m$^2$) | 34.4 ± 12.6 |
| Neck circumference (cm) | 42.2 ± 5.1 |
| Mallampati Score | 3.6 ± 0.7 |
| Smoking (pack-years) | 10.2 ± 16.3 |
| Epworth Sleepiness Scale (ESS) immediately prior to polysomnography | 12.1 ± 4.9 |
| Fasting blood sugar (mmol/L) | 6.0 ± 1.9 |
| Total Cholesterol and Lipid Profile (mg/dL) | |
| Total cholesterol (borderline high=200-239 | 174.7 ± 46.8 |
| LDL (borderline high = 130-159) | 108.6 ± 36.4 |
| Triglyceride (borderline high = 150-199) | 156.3 ± 95.4 |
| Comorbidities: | |
| Hypertension | 78 (72) |
| Diabetes Mellitus | 40 (37) |
| Coronary artery disease | 30 (28) |
| Congestive heart failure | 10 (9) |
| Chronic renal failure | 3 (3) |
| COPD | 9 (8) |
| Bronchial asthma | 10 (9) |
| Malignancy | 1 (1) |
| Previous cerebrovascular disease | 5 (5) |
| Apnea-hypopnea index (AHI) during diagnostic study | 56.0 ± 31.6 |
| Mild (AHI 5 to ≤ 15 | 9 (8.3) |
| Moderate (AHI 15 to 30) | 17 (15.7) |
| Severe (AHI ≥30) | 82 (75.9) |
| Apnea-hypopnea index (AHI) at best CPAP level | 1.3 ± 1.5 |
| Lowest oxygen saturation during diagnostic study | 74.9 ± 12.6 |
| Mean oxygen saturation during diagnostic study | 93.7 ± 4.5 |
| Total sleep time (in minutes) | 475.0 ± 130.9 |
| Total titration duration (in minutes) | 260.0 ± 89.7 |

**Table 2.** Clinical factors re ated to startmg pressure with optimal CPAP titration

| Clinical Factors | Coefficient | p value |
|---|---|---|
| Age | 0.045 | 0.046 |
| Sex | 0.567 | 0.407 |
| BMI (kg/m$^2$) | 0.106 | 0.000 |
| Neck circumference (cm) | 0.297 | 0.000 |
| Mallampati Score | 1.238 | 0.008 |
| Smoking (pack-years) | 0.034 | 0.074 |
| Epworth Sleepiness Scale (ESS) immediately prior to polysomnography | 0.144 | 0.023 |
| Fasting blood sugar (mmol/L) | 0.406 | 0.013 |
| Total Cholesterol and Lipid Profile (mg/dL) | | |
| Total cholesterol | 0.006 | 0.386 |
| LDL | -0.006 | 0.459 |
| Triglyceride | 0.006 | 0.061 |
| Comorbidities: | | |
| Hypertension | 1.654 | 0.15 |
| Diabetes Mellitus | 0.763 | 0.232 |
| Coronary artery disease | 1.023 | 0.137 |
| Congestive heart failure | 2.541 | 0.016 |
| Chronic renal failure | 0.657 | 0.727 |
| COPD | 1.667 | 0.135 |
| Bronchial asthma | 1.439 | 0.176 |
| Malignancy | 10.402 | 0.001 |
| Previous cerebrovascular disease | 0.320 | 0.828 |
| Apnea-hypopnea index (AHI) during diagnostic study | 0.044 | 0.000 |

**Table 3.** Significant clinical factors related to starting pressure with optimal CPAP titration

| Clinical Factors | Coefficient | p value |
|---|---|---|
| Age | 0.046 | 0.010 |
| BMI (kg/m$^2$) | 0.077 | 0.001 |
| Neck circumference (cm) | 0.119 | 0.048 |
| Apnea-hypopnea index (AHI) during diagnostic study | 0.034 | 0.000 |

The coefficients of these factors were used to develop the predictive formula for starting pressure during CPAP titration as follows:

Starting CPAP level =

$$(0.046 \times \text{Age}) + (0.077 \times \text{BMI}) + (0.119 \times \text{NC}) + (0.034 \times \text{Am dx}) - 5.3$$

## DISCUSSION

There were minimal data on the prevalence of OSA in the Philippines. A systematic review by Mirrakhimov et al,[1] showed that OSA prevalence ranged from 3.7% to 97.3% in the Asian population. In addition, an extrapolated statistics done by www.rightdiagnosis.com last 2004 (based on the US prevalence of 12 million), reported an OSA prevalence of around 3.8 million Filipinos but this data had very limited relevance to the actual prevalence rate in the Philippines. With these data, the disease burden of OSA in the Philippines is alarming which warrants further investigation especially on its confirmatory diagnosis through polysomnography and its treatment.

Polysomnography entails an extensive time in order to get results that best represent the sleep of patient. It requires at least 3 hours of therapeutic study in order to achieve the optimal CPAP titration in accordance to the AASM recommendations.[3] However, there were some cases wherein the titration becomes ineffective due to inadequate time of CPAP titration. A study by Goshal et a1,[9] reported that one of the reasons for ineffectiveness of CPAP titration included inadequate CPAP titration time which was approximately 18% (13 out of 115 unsuccessful titration in split study cases). Hence, the formula for predicting starting CPAP level has been hypothesized in this study in order to hasten the CPAP titration and achieve the optimal outcome suitable for the patients with OSA. Substantial inclusion of predictive factors that may be significant in its formulation is considered in this study including demographic profile of diagnosed OSA cases particularly among Filipino patients, their anthropometric data, comorbidities, clinical laboratory results, and diverse diagnostic sleep study parameters.

The presence of certain risk factors can strengthen the clinical suspicion of OSA. The strongest risk factors are obesity and age older than 65 years.[10] These risk factors also have an effect in this study wherein there were four (4) significant clinical factors associated with starting pressure with optimal CPAP titration were age (p=0.010), BMI (p=0.001), neck circumference (p=0.048), and AHI during diagnostic study (p=0.000).

According to Bixler et al,[11] OSA increases in prevalence to about age 55 years in men, after which it fails to increase or decrease, depending on the diagnostic criteria employed. The prevalence of this diagnosis changed with age in a quadratic fashion, increasing from over 1% in the youngest age group to almost 5% in the middle age group and then returning to less than 2% in the older subjects. This age distribution is also observed in a Sleep Disorders Clinic setting.[12] In this study, the mean age of patients is 50.8 ± 13.8 years with male predominance. This data is consistent with that of Bixter et al.[11] In addition, the relationship between age and severity of sleep apnea support the hypothesis that sleep apnea in older patients is less severe than sleep apnea in the young. Hence, the authors support the position that sleep laboratory criteria employed for the diagnosis of sleep apnea should be age adjusted. With these findings, age may also influence the CPAP titration study in which it has an impact in the diagnosis of OSA and its severity.

In one study, a body-mass index (BMI) of at least 25 kg/m$^2$ had a sensitivity of 93% and a specificity of 74% for OSA.[13] A study by Quintas et al[14] showed that ninety (90%) percent of patients referred to the clinic were diagnosed with OSA, with most normal weight (mean BMI = 23.02 ± 1.78) patients had mild OSA, in the overweight (mean BMI = 27.63 ± 1.39) group most were diagnosed with moderate OSA and in the obese (mean BMI = 35.63 ± 5.77) group most were severe OSA, with significant differences between the diagnosis of OSA and the BMI classified. This implies that as the degree of obesity measured by the BMI increases, so too does the severity of the OSA, being most severe in the more obese patients. Moreover, in the study by Namyslowski et al[15] which compared sleep parameters between overweight and obese patients, a significant relationship was found between the increase in BMI and sleep parameters in obese subjects only, but not in overweight patients. Whether obesity is a comorbid condition associated with OSA or is actually the primary problem and OSA is a consequence of the obesity is still in question. The mean BMI in this study is 34.4 ± 12.6 kg/m$^2$ which is almost similar to the mean BMI of obesity group in the study by Quintas et al.[14] Hence, there was 75.9% of severe OSA observed in this study which could be related to the obesity of the patients enrolled. The AHI during diagnostic study is also an important consideration in the assessment of starting CPAP level since its severity has a substantial connotation between the age and BMI.

There is an ongoing evaluation regarding the association between OSA and android-type obesity (fat deposition predominantly in the neck and abdomen, in contrast to the gynecoid-type obesity with fat deposition in hips and legs). In this study, the neck circumference (p=0.048) has a significant association between starting pressure with optimal CPAP titration. This could be attributable to the fat deposition in the parapharyngeal fat pads which may directly narrow the upper airway and predispose it to collapse when neuromuscular activation of upper airway muscles declines with sleep.[10]

Other factors measured in this study include serum tests such as fasting blood sugar, total cholesterol and lipid profile, and comorbidities. Accumulating data suggest that OSA per se may also contribute to the development of hypertension. For instance, a prospective analysis from the Wisconsin Sleep Cohort[16] showed that even mild OSA was associated with a 42% (95% confidence interval [CI], 13%-78%) increased odds of developing hypertension over a 4-year follow-up period. A dose-response relationship was observed for more severe categories of OSA, with an odds ratio of 2.9 (95% CI, 1.5-5.6) for moderate to severe disease compared to patients without OSA.

Obstructive sleep apnea is also common in patients with coronary disease. Andreas et al[17] found an AHI of 10 per hour or more in 25 of 50

patients (50% prevalence) who were diagnosed as having coronary artery disease by angiography. Similarly, Shahar et al[18] found a significant cross-sectional association of OSA with prevalent cardiovascular disease in persons undergoing in-home polysomnography in the Sleep Heart Health Study. Among the 6424 participants, those in the upper quartile of AHI (≥ 11.0 per hour) had a 42% (95% Cl, 13%-78%) greater odds of prevalent cardiovascular disease including coronary heart disease, stroke, and congestive heart failure, than participants in the lowest quartile (AHI <1.3 per hour), after adjusting for multiple potential confounders. The analysis included adjustment for hypertension, suggesting that hypertension is not the only mechanism by which the risk of cardiovascular sequelae is increased in persons with OSA. Meanwhile, in this study, univariate analysis showed that hypertension and congestive heart failure have significant correlation with starting pressure and optimal CPAP titration. However, after multiple linear regression analysis, both comorbidities became insignificant.

One study in Japan[19] determined the association between sleep apnea, sleep duration, and serum lipid profile among urban, male, working population. Stepwise multiple regression analysis revealed that triglyceride was correlated with RDI ($\beta = 0.14$, $P = .02$), BMI ($\beta = 0.20$, $P = .01$), and alcohol intake ($\beta = 0.20$, $P = .01$), and that total cholesterol level was correlated with sleep duration ($\beta = 0.13$, $P = .03$), age ($\beta = 0.15$, $P = .02$), and waist/hip ratio ($\beta = 0.15$, $P = .02$). However, this study showed that the total cholesterol and lipid profile have no significant association with starting pressure and optimal CPAP titration.

Another report by Strohl et al[20] indicated that mean morning blood pressure and fasting insulin levels each correlated positively with BMI and AHI, whereas fasting blood glucose correlated only with BMI. In this study, fasting blood sugar has significant association between starting pressure and optimal CPAP titration but further analysis resulted otherwise.

Although there were several other clinical factors being tested, only age, BMI, neck circumference, and Am during diagnostic study were found to have significant effect in predicting starting pressure with optimal CPAP titration. These could be due to some limitations of this study. First, this is a retrospective study which implies that there are some data retrieved that may not be properly documented. Second, the patients who underwent polysomnography were diagnosed with comorbidities such as hypertension, diabetes, COPD, or stroke that may be already controlled with medications as noted partly in their total cholesterol and lipid profile.

## CONCLUSION

After multiple linear regression analysis, the factors related to starting CP AP level among Filipino patients with obstructive sleep apnea who achieved optimal CPAP titration during polysomnography were age, BMI, neck circumference, and AHI during diagnostic study. The coefficients of these factors were used to develop the predictive formula for starting pressure during CPAP titration as follows:

Starting CPAP level =

$$(0.046 \times \text{Age}) + (0.077 \times \text{BMI}) + (0.119 \times \text{NC}) + (0.034 \times \text{Am dx}) - 5.3$$

## REFERENCES


1. Mirrakhimov AE, Sooronbaev T, Mirrakhimov EM. Prevalence of obstructive sleep apnea in Asian adults: a systematic review of the literature. BMC Pulm Med. 2013 Feb 23;13:10.
2. Epstein LJ, Kristo D, Strollo PJ Jr, Friedman N, Malhotra A, Patil SP, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med. 2009 Jun 15;5(3):263-76.
3. Kushida CA, Chediak A, Berry RB, Brown LK, Gozal D, Iber C, et al. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. J Clin Sleep Med. 2008 Apr 15;4(2):157-
4. Oliver Z, Hoffstein V. Predicting effective continuous positive airway pressure. 71. Chest. 2000 Apr; 117 (4):1061-4.
5. Redline S, Tishler PV, Hans MG, Tosteson TD, Strohl KP, Spry K, et al. Racial differences in sleep-disordered breathing in African-Americans and Caucasians. Am J Respir Crit Care Med. 1997 Jan;155(1):186-92.

6. Palmer LJ, Buxbaum SG, Larkin EK, Patel SR, Elston RC, Tishler PV, et al. Whole genome scan for obstructive sleep apnea and obesity in African-American families. Am J Respir Crit Care Med. 2004 Jun 15; 169(12):1314-21.
7. Wetter DW, Young TB, Bidwell TR, Badr MS, Palta M. Smoking as a risk factor for sleep-disordered breathing. Arch Intern Med. 1994 Oct 10;154(19):2219-24.
8. Theorell-Haglöw J, Berne C, Janson C, Lindberg E. The role of obstructive sleep apnea in metabolic syndrome: a population-based study in women. Sleep Med. 2011 Apr;12(4):329-34.
9. Ghoshal AG, Sarkar S, Roy DJ, Das RK, Ray M. Polysomnographic profile in a sleep laboratory in Kolkata: a retrospective analysis of 714 cases. J Assoc Physicians India. 2010 Jul;58:415-9.
10. Kryger MH, Roth T, Dement Wc. Principles and practice of sleep medicine. 5th ed.. Elsevier Saunders, 2011. 1206-1216.
11. Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men: I. Prevalence and severity. Am J Respir Crit Care Med. 1998 Jan; 157(1):144-8.
12. Kales A, Cadieux RJ, Bixler EO, Soldatos CR, Vela-Bueno A, Misoul CA, Locke TW. Severe obstructive sleep apnea--I: Onset, clinical course, and characteristics. J Chronic Dis. 1985;38(5):419-25.
13. Grunstein R, Wilcox I, Yang TS, Gould Y, Hedner J. Snoring and sleep apnoea in men: association with central obesity and hypertension. Int J Obes Relat Metab Disord. 1993 Sep;17(9):533-40.
14. Dacal Quintas R, Tumbeiro Novoa M, Alves Pérez MT, Santalla Martínez ML, Acuña Fernández A, Marcos Velázquez P. Obstructive sleep apnea in normal weight patients: characteristics and comparison with over-
15. weight and obese patients. Arch Bronconeumol. 2013 Dec;49(12):513-7.
Namysłowski G, Scierski W, Mrówka-Kata K, Kawecka I, Kawecki D, Czecior E. Sleep study in patients with overweight and obesity. J Physiol Pharmacol. 2005 Dec;56 Suppl 6:59-65.
16. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med. 2000 May 11;342(19):1378-84.
17. Andreas S, Schulz R, Werner GS, Kreuzer H.Prevalence of obstructive sleep apnoea in patients with coronary artery disease. Coron Artery Dis. 1996 Jul; 7(7):541-5.
18. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Nieto FJ, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med. 2001 Jan;163(1):19-25.
19. Toyama Y, Chin K, Chihara Y, Takegami M, Takahashi KI, Sumi K, Nakamura T, et al. Association between sleep apnea, sleep duration, and serum lipid profile in an urban, male, working population in Japan. Chest. 2013 Mar;143(3):720-728.
20. Strohl KP, Novak RD, Singer W, Cahan C, Boehm KD, Denko CW, et al. Insulin levels, blood pressure and sleep apnea. Sleep. 1994 Oct;17(7):614-8.

# Predictors of Successful Extubation Among Patients Undergoing Complete Repair of Tetralogy of Fallot

Arnold Nicholas T. Lim, MD; Ma. Dulce Requiron-Sy, MD; Gari A. Astrologio, MD;
Ma. Encarnita B. Limpin, MD; Ma. Nerissa A. De Leon, MD

***Background*** --- Cardiac lesions that have decreased pulmonary blood flow especially Tetralogy of Fallot have an increased risk of extubation failure after complete repair. This is ascribed to the development of lung reperfusion injury and the effects of cardiopulmonary bypass on the lungs after surgery. This is the rationale of this study which is to determine variables that could predict a successful extubation.
***Method*** --- This was a prospective cohort study conducted at the Philippine Heart Center and included subjects aged 1 month to 18 years old who underwent complete repair of Tetralogy of Fallot (TOF) from June to December 2015. Demographics, clinical characteristics, preoperative, intraoperative, and pre-extubation variables were gathered. Patients were grouped according to extubation success and failure. Extubation success was defined as spontaneously breathing for 48 hours without any form of positive pressure ventilation support.
***Results*** --- This study showed that the extubation success rate of subjects who underwent TOF repair was high at 93%. Among the variables included in the study, only the duration of mechanical ventilation showed significant difference, with shorter mean duration of success group at 24.6 hours (±14.9) compared to 46.2 hours (± 24.9) for the failure group (p=0.026).
***Conclusion*** --- The success of extubation among postoperative TOF patients remains high. The success was related to shorter duration of mechanical ventilation. All other variables included in this study (preoperative, intraoperative, and pre-extubation) were not found to be useful predictors of successful extubation.
***Phil Heart Center J 2017;22(1):72-78.***

**Key Words: Tetralogy of Fallot ■ Extubation failure ■ Extubation success predictors ■ predictors ■ Weaning**

Tetralogy of Fallot (TOF) is a congenital heart defect which involve four anatomical abnormalities namely: (1) ventricular septal defect, (2) pulmonary stenosis, (3) right ventricular hypertrophy, and (4) overriding of the aorta.[1] This condition is classified as a cyanotic heart disorder as blood flow to the lungs for oxygenation is diminished. After complete repair of TOF, pulmonary reperfusion injury is a well-recognized complication which places these patients at risk for extubation failure. This typically manifest as pulmonary edema and was believed to be due to increased blood flow in areas of previously less perfused lung.[2]

Moreover, patients undergoing cardiovascular surgery frequently involve the use of cardiopulmonary bypass wherein metabolic and physiologic alterations in major organs are most likely to continue up to the postoperative period. Apart from its effect on the cardiovascular system, it also alters the pulmonary function. There is occurrence of atelectasis which causes a ventilation/perfusion mismatch that would in turn result in reduction in arterial saturation and blood oxygen content, both of which are poorly tolerated by neonates and young children. There is also reduction in static and dynamic compliance and functional residual capacity that all together predispose the patient to extubation failure.[3] In a study done by Dodgen et al.[4] extubation failure only occurred in 7% of children who underwent complete repair of TOF. However, even with this low incidence it is

*Finalist*, Oral Presentation - Original Paper. 24th PHC Annual Research Paper Competition and Poster Presentation held on February 26, 2016 at Philippine Heart Center. Correspondence *to Dr. Arnold Nicholas T. Lim.* Division of Pulmonary and Critical Care Medicine. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication**  ISSN 0018-9034

associated with five-fold increased risk of death in pediatric patients, hence recognition of children who can be extubated successfully after cardiac surgery is important.[5]

It is with these reasons that the experts of pediatric pulmonology in this institution had agreed upon an extubation protocol for TOF patient undergoing complete repair. This protocol entails weaning from the mechanical ventilator and extubation 48 hours after surgery. Tablante[6] did a study on the effectiveness of compliance to this protocol on success of extubation but results revealed that the compliance to the protocol was not significant in predicting a successful extubation. The study was not able to establish the variables that may affect the success of extubation. Hence, it is the goal of this study to determine such predictors.

## METHODS

The study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki. The Institutional Review Board of the Philippine Heart Center approved the study and the need for informed consent was waived.

The study was a prospective cohort study conducted at the Philippine Heart Center, a tertiary subspecialty care center that accommodates over 500 pediatric cardiothoracic surgeries each year, including complete repair of TOF. The study was conducted from June to December 2015.

The study included all patients 1 month to 18 years old who underwent complete repair of TOF. Patients who had palliative surgery, patients with creation of patent foramen ovale, and patients with tracheostomy were excluded from the study. The study withdrew patients that had unplanned extubation and those who were never extubated.

Upon inclusion into the study, the following variables were recorded using a data extraction form. Pre-operative, intra-operative, pre-extubation, and postextubation variables formed part of the data extraction form. The investigator did not have direct involvement in the management of the patient. The adjustment of the mechanical ventilator and the decision when to extubate the patient were made by the surgical intensive care unit (SICU) attending physicians caring for the patient.

Preoperative variables collected included oxygen saturation measured using a portable pulse oximetry; and latest 2D-echocardiography findings such as pulmonary artery (PA) size and z-score, pulmonic stenosis (PS) gradient, and pulmonic valve annulus (PVA) and z-score. Intraoperative data included cardiopulmonary bypass time and cross-clamp time which were reflected in the chart. Pre-extubation variables included were arterial blood gas pH, $pC0_2$, and p02; duration of mechanical ventilation; duration of spontaneous ventilation; and white blood cell count and hematocrit. Radiologic findings (e.g. atelectasis, pulmonary congestion/edema, pleural effusion, and pneumothorax) that were noted prior to extubation and read by a radiologist were also recorded. Cardiorespiratory variables collected before and immediately after extubation included heart rate, respiratory rate and oxygen saturation (the data for all these variables were collected hourly for 6 hours before and after extubation). For the purpose of the study, success of extubation was defined as spontaneously breathing for 48 hours without any form of positive pressure ventilation support; and failure of extubation is the need of any form of positive pressure ventilation support within 48 hours after extubation.

*Sample size calculation.* The sample size computed was at $n \geq 44$ based on Alpha ($\alpha$) of 5% and maximum --- tolerable error of 7.5%. This was with an assumed incidence of extubation failure of 7% in patients who underwent complete repair of Tetralogy of Fallot in the study by Dodgen et al.[5]

*Statistical Analysis.* Data analysis was done using Stata SE version 13. For the descriptive analysis, frequency and percentage distribution were used for qualitative variables. Means and standard deviation were used for quantitative variables. To determine the homogeneity of baseline characteristics between the success and failure of extubation, *T*-test and Fisher's exact test were used for quantitative and qualitative variables respectively. The values of mean $O_2$

saturation, mean change of heart rate and respiratory rate across different time points before and after extubation were presented in a line graph. The level of significance will be set at 0.05.

## RESULTS

Of the 45 consecutive subjects who underwent complete repair of TOF, 41 subjects were qualified for inclusion in the study. Two subjects were excluded from the study because a palliative shunt was performed instead of total correction. Another 2 subjects were withdrawn from the study because these subjects expired and were never extubated. Thirty-eight of the 41 subjects were successfully extubated with a 93% success rate.

Table 1 depicts the baseline characteristics and demographics of patients included in the study. There was no significant difference between the groups as to age, gender, weight, and presence of preexisting comorbidities.

Table 2 presents the preoperative, intraoperative, and pre-extubation variables for the study patients. The preoperative and intraoperative variables did not differ between the two groups. Among the pre-extubation variables, only the duration of mechanical ventilation showed significant difference, with shorter mean duration of success group at 24.6 hours (±14.9) compared to 46.2 hours (± 24.9) for the failure group (p=0.026) .

The mean change in heart rate from baseline six (6) hours before and after extubation between the groups are shown in Figure 1. The change in heart rate before extubation were similar between the two group. After extubation, the heart rate of the success group decreased from baseline, with a mean change of 0.7, -6.0, -5.1, -5.7, -7.6, and -8.5 during the 1st to 6th hour respectively. This was in contrast to the failure group which had an increasing mean change of heart rate from baseline (6.7, 12,5.3,9,9.7, and 10.7).

**Table 1.** Baseline Characteristics and Demographics of Patients in the Study

| Characteristics | Extubation success (n=38) | Extubation failure (n=3) | p value |
|---|---|---|---|
| Age at surgery (years) | 5.4 ±4.2 | 3.0 ± 1.2 | 0.343 |
| Gender | | | |
| Female | 30 (79) | 3 (100) | 1.000 |
| Male | 8 (21) | 0 | |
| Weight (kg) | 18.2 ± 10.9 | 15.0 ± 4.4 | 0.635 |
| Intubation before surgery | 0 | 0 | |
| Comorbidities: | | | |
| Acute rhinosinusitis | 2 (5.3) | 0 | 1.000 |
| Bronchial Asthma | 1 (2.6) | 0 | 1.000 |
| Tuberculosis | 1 (2.6) | 0 | 1.000 |
| Acute Bronchitis | 2 (5.3) | 0 | 1.000 |
| Allergic Rhinitis | 1 (2.6) | 0 | 1.000 |

**Table 2.** Univariate analysis on the preoperative, intraoperative, and pre-extubation variables for the study subjects

| Variables | Extubation success (n=38) | Extubation failure (n=3) | p Value |
|---|---|---|---|
| *Preoperative variables* | | | |
| ECHO, RPA size (cm) | 0.86 ±0.26 | 0.82 ±0.17 | 0.824 |
| RPA z-score | | | |
| -3 | 1 (2.7) | 1 (33.3) | |
| -2 | 8 (24.2) | 0 | |
| -1 | 13 (39.4) | 0 | 0.079 |
| 0 | 8 (24.2) | 2 (66.7) | |
| +1 | 3 (9.1) | 0 | |
| LPA size (cm) | 0.86 ± 0.25 | 0.70 ± 0.17 | 0.307 |
| LPA z-score | | | |
| -3 | 1 (2.9) | 1 (33.3) | |
| -2 | 1 (3.0) | 0 | |
| -1 | 12 (34.3) | 1 (33.3) | 0.247 |
| 0 | 17 (48.6) | 1 (33.3) | |
| +1 | 1 (11.4) | 0 | |
| PS gradient (mmHg) | 81.0 ± 18.9 | 74.5 ± 10.6 | 0.636 |
| PV annulus ($cm^2$) | 1.36 ± 2.02 | 0.84 ± 0.14 | 0.665 |
| PV annulus z-score | | | |
| -5 | 1 (3.0) | 1 (33.3) | |
| -4 | 5 (14.3) | 0 | |
| -3 | 9 (25.7) | 1 (33.3) | 0.473 |
| -2 | 12 (34.3) | 1 (33.3) | |
| -1 | 1 (8.6) | 0 | |
| 0 | 5 (14.3) | 0 | |
| Oxygen saturation (%) | | | |
| ≥80 | 14 (37.8) | 1 (33.3) | |
| 60-79 | 20 (54.1) | 2 (66.7) | 1.000 |
| 40-59 | 3 (8.1) | 0 | |
| <40 | 0 | 0 | |
| *Intraoperative variables* | | | |
| CPB time (hrs) | 2.2 ± 0.6 | 2.5 ± 0.7 | 0.409 |
| Cross-clamp time (hrs) | 1.6 ± 0.4 | 1.9 ± 0.7 | 0.195 |
| *Pre-extubation variables* | | | |
| WBC ($10^3/mm^3$) | 16.5 ± 5.1 | 13.5 ± 2.4 | 0.328 |
| Hct (%) | 0.42 ± 0.05 | 0.41 ± 0.08 | 0.865 |
| ABG, pH (mmHg) | 7.45 ± 0.06 | 7.43 ± 0.04 | 0.577 |
| $pCO_2$ (mmHg) | 33.9 ± 4.4 | 38.5 ± 5.2 | 0.166 |
| $pO_2$ (mmHg) | 156.4 ± 46.0 | 109.6 ± 27.5 | 0.167 |
| Duration of mechanical ventilation (hrs) | 24.6 ± 14.9 | 46.2 ± 24.9 | 0.026 |
| Duration of spontaneous ventilation (hrs) | 1.6 ± 1.4 | 2.0 ± 1.0 | 0.658 |
| *Chest radiographic findings:* | | | |
| Pleural effusion | 3 (7.9) | 0 | 1.000 |
| Atelectasis | 4 (10.5) | 0 | 1.000 |
| Pulmonary Congestion | 1 (2.6) | 1 (33.3) | 0.143 |
| Pneumothorax | 3 (7.9) | 0 | 1.000 |

The mean change in heart rate from baseline six (6) hours before and after extubation between the groups are shown in Figure 1. The change in heart rate before extubation were similar between the two group. After extubation, the heart rate of the success group decreased from baseline, with a mean change of 0.7, -6.0, -5.1, -5.7, -7.6, and -8.5 during the 1st to 6th hour respectively. This was in contrast to the failure group which had an increasing mean change of heart rate from baseline (6.7, 12,5.3,9,9.7, and 10.7).

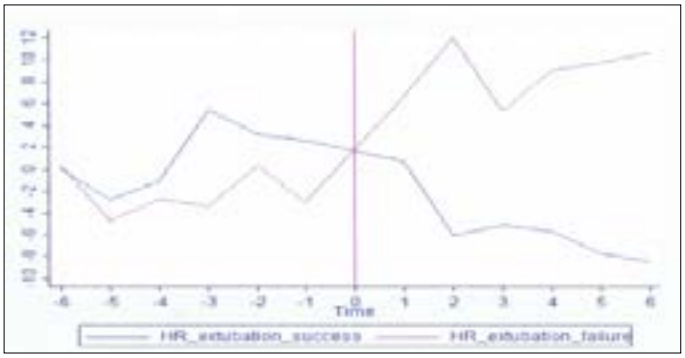


**Figure 1.** Mean change of heart rate from baseline six (6) hours before and after extubation

The mean change in respiratory rate from baseline six (6) hours before and after extubation between the groups are shown in Figure 2. In the success group, the change in respiratory rate remained stable during the 1st to 6th hour prior to extubation. When compared to the failure group, there was a decrease in respiratory rate with a mean change from baseline (4.3, 0.7, -0.3, -3.3, -4.7, and -7.7 at 6th to 1st hour respectively). After extubation, the change in respiratory rate of the success group remained stable. This was different when compared to the failure group which had an ascending respiratory rate with a mean change of -3.7, 10, 3.3, 0.7, 3.7, and 8.3 from 6th to 1st hour respectively.

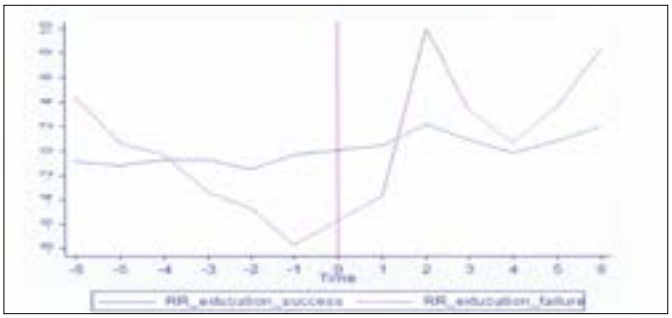


**Figure 2.** Mean change of respiratory rate from baseline six (6) hours before and after extubation

The mean oxygen ($0_2$) saturation values of the two groups taken six (6) hour before and after extubation are shown in Figure 3. The $O_2$ saturation of the subjects in both groups were stable and similar before extubation. After extubation, $0_2$ saturation of the success group remained stable. This was in contrast to the failure group which had a decreasing $O_2$ saturation (97, 90, 91, 92, 91, and 89 at 1st to 6th hour respectively).

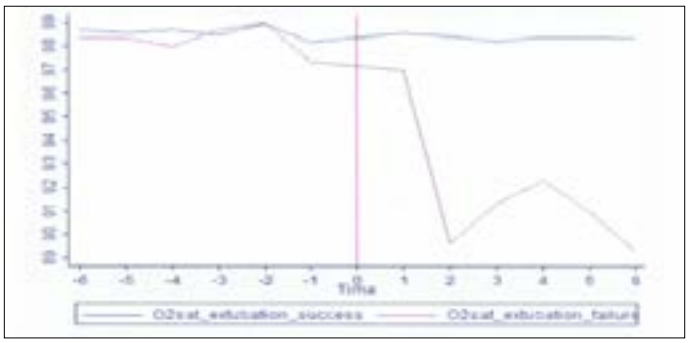


**Figure 3.** Mean oxygen (02) saturation taken six (6) hours before and after extubation

## DISCUSSION

This study shows that the success rate of extubation among TOF patients who underwent complete repair was high at 93% with a failure rate of only 7%. Among the variables obtained before extubation, only the duration of mechanical ventilation showed a significant difference between the two groups. The success group were ventilated for a shorter duration (24.6 ± 14.9 hours) when compared to the failure group (46.2 ± 24.9 hours). The cardiorespiratory variables before extubation, as presented in a line graph, showed that the mean change in respiratory rate in the failure group had a decreasing trend when compared to the success group. Conversely, the mean change in heart rate and mean $O_2$ saturation in both groups were stable and similar. After extubation, changes in the cardiorespiratory parameters were also evident. The failure group demonstrated an increasing heart rate and decreasing $0_2$ saturation pattern when compared to the success group.

Previous studies[5,6] that looked into extubation failure among patients who underwent complete repair of TOF showed a low failure rate between 4.5% - 7.5%, which was comparable to this study. Other studies have shown that the degree of cardiopulmonary pulmonary stenosis[7] and longer cardiopulmonary bypass time[8] were were independent risk factors for extubation failure the degree of pulmonary stenosis[7] and longer cardiopulmonary bypass time[8] were independent risk factors for extubation failure. They believed that the increased risk was due to the development of pulmonary reperfusion injury resulting in pulmonary edema which in turn will lead to decreased functional residual capacity of the lungs and alveolar collapse.

However, these were not consistent in the present study. Instead, the duration of mechanical ventilation was shown to be significantly different among the two groups with the failure group being ventilated longer. One explanation for this result is that prolonged duration of ventilation would increase the risk of airway trauma and nosocomial infection.[9] In addition, several studies[10-12] have supported that shifting to spontaneous breathing can augment the cardiac output and increase the pulmonary blood flow in children after TOF repair. With this reason, the outcome of extubation is more favorable when the duration of mechanical ventilation is shorter.

Successful extubation is based on a clinical evaluation of the patient's ability to sustain spontaneous breathing after mechanical ventilation is discontinued. Current practice of extubation follows a period weaning, a transition from full ventilatory support to what the clinician considers a low level of ventilatory support.[13] During this period, several parameters may be used to evaluate extubation readiness. One of the parameter is the respiratory rate, in which an increase or decrease rate would indicate weaning intolerance and mechanisms of respiratory failure. When this occurs, extubation should be delayed to avoid extubation failure.[4,14] As mentioned earlier, this study demonstrated that the mean change of respiratory rate from baseline six (6) hours prior to extubation was different between the two groups. The success group showed a stable pattern of respiratory rate while the failure group had a decreasing trend. The author believes that the reason for the decrease in respiratory rate was due to over-sedation which led to the reduction of the patient's respiratory drive. Unfortunately, this study was not able to document the level of sedation among subjects prior to extubation.

After extubation, the failure group showed a decreasing $O_2$ saturation (desaturations), an increasing change in heart rate (tachycardia) and respiratory rate (tachypnea). These are the usual manifestations seen in patients with respiratory failure requiring re-intubation. Both tachypnea and tachycardia are early compensatory mechanisms to maintain adequate oxygen delivery to the tissues and to compensate for inadequate ventilation.[15]

This study had several limitations. The number of subjects was disproportionately uneven between the two group, limiting our capability to identify precisely the predictors for successful extubation. This study did not include specific ventilation indices such as $V_E$, $V_T$, MIP, and RSBI which have been used to make decisions regarding the ideal time to extubate

adult and pediatric patients.[14] These ventilator variables would have strengthened this study.

## CONCLUSION

In conclusion, this study demonstrated that extubation success in patients after complete repair for TOF was high (93%). Moreover, the success was related to shorter duration of mechanical ventilation (24.6 ± 14.9 hours). All other variables included in this study (preoperative, intraoperative, and pre-extubation) were not found to be useful predictors of successful extubation.

## REFERENCE


1. Breitbart R, Fyler, D. Tetralogy of Fallot. Nadas' pediatric Cardiology. 2nd ed. Philadelphia: Elsevier-Saunders, c2006.
2. Kreutzer J, Perry SB, Jonas RA, Mayer JE, Castañeda AR, Lock JE. Tetralogy of Fallot with diminutive pulmonary arteries: preoperative pulmonary valve dilation and transcatheter rehabilitation of pulmonary arteries. J Am Coll Cardiol. 1996 Jun;27(7):1741-7.
3. Meliones IN, Nichols DG, Wetzel RC, Greeley WJ. Perioperative management of patients with congenital heart disease: a multidisciplinary approach. In: Nichols DG, et al, editors. Critical heart disease in infants and children. St. Louis: Mosby; 1995. p. 553-78.
4. Newth CJ, Venkataraman S, Willson DF, Meert KL, Harrison R, Dean JM, et al. Weaning and extubation readiness in pediatric patients. Pediatr Crit Care Med. 2009 Jan;10(1):1-11.
5. Dodgen AL, Dodgen AC, Swearingen CJ, Gossett JM, Dasgupta R, Butt W, et al. Characteristics and hemodynamic effects of extubation failure in children undergoing complete repair for tetralogy of Fallot. Pediatr Cardiol. 2013 Aug;34(6):1455-62.
6. Tablante M. Effectiveness of compliance to the tetralogy of Fallot postoperative protocol on success of extubation among patients undergoing complete repair of tetralogy of fallot. Philippine Heart Center, 2015 (Unpublished)
7. Maskatia SA, Feinstein JA, Newman B, Hanley FL, Roth SJ. Pulmonary reperfusion injury after the unifocalization procedure for tetralogy of Fallot, pulmonary atresia, and major aortopulmonary collateral arteries. J Thorac Cardiovasc Surg. 2012 Jul;144(1):184-9.
8. Mittnacht AJ, Thanjan M, Srivastava S, Joashi U, Bodian C, Hossain S, Kin N, Hollinger I, Nguyen K. Extubation in the operating room after congenital heart surgery in children. J Thorac Cardiovasc Surg. 2008 Jul;136(1):88-93.
9. Rothaar RC, Epstein SK. Extubation failure: magnitude of the problem, impact on outcomes, and prevention. Curr Opin Crit Care. 2003 Feb;9(1):59-66.
10. Bronicki RA, Checchia PA, Anas NG, Adams GJ, Penny DJ, Bleiweis MS, et al. Cerebral and somatic oxygen saturations after repair of tetralogy of Fallot: effects of extubation on regional blood flow. Ann Thorac Surg. 2013 Feb;95(2):682-6.
11. Bronicki RA, Herrera M, Mink R, Domico M, Tucker D, Chang AC, et al. Hemodynamics and cerebral oxygenation following repair of tetralogy of Fallot: the effects of converting from positive pressure ventilation to spontaneous breathing. Congenit Heart Dis. 2010 Sep-Oct;5(5):416-21.
12. Shekerdemian LS, Bush A, Shore DF, Lincoln C, Redington AN. Cardiorespiratory responses to negative pressure ventilation after tetralogy of fallot repair: a hemodynamic tool for patients with a low-output state. J Am Coll Cardiol. 1999 Feb;33(2):549-55.
13. Khan N, Brown A, Venkataraman ST. Predictors of extubation success and failure in mechanically ventilated infants and children. Crit Care Med. 1996 Sep; 24(9):1568-79.
14. Johnston C, da Silva PSL. Weaning and extubation in pediatrics. Curr Respr Med Rev 2012; 8(1): 68-78.
15. Nitu ME, Eigen H. Respiratory failure.Pediatr Rev. 2009 Dec;30(12):470-7; quiz 478.

# A Cross Sectional Study on the Venous-Arterial $PCO_2$ Gap as a Surrogate Parameter to Assess the Adequacy of Tissue Perfusion During the Immediate Postoperative Period in Post CABG Patients

Darwin James G. Alvarez, MD; Florian R. Nuevo, MD

***Background*** --- Inadequacy of tissue perfusion measured by blood lactate after cardiac surgery leads to increased morbidity and high mortality. Poor tissue perfusion also causes venous hypercarbia or an increased Pv-a$C0_2$ difference. This study investigates Pv-a$C0_2$ difference as a surrogate parameter in assessing the adequacy of tissue perfusion.

***Method*** --- In a cross sectional study from October 2015 to May 2015 at the Philippine Heart Center, 150 consecutive adult patients who underwent elective or emergency coronary artery bypass grafting under cardiopulmonary bypass surgery were enrolled. The Pv-a$C0_2$ difference (mmHg) and blood lactate (mmol/L) levels were measured withjn the 1st hour of admission to the SICU The Pearson product moment correlation and scatterplot graph were used to determine the correlation between Pv-a$C0_2$ and lactate. The accuracy of different values for the Pv-a$C0_2$ gap against a blood lactate cut-off value of 2mmol/L was computed.

***Results*** --- The mean Pv-a$CO_2$ difference was 7.66 ± 4.48 mmHg and the mean blood lactate was 4.12 ± 2.35 mmol/L. A mild correlation (r=0.34, p= <0.0001) between Pv-a$C0_2$ difference and blood lactate levels was observed. The diagnostic accuracy of the Pv-a$C0_2$ difference of 6mmHg had a sensitivity of 62.39 and a specificity of 66.67 with a positive predictive value of 86.9 and a negative predictive value of 33.33.

***Conclusion*** --- The Pv-a$C0_2$ difference taken after cardiac surgery is a weak surrogate parameter in assessing the adequacy of tissue perfusion. ***Phil Heart Center J 2017;22(1):79-83.***

**Key Words: venous-arterial $PCO_2$ difference ■ gap ■ gradient ■ blood lactate ■ coronary artery bypass grafting ■ cardiopulmonary bypass ■ tissue perfusion**

Changes in the systemic and pulmonary blood flows in 'cardiac surgery under cardiopulmonary bypass affect global tissue perfusion.[1] Currently, arterial lactate is a well-accepted routine marker of global tissue oxygenation and perfusion.[2] Bakker et al[3] concluded that increased lactate levels usually reflect increased morbidity and high mortality. This was validated by Toraman[4] in the setting of cardiac surgery where the elevated blood lactate group (>2mmol/L) wa.s associated with adverse outcome.

Increased venous $CO_2$ tension or venous hypercarbia and increased venous arterial $pC0_2$ difference (Pv-a$C0_2$) are two distinct events that have been observed in circulatory arrest, traumatic shock, and severe sepsis.[5-9] The common denominator in these situations is circulatory failure that affects tissue perfusion. The venous hypercarbia is due to reduced cardiac output (CO) in the presence of increased cellular demands while the increase in venous-arterial gap of $PC0_2$ in these conditions appear to be related to the critical reductions in both the systemic and pulmonary blood flow.[10]

In a study by Valee et al[11] investigating the use of central venous to carbon dioxide difference as a target for goal directed therapy for severe sepsis and septic shock, it was observed that a gap larger than 6 mmHg may be a useful

*Finalist*, Oral Presentation - Original Paper. 24th PHC Annual Research Paper Competition and Poster Presentation held on February 26, 2016 at Philippine Heart Center. Correspondence *to Dr. Darwin James G. Alvarez.* Division of CV Anesthesia. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication**  2017 ISSN 0018-9034

tool to identify patients who remained inadequately resuscitated.

Takami et al[12] demonstrated the increases in the Pv-a$C0_2$ gradients in patients undergoing cardiovascular surgery with CPB. The degree of increased Pv-a$C0_2$ was closely associated with the invasiveness of the surgery under CPB. Longer CPB time and aortic cross clamp time correlated positively with Pv-a$C0_2$.

In another study by Silva et al[13] correlated that a widened preoperative Pva$C0_2$ gap of $\geq$ 5 mmHg in patients undergoing major high risk surgeries had poorer postoperative outcomes. The study recommended that this parameter may be used to risk stratify patients preoperatively and suggests this parameter as a useful additional tool for perioperative management.

To date, there is no local study investigating the significance of Pv-a$CO_2$, gap as a surrogate parameter to assess tissue perfusion among cardiac surgery patients. Hence, this study's general objective was to investigate the clinical significance of Pv-a$CO_2$, gap as a surrogate parameter to assess the adequacy of tissue perfusion during the immediate postoperative period in post CABG patients.

Specific objectives were to determine the venous-arterial $PCO_2$ difference and lactate levels of consecutive post CABG patients during the 1st hour of SICU stay, to determine the correlation of venous-arterial $PCO_2$ difference and lactate levels and to determine the accuracy of venous-arterial $PCO_2$ difference against lactate of CABG patients by computing for its sensitivity, specificity, positive-predictive value, and negative predictive value.

## METHODS

The study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki. Prior to study initiation, a review and approval of the study protocol and informed consent by the Philippine Heart Center Institutional Ethics Review Board (PHC-IERB) was done. A written informed consent was obtained prior to participation of the study.

This is a cross-sectional study which collected data during a 7-month period (October 2014 to May 2015) at the Philippine Heart Center. The choice of anesthetic technique depended entirely on the choice of the attending anesthesiologist. This study included adult patients from 19 years old and above who underwent elective or emergency coronary artery bypass grafting under cardiopulmonary bypass at the Philippine Heart Center during the allotted time period.

Excluded in the study were patients who had post cardiopulmonary resuscitation, septic patients, cardiac tamponade, intubated patients, off pump coronary artery bypass (OPCAB).

*Sample size:* was computed using a study by Takami,Y. et al[7] where the correlation of lactate level and Pv-a$C0_2$ was observed to be 0.26. Using this correlation coefficient, the minimum sample size requirement is 150 using the alpha level of 0.05 and confidence interval width of 0.2.

Consecutive patients undergoing coronary artery bypass within the study period who have met the inclusion criteria were included in the study. The data for the patient's age, gender, and diagnosis of Diabetes Mellitus Type 2, were gathered. The operative time, aortic cross clamp time and total cardiopulmonary bypass time were collected for each patient. The number of coronary artery bypass vessel grafts for each was also gathered. The Pv-a$C0_2$ difference (mmHg) and blood lactate (mmol/L) levels were measured within the 1st hour .of admission to the surgical intensive' care unit (SICU). The Pv-a$C0_2$ difference is the difference between the mixed venous $PC0_2$ and arterial $PC0_2$ values taken from the pulmonary artery catheter line and the arterial line respectively.

Statistical analysis were employed using STATA SE version 13. For descriptive statistics, the mean and standard deviation were employed for the quantitative variables and the frequency and percentage distribution for the qualitative variabless. The Pearson product moment correlation and scatterplot graph were used to

determine the correlation between Pv-a$C0_2$ and lactate. The accuracy of different values for the Pv-a$C0_2$ gap against a blood lactate cut-off value of 2mmol/L were computed.

## RESULTS

One hundred fifty patients were included in the study of which 133 (88.67%) were male while 17 (11.33%) were female. The mean age of the subjects was 59.1 years old (SD ± 8.7). Forty-five (30%) of the subjects were diagnosed with concomitant Diabetes Mellitus Type 2. The operation time, cardiopulmonary bypass time and aortic cross clamp time were 406.9 ± 75.4 min, 143 ± 38.5 min, and 109.8 ± 32.5 min respectively. The average number of vessel grafts done to the patients was four as shown in Table 1.

The corresponding value of the Pv-a$C0_2$ difference and blood lactate of post CABG patients included in the study taken within the first hour of SICU admission. In the study, the mean Pv-a$C0_2$ difference was noted to be 7.66 ± 4.48 mmHg and the-mean blood lactate was noted to be 4.12 ± 2.35 mmol/L. *(Table 2*) Using the Pearson product moment correlation coefficient, a mild to moderate positive correlation (r=0.34, p= <0.000l) between Pv-a$C0_2$ difference and blood lactate levels. (*Figure 1*)

Different values from 2 to 7mmHg for the Pv-a$C0_2$ difference were assigned and their respective diagnostic accuracies determined against blood lactate where a normal value of up to 2 mmol/L was used. *(Table 3)* A Pv-a$C0_2$ difference of 2 mmHg showed the highest sensitivity of 97.44 but the lowest specificity of 9.09. Its positive predictive value-and negative predictive values were 79.17 and 50 respectively. The sensitivity of the different values were noted to decrease and the specificity was noted to increase as the Pv-a$C0_2$ difference increased. The positive predictive values were directly proportional and the negative predictive values were indirectly proportional to the Pv-a$C0_2$ difference values. The Pv-a$C0_2$ difference of 6 mmHg was observed to have almost similar sensitivity and specifity (62.39 and 66.67 respectively) with a positive predictive value of 86.9 and a negative predictive value of 33.33 .

**Table 1.** Baseline clinical data and demographics

| Characteristics n = 150 | Mean ± SD n = % |
|---|---|
| Age | 59.1 ± 8.7 |
| Gender | |
| Female | 17 (11.33) |
| Diabetes Mellitues Type 2 | 45 (30) |
| Operation time (minutes) | 406.9 ± 75.4 |
| CPB time (minutes) | 143 ± 38.5 |
| Aortic closs clamp time (minutes) | 109.8 ± 32.5 |
| Number of vessel grafts | 4 ± 1 |

**Table 2.** Correlation of P (v-a) $CO_2$ and Lactate during the I$^{st}$ hour of SICU stay (n= 150).

| Variables | Mean ± SD | Correlation | p value |
|---|---|---|---|
| P (v-a) CO2 difference (mmHg) | 7.66 ± 4.48 | 0.34 | <0.0001 |
| Lactate levels (mmol/L) | 4.12 ± 2.35 | | |

**Table 3.** Diagnostic accuf'"dcyof P (v-a) $CO_2$ cut-off values in detemlining the adequacy of tissue perfusion.

| P (v-a) CO2 | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| 2 | 97.44 | 9.09 | 79.17 | 50.00 |
| 3 | 90.60 | 27.27 | 81.54 | 45.00 |
| 4 | 82.91 | 36.36 | 82.20 | 37.50 |
| 5 | 70.94 | 48.48 | 83.00 | 32.00 |
| 6 | 62.39 | 66.67 | 86.90 | 33.33 |
| 7 | 53.85 | 72.73 | 87.50 | 30.77 |

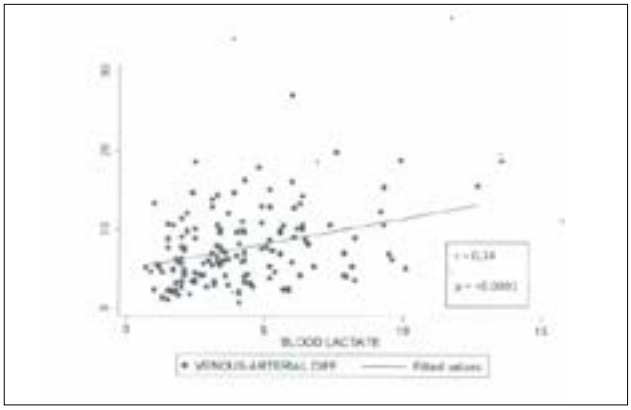

**Figure 1.** Scatterplot graph of P(v-a) $CO_2$ difference against lactate levels

## DISCUSSION

The Pv-aC0$_2$ difference had a mild correlation (r=0.34, p<0.0001) with blood lactate taken post cardiac surgery. This was already an improvement from the study of Takami[12] that showed a Pv-aC0$_2$ difference and blood lactate correlation of 0.26. Takami demonstrated that the mean blood lactate (4.6 ± 3.1 mmol/L) and mean Pv-aC0$_2$ difference (5.0 ± 3.3 mmHg) were elevated in post cardiopulmonary bypass patients. In this study the mean lactate (4.12 ± 2.35 mmol/L) and mean Pv-aC0$_2$ difference (7.66 ± 4.48 mmHg) were also elevated. This is probably due to the effects of cardiopulmonary bypass on tissue perfusion and oxygen delivery.[1] In a study published in 1891, Araki and Zillessen[14] observed that when they interrupted oxygen supply to muscles in mammals and birds, lactic acid was formed and increased. This has shaped the association of hyperlactemia and tissue hypoxia. Many experimental studies have confirmed the relationship between tissue hypoxia and the generation of lactate by reducing the components of systemic oxygen delivery (haemoglobin level, oxygen saturation, and cardiac output) until the extraction of oxygen can no longer maintain oxygen availability to the cells to meet their demands.[15,16] At a critical level of oxygen delivery, oxygen consumption becomes limited by oxygen delivery, and this coincides with a sharp increase in lactate levels. Also, clinical data indicate the relationship between the presence of this supply dependent state of oxygen consumption and increased lactate levels similar to animal studies.[17]

Aside from derangements in tissue perfusion brought about by cardiopulmonary bypass, other factors also lead to hyperlactemia. These include the number of transfused blood units, EF before surgery, having diabetes, duration of using pump and storage time of blood.[18]

Studies on Pv-aC0$_2$ difference on sepsis peg the cut-off value for increased morbidity at >5 mmHg[13] and >6mmHg[11] respectively. In order to determine a probable cut-off value for Pv-aC0$_2$, different were used ranging from a difference of 2 to 7 mmHg and their corresponding diagnostic accuracies tabulated. (*Table 3)*

The cut-off value for blood lactate used was 2 mmol/L because at levels higher than 2 mmol/L, the risk for morbidity also increased.[4] The sensitivity was highest when the Pv-aC02 difference was at its narrowest. However, at these values the specificity and positive predictive values were low and the negative predictive value was high when the Pv-aC0$_2$. In this study, a proposed cut-off value for Pv-aC0$_2$ difference in the setting of cardiac surgery under cardiopulmonary bypass is 6 mmHg. This was chosen because it was at this difference that the sensitivity and specificity were almost equal. This also had a relatively high positive predictive value.

We recommend the use of Pv-aC0$_2$ difference as a weak surrogate parameter in assessment of tissue perfusion after cardiopulmonary bypass. The author suggests another study with more subjects and not limiting to coronary artery bypass surgery to further verify Pv-aC0$_2$ difference as a surrogate parameter to tissue perfusion. The author also proposes a follow-up study focusing on the clinical out comes of post cardiac surgery patients with 6 mmHg as the cut-off value for Pv-aC0$_2$ difference.

The limitation of this study is that the number of blood transfusion and the number of days blood was stored which could both affect the blood lactate levels were not collected. Standardization of the anesthetic technique was also not employed since it was left to the discretion of the attending anesthesiologist.

## REFERENCES


1. Gravlee GP, Davis RF, Kurusz M, Utley JR. Cardiopulmonary bypass: principles and practice. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2000.
2. Bakker J.Lactate: may I have your votes please? Intensive Care Med. 2001 Jan;27(1):6-11.
3. Bakker J, Nijsten MW, Jansen TC. Clinical use of lactate monitoring in critically ill patients. Ann Intensive Care. 2013 May 10;3(1):12.
4. Toraman F, Evrenkaya S, Yuce M, Aksoy N, Karabulut H, et al.Lactic acidosis after cardiac surgery is associated with adverse outcome. Heart Surg Forum. 2004 Apr 1;7(2):E155-9.

5. Grundler W, Weil MH, Rackow EC.Arteriovenous carbon dioxide and pH gradients during cardiac arrest. Circulation. 1986 Nov;74(5):1071-4.
6. Kazarian KK, Del Guercio LR. The use of mixed venous blood gas determinations in traumatic shock. Ann Emerg Med. 1980 Apr;9(4):179-82.
7. Weil MH, Rackow EC, Trevino R, Grundler W, Falk JL, Griffel MI. Difference in acid-base state between venous and arterial blood during cardiopulmonary resuscitation. N Engl J Med. 1986 Jul 17;315(3):153-6.
8. Adrogué HJ, Rashad MN, Gorin AB, Yacoub J, Madias NE. Assessing acid-base status in circulatory failure. Differences between arterial and central venous blood. N Engl J Med. 1989 May 18;320(20):1312-6.
9. Mecher CE, Rackow EC, Astiz ME, Weil MH. Venous hypercarbia associated with severe sepsis and systemic hypoperfusion. Crit Care Med. 1990 Jun;18(6):585-9.
10. Myer G, Morrison S, Merchant A, Johnstone D, Hawkins J, Swyer W, Gardner K. The significance of arterio-venous carbon dioxide gradients. A review of this guide to the adequacy of peripheral tissue perfusion. Canadian Perfusion Canadienne. 2008; 18: p. 62-64.
11. Vallée F, Vallet B, Mathe O, Parraguette J, Mari A, Silva S, Samii K, et al. Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock. Intensive Care Med. 2008 Dec;34(12):2218-25.
12. Takami Y, Masumoto H. Mixed venous-arterial CO2 tension gradient after cardiopulmonary bypass. Asian Cardiovasc Thorac Ann. 2005 Sep;13(3):255-60.
13. Silva JM Jr, Oliveira AM, Segura JL, Ribeiro MH, Sposito CN, Toledo DO, Rezende E, et al. A large venous-arterial PCO2 is associated with poor outcomes in surgical patients. Anesthesiol Res Pract. 2011;2011:759792.
14. Ueber die Bildung von Milchsaure und Glvcose im Organismus bei Sauersfoffmangel. Z. Physiol Chem. 1891; 15: p. 335-370.
15. Cain SM. Appearance of excess lactate in anesthetized dogs during anemic and hypoxic hypoxia. Am J Physiol. 1965 Sep;209(3):604-10.
16. Zhang H, Vincent JL. Oxygen extraction is altered by endotoxin during tamponade-induced stagnant hypoxia in the dog. Circ Shock. 1993 Jul;40(3):168-76.
17. Bakker J, Vincent JL. The oxygen supply dependency phenomenon is associated with increased blood lactate levels. 1991 Sept;6(3):152-159.
18. Joudi M, Fathi M, Soltani G, Izanloo A. Factors affecting on serum lactate after cardiac surgery. Anesth Pain Med. 2014 Oct 14;4(4):e18514.

Cardiovascular Radiological Sciences

# Correlation of Sterno-Aortic Distance with FEV1/FVC and FEV1 in Patients with COPD

Regina Cristina Q. Mangada, MD; Alfredo F. Villarosa, MD

***Background*** --- Chronic obstructive pulmonary disease (COPD) is defined by the Global Initiative for Chronic Obstructive Lung Disease as "a disease state characterize by airflow limitation that is not fully reversible." Several qualitative and quantitative CT parameters have been studied in diagnosing patients with COPD. The clinical application of CT scan in quantitative assessment of the morphologic features of airways in patients with COPD has been subjects of numerous investigations. However, studies on sterno-aortic distance as a parameter in assessing morphologic feature of COPD in CT scan has been rare. Hence, this study aims to find a correlation of sterno-aortic distance with pulmonary function test in patients with COPD.

***Method*** --- Eighty-one patients diagnosed with COPD who underwent chest CT scan and PFT within the period of one year were included. Sterno-aortic distance were measured and correlated with PFT results and severity of COPD.

***Results*** --- Most patients enrolled were males with average age of 64 ± 11years old. Most of these patients are categorized as mild COPD with 38 % and severe COPD with 38% of the total population. Patients classified as moderate COPD comprise 24 % of the total population. There is significant weak inverse correlation between sterno-aortic distance and PFT results, FEV1 ($r = -0.419$, $p < 0.001$) and FEV1/FVC($r = -0.322$, p value of 0.003). There is a significant correlation derived between sterno aortic distance and severity of COPD (rho = 0.88, p-value of <0.001).

***Conclusion*** --- Sterno-aortic distance is a valuable parameter in patients with COPD as well as its severity.
***Phil Heart Center J 2017;22(1):84-87.***

**Key Words: chronic obstructive pulmonary disease ■ COPD ■ sterno-aortic distance ■ chest CT scan**

Chronic obstructive pulmonary disease (COPD) is defined by the Global Initiative for Chronic Obstructive Lung Disease as "a disease state characterize by airflow limitation that is not fully reversible". The airflow limitation is caused by a combination of small airway remodeling and emphysema with varying distribution and severity.[1] COPD is characterized by decreased maximal expiratory airflow, hyperinflation, and gas trapping. The physiologic abnormalities are caused by a combination of loss of elastic recoil and narrowing of small airways.[2]

COPD consist of heterogenous group of disorders i.e. chronic bronchitis, emphysema and peripheral airway disease. The diagnosis of COPD is conventionally based upon spirometry.[3] Spirometry (meaning the measuring of breath) is the most common of the pulmonary function tests (PFTs), measuring lung function, specifically the amount (volume) and/or speed (flow) of air that can be inhaled and exhaled. Spirometry is an important tool used for generating pneumatographs, which are helpful in assessing conditions such as asthma, pulmonary fibrosis, cystic fibrosis, and COPD.[4] Total lung capacity is the amount of air that remains in the lungs at the end of maximal inspiration. In patients with COPD, the greatest increase in total lung capacity is seen in patients with severe emphysema.

Several qualitative and quantitative CT parameters have been studied in diagnosing patients with COPD. In a study done by Arakawa et al., parameters such as tracheal index, thoracic cage ratio, thoracic cross sectional area and sterno-aortic distance were used in patient

*Finalist*, Oral Presentation - Original Paper. 24th PHC Annual Research Paper Competition and Poster Presentation held on February 26, 2016 at Philippine Heart Center. Correspondence *to Dr. Regina Cristina Q. Mangada.* Division of CV Radiological Sciences. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication**  ISSN 0018-9034

with COPD. Their study showed that these parameters are significantly correlated with FEV1/FVC ratio.

The clinical application of CT scan in in quantitative assessment of the morphologic features of airways in persons with COPD has been subjects of numerous investigations. Some imaging indices used are wall area, percentage, luminal area, and bronchial wall attenuation.[5] It has been said that patients with COPD develop an increase in their thoracic cage diameter as the disease progresses. Parameters such as thoracic cage ratio and tracheal index have been studied in the past. However, studies on sterno-aortic distance as a parameter in assessing morphologic feature of COPD in CT scan has been rare. Hence, this study aims to find a correlation of sterno-aortic distance with pulmonary function test in patients with COPD.

## METHODS

This study is a cross-sectional study conducted at the Philippine Heart Center (PHC) from January 2007 to December 2014. Included were patients diagnosed with COPD who are >40 years old underwent CT scan and pulmonary function test with a maximum interval of one year. While patients whose CT scan was done outside PHC, clinically unstable patient, those with other chest CT scan findings (bullae, mass, plural effusion), and patients with coexisting bronchiectasis, asthma PTB or bronchogenic cancer were excluded from the study.

*Sample size*. Using NCSS-PASS 13 software, the minimum sample size requirement was estimated to be at least 61 patients base on the following parameter: Alpha = 5%, power = 80%. Correlation coefficient between sterno-aortic distance and pulmonary function test in patients with COPD is -0.351 based on the paper of Arakawa et al.[6]

*Study Maneuver.* Patients who fulfilled the inclusion criteria were included in this study. Patient's age, gender, height, and weight were recorded. The sterno-aortic distance was obtained thru their CT scan. The sterno-aortic distance was measured from the posterior surface of the sternum to the anterior margin of the aorta at the level of the carina. Two radiologists reviewed the CT scan images independently. These radiologists were blinded to the results of the pulmonary function tests (FEV1/FVC and FEV1). Measurements obtained by these radiologists were analyzed using *t*-test to check for inter-observer variability. These measurements were correlated with the FEV1/FVC and FEV1 of patients who underwent pulmonary function tests results using Pearson correlation. These measurements were correlated with the severity of COPD according to the GOLD criteria.

## RESULTS

The demographic characteristics of patients with COPD included in this study is shown in Table 1. In this study, 81 records of patients who are diagnosed with COPD and underwent chest CT scan within one year interval were included and reviewed. There were 62 ( 77%) male subjects and 19 (23%) females. Most patients have an average age of 64 years old. The subjects have a mean height of 163.19 cm and mean weight of 62.83 kg. Most of these patients are categorized as mild COPD with 38 % and severe COPD with 38% of the total population. Patients classified as moderate COPD comprise 24% of the total population. Two radiologists reviewed the records of these 81 patients.

**Table 1.** Demographics of patients with COPD included in this study

| Characteristics n = 81 | Mean ± SD n = % |
|---|---|
| Age | 64.42 ± 11.19 |
| Gender | |
| Male | 62 (77) |
| Female | 19 (23) |
| Height (cm) | 163.19 ± 7.71 |
| Weight (kg) | 62.83 ± 15.07 |
| COPD | |
| Mild | 31 (38) |
| Moderate | 19 (24) |
| Severe | 31 (38) |

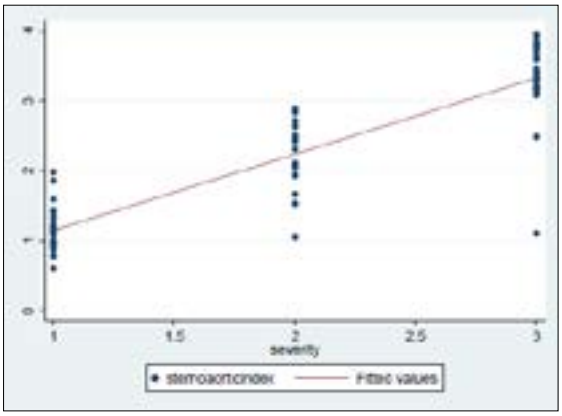


**Figure 1.** shows that sterno-aortic distance have a significant correlation with the severity grading of COPD by GOLD criteria (r of 0.3 - 0.4). The greater is the sterno-aortic distance, the more severe is the obstructive process.

**Table 2.** Correlation coefficient of sterno-aortic distance in CT scan with PFT

| PFT Parameters | Sterno-aortic Distance | |
|---|---|---|
| | r | p value |
| FEV1/FVC | -0.322 | 0.003 |
| FEV1 | -0.419 | < 0.001 |

P = < 0.05 will be considered significant
r = Pearson's correlation

Table 2 shows that there is significant weak inverse correlation between sterno-aortic distance and FEV1 (r = -0.419, p value of <0.001). There is likewise a significant weak inverse correlation between sterno-aortic distance and FEV1/FVC (r = -0.322, p value of 0.003).

**Table 3.** Correlation of sterno-aortic distance by CT scan with severity of COPD

| COPD | rho | p value |
|---|---|---|
| Severity | 0.88 | <0.001 |

P = < 0.05 will be considered significant
r = Spearman's correlation

Table 3 shows that there is a strong direct significant correlation between sterno-aortic distance and severity of COPD (rho = 0.88, p-value of <0.001).

**Table 4.** Interobserver variability of the sterno-aortic distance measured by the two radiologists.

| | Radiologist 1 Mean ± SD | Radiologist 2 Mean ± SD | p value |
|---|---|---|---|
| Sterno-aortic distance | 2.24 ± 1.06 | 2.24 ± 1.05 | 0.316 |

In assessing for interobserver variability between the two radiologists who reviewed the chest CT scan of the subjects, a *t*-test was done (*Table 3*). A value of 0.316 was obtained indicating that there is no significant variability between the measurements of the two observers.

## DISCUSSION

This study showed that measurement of the sterno-aortic distance could be potentially used as a quantitative CT index in patients with COPD. It showed significant weak inverse correlation with FEV1 (r = -0.419, p < 0.001) and FEV1/FVC (r = -0.322, p < 0.003), which are parameters of obstructive pulmonary disease in pulmonary function test. These findings showed that as we observe an increase in the sterno-aortic distance, there is likewise a corresponding decrease in the FEV1 and FEV1/FVC values, which are measures of an obstructive process. This is in congruent with the study of Gupta et al., that various CT parameters such as tracheal index, sterno-aortic distance, thoracic cage ration and thoracic cross sectional area are said to be suggestive of hyperinflation in COPD.[3] These findings are also in agreement with the paper done by Arakawa et al., which showed that parameters such as tracheal index, thoracic cage ratio, thoracic cross sectional area and sterno-aortic distance are used in patient with COPD. However, their study showed that these parameters are significantly correlated with FEV1/FVC ratio.[6]

This study also showed a strong direct significant correlation between sterno-aortic distance and severity of COPD (rho = 0.88, p-value of <0.001). The study Mostafa and Mostafa showed a correlation between HRCT and spirometry in patients for early diagnosis of emphysema, however, their study revealed moderate correlation.[7] Nakano, et al., made an attempt to correlate HRCT of emphysema and

and spirometry that with moderate and showed significant correlation.[7]

These findings can be explained by the fact that changes in the thoracic diameter were observed in patients with chronic obstructive disease of the airways. This can be attributed to the fact that as an increase in the severity of the obstructive disease, an increase in the degree of hyperinflation of the thorax is likewise noted.[3]

Emphysema causes abnormal enlargement of the airspaces distal to the terminal bronchiole, hence, airway wall obstruction is evident. This causes air trapping and subsequent hyperinflation of the lungs.[7]

In addition, this study was able to establish the range of sterno-aortic distance of patients with COPD. As shown in Figure 1, the higher the severity of COPD, the wider is range of sterno-aortic distance. This can be attributed to a relatively difference in the degree of compensation of the thorax to the degree of air trapping in hyperinflation.

The subjects in this study were those patients who underwent chest CT scan and pulmonary function test within one year period from 2007 to 2014. One of the limitations in this study would be the fact that the CT images from this period would be compressed and reconstructed, hence, this would limit the radiologist from obtaining optimal sterno-aortic distance measurement. Also the distribution of patients should be more equal and groups the severity should be well-represented since in this study most patients included were patients with mild and severe COPD, both occupying 38% of the entire population of subjects. A follow-up should have been also done in these patients so the progression of the disease can be evaluated. This can give a stronger and more predictive diagnostic value.

In order to obtain a more specific CT parameter that can give predictive value to COPD, a comparison with sterno-aortic distance and other CT parameters such as tracheal index, thoracic cage ratio and bronchial wall attenuation can be an area for further research.

## CONCLUSION

This study shows that sterno-aortic distance is a valuable index in evaluating patients with COPD. The sterno-aortic distance measured in chest CT scan showed significant weak inverse correlation when correlated with FEV1 and FEV1/FVC, and that there is a strong direct significant relationship between sterno-aortic distance and severity of COPD.

## REFERENCES

1. Matsuoka S, Yamashiro T, Washko GR, Kurihara Y, Nakajima Y, Hatabu H. Quantitative CT assessment of chronic obstructive pulmonary disease. Radiographics. 2010 Jan;30(1):55-66.
2. Nakano Y, Wong JC, de Jong PA, Buzatu L, Nagao T, Coxson HO, et al. The prediction of small airway dimensions using computed tomography. Am J Respir Crit Care Med. 2005 Jan 15;171(2):142-6.
3. Gupta PP, Yadav R, Verma M, Agarwal D, Kumar M. Correlation between high-resolution computed tomography features and patients' characteristics in chronic obstructive pulmonary disease. Ann Thorac Med. 2008 Jul;3(3):87-93.
4. Wikipedia. Spirometry. [Internet]. 2014. cited 2014 Nov]. Available from http://en.wikipedia.org/wiki/Spirometry
5. Yamashiro T, Matsuoka S, Estépar RS, Dransfield MT, Diaz A, Reilly JJ, et al. Quantitative assessment of bronchial wall attenuation with thin-section CT: An indicator of airflow limitation in chronic obstructive pulmonary disease. AJR Am J Roentgenol. 2010 Aug;195(2):363-9. doi: 10.2214/AJR.09.3653.
6. Arakawa H, Kurihara Y, Nakajima Y, Niimi H, Ishikawa T, Tokuda M. Computed tomography measurements of overinflation in chronic obstructive pulmonary disease: evaluation of various radiographic signs. J Thorac Imaging. 1998 Jul;13(3):188-92.
7. Mostafa M, Mostafa S. Role of chest radiography, spirometery and high resolution computed tomography in the early diagnosis of emphysema. The Egypt J of Rad and Nuc Med. Oct 2010 (41) 1509-1515.

# Vascular Malformations in Klippel-Trenaunay Syndrome: a case series

Dedric Christi Paul D. Yulo, MD

***Background*** --- Klippel-Trenaunay Syndrome (KTS) is a rare congenital syndrome that is classically defined as a triad of (1) an extensive nevus or port-wine stain on an involved limb, (2) varicose veins or venous malformations on the involved limb arising in childhood, and (3) hypertrophy of all the tissue and especially of the bones in the impaired limb.[3] Owing to the unpredictable nature of the vascular malformations, KTS presents with varied clinical manifestations.

***Case*** --- We present the three cases of Klippel-Trenaunay Syndrome diagnosed and managed at the Philippine Heart Center, each with unique vascular malformations.

***Conclusion*** --- Patients with Klippel-Trenaunay Syndrome have varying vascular malformations and limb hypertrophy which must be given individualised treatment. Because treatment of KTS is best started in childhood, it should be recognised early despite the perplexity of diagnosis. ***Phil Heart Center J 2017;22(1):88-91.***

**Key Words: Klippel-Trenaunay Syndrome ■ vascular malformations ■ port-wine stain ■ limb hypertrophy**

In 1900, French physicians Maurice Klippel and Paul Trenaunay were the first to describe an entity they named naevus variqueus osteo-hypertrophique or varicose osteohypertrophic nevus. Recognised by the International Society for the Study of Vascular Anomalies as Klippel-Trenaunay Syndrome (KTS) in 1996, this rare congenital syndrome is classically defined as a triad of (l) an extensive nevus or port-wine stain on an involved limb, (2) varicose veins or venous malformations on the involved limb arising in childhood, and (3) hypertrophy of all the tissue and especially of the bones in the impaired limb. While various theories have been proposed for the pathophysiologic characteristics of this syndrome, the etiology remains elusive. Also, owing to the unpredictable nature of the vascular malformations, KTS presents with perplexing clinical manifestations.

Because KTS is a rare congenital syndrome with no Philippine registry, and because it has variable manifestations that might preclude timely recognition in inexperienced local centers, KTS deserves attention through this report.

## *Cases*

We present the three cases of Klippel-Trenaunay Syndrome diagnosed and managed at the Philippine Heart Center, giving focus on the unique vascular malformations each patient exhibits.

Case 1 is an 8-year old boy diagnosed with congenital heart disease, double-outlet right ventricle and pulmonic stenosis. He was referred to our institution for evaluation of an enlarging right arm. On physical examination, his right arm had muscular hypertrophy with visible and prominent superficial veins and red to purple birthmarks at the right arm, forearm and axillary areas. On venous duplex study, he had an absent brachial vein with a prominent basilic vein and its tributaries, as well as evidence of muscular hypertrophy. *Figure 1*

Case 2 is an 11-year old boy who was referred to our institution for a swelling and enlarging right lower leg. Pertinent physical findings

*Finalist*, Poster-Case Report Presentation - Original Paper. 24th PHC Annual Research Paper Competition and Poster Presentation held on February 26, 2016 at Philippine Heart Center. Correspondence *to Dr. Dedric Christi Paul D. Yulo.* Department of Adult Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication**  2017 ISSN 0018-9034

include multiple red to purple birthmarks at the right leg with muscle hypertrophy and leg length discrepancy. On palpation, there had been a bruit over the right leg. Venous duplex study showed multiple vascular confluences with a monophasic low-resistance waveform pattern suggestive of multiple arteriovenous malformations (AVMs). He subsequently underwent peripheral conventional angiography, confirming the presence of multiple AVMs involving the right distal superficial femoral artery. *Figure 2*

Case 3 is a 26-year old male who was referred for evaluation of chronic venous insufficiency. Pertinent physical findings include swelling of the right lower extremity with multiple red to purple birthmarks and visible varicosities on the right calf area. Venous duplex study showed a relatively hypoplastic right proximal femoral vein with a dilated great saphenous vein exhibiting incompetent valves during standing and valsalva maneuver. *Figure 3*

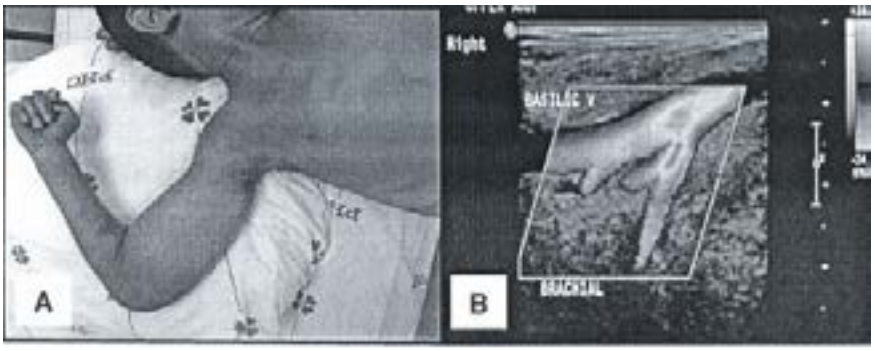


**Figure 1.** (A) Physical features of an 8-year old boy with muscular hypertrophy, prominent superficial veins and multiple reddish to purplish birthmarks of the right upper extremity. (B) Venous Duplex study of the right arm showing a prominent basilic vein and its tributaries with absent brachial vein (deep vein agenesis).

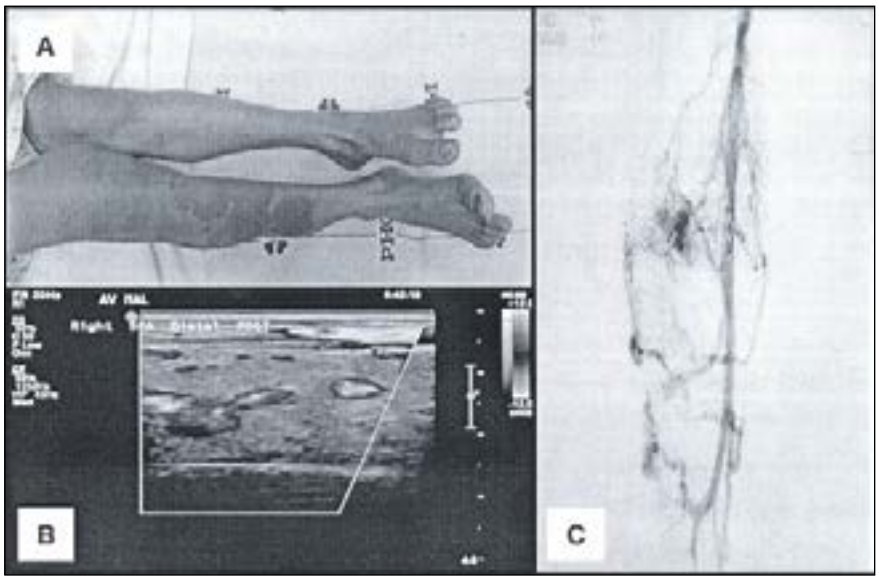


**Figure 2.** ((A) Physical features of an 11-year old boy with musculoskeletal hypertrophy and multiple reddish to purplish birthmarks of the right lower extremity. (B & C) Venous Duplex study and peripheral conventional angiography of the right lower extremity showing multiple AVMs.

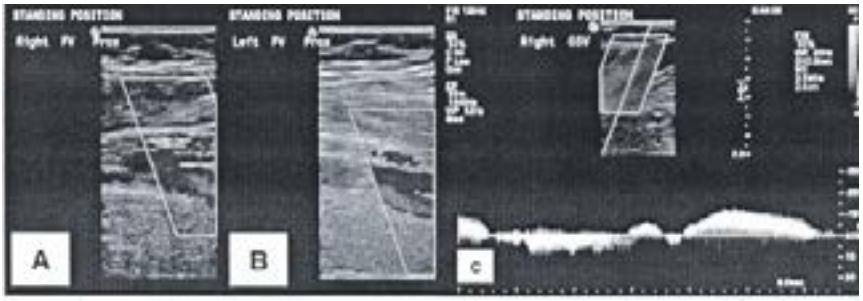


**Figure 3.** (A) Venous Duplex scans showing a relatively hypoplastic right proximal femoral vein compared to the left. (B) Dilated right great saphenous vein exhibiting incompetent valves during standing and Valsalva maneuver

## DISCUSSION

Klippel-Trenaunay Syndrome is a sporadically-occuring entity and is estimated to affect at least 1 in 100,000 persons worldwide.[1] KTS affects slightly more females (54% of cases) than males, with a mean age of 11.9 years at the time of diagnosis.[2] In most cases (up to 86% in one series), the syndrome affects only one limb: 40% at the left lower limb and 46% at the right lower limb. In 9%, KTS affects both lower limbs, in 3% it affects both upper and lower limbs on the same side, and in 2% it affects only an upper limb.[3]

Each of our three cases presented with an extensive nevus or port-wine stains. These lesions are capillary malformations lined by a single layer of endothelial cells localised to the superficial dermis. They are red to purple, flat, irregular, and mayor may not blanch on pressure. They occur on the ipsilateral limb in up to 86% of patients with KTS; in the remainder of patients, nevi or port-wine stains may be seen in the contralateral limb, trunk, head or neck. These capillary malformations become more pronounced with puberty and pregnancy, and can fade with age but will never completely disappear.[4]

Each of our three cases present with hypertrophy of the soft tissues and bones of the affected limb. The discrepancy in limb length is attributed to long bone growth, while the increase in limb girth is caused by soft-tissue hypertrophy.[4] These are postulated to be due to mesodermal developmental anomalies resulting in abnormal muscle and bone growth, and the persistence of the embryonic vascular reticular network. This vascular network subjects the developing limb to increased blood flow and temperature that in turn enhances the circumferential size and elongation of the limb, and promotes the formation of varicosities, hemangiomas and enlarged venous channels.[5]

Each of our three cases present with vascular malformations other than the aforementioned nevi/port-wine stains. Case 1 has deep vein agenesis, Case 2 has AVMs, while Case 3 has hypoplastic deep veins with venous insufficiency. Although the KTS had classically been a triad of (1) limb hypertrophy, (2) extensive nevus and port-wine stain on an involved limb, and (3) varicose veins or venous malformations, a diagnostic criteria put forward by Oduber et al. in 2008 has since expanded on the classic definition. Vascular malformations other than nevi/port-wine stains could now include venous malformations such as agenesis, hypoplasia or aplasia of veins, persistence of fetal veins, varicosities, hypertrophy, tortuosity, and valvular incompetence; small arteriovenous malformations or arteriovenous fistulas; and any lymphatic malformation.[6] These vascular malformations are mainly located in the extremities and adjacent parts of the trunk, but these may be found in other visceral organs.[7]

Because the presentation of KTS is extremely variable, and because its pathophysiologic characteristics and etiology are unclear, management of the disease is individualised but is generally supportive.[4,8] While most patients complain of physical disturbances, up to 25% will seek medical attention for cosmetic reasons.[4] Surgery and minimally invasive therapies such as vein ligation and stripping, sclerotherapy, laser therapy and endovenous thermal ablation may be necessary to reduce the threat of serious complications.[4,8] Conventional management such as graduated compressive stockings are efficacious for patients with venous stasis and phlebitis.[8] Anticoagulation may be necessary to decrease VTE risk.[9] In some cases, insole orthotics (heel inserts) and limb shortening procedures (i.e., epiphyseal stapling, epiphysiodesis, femoral and tibial shortening) may be necessary for functionally disabling limb malformations.[4,8]

Patients with Klippel-Trenaunay Syndrome should be monitored at least yearly, and more often if the disease is progressive and if complications are noted.[10] Ideally, patients with KTS should be identified and treated in childhood when they still do not present with clinical changes of high morbidity.[3] Currently, no prospective study has been conducted to investigate the long-term prognosis of KTS. Despite numerous retrospective studies, no clear conclusions have been drawn regarding prognostic factors that might determine its clinical course.[8]

## CONCLUSION

Klippel-Trenaunay Syndrome is a rare congenital anomaly presenting with various vascular malformations in addition to limb hypertrophy. Its management ranges from supportive measures to extensive surgeries, and needs to be individualised. Although there is insufficient data regarding long-term prognosis, treatment of KTS is best started in childhood-highlighting the importance of the timely recognition of its variable manifestations.

## REFERENCES


1. Servelle M. Klippel and Trénaunay's syndrome. 768 operated cases. Ann Surg. 1985 Mar; 201 (3): 365-73.
2. Jacob AG, Driscoll DJ, Shaughnessy WJ, Stanson AW, Clay RP, Gloviczki P. Klippel-Trénaunay syndrome: spectrum and management. Mayo Clin Proc. 1998 Jan; 73(1):28-36.
3. Villela ALC, Gustavo G, Guedes S, Paschoa A, David AB, Tenório TM, et al. Epidemiological profile of 58 patients with Klippel-Trenaunay-Weber syndrome followed at Ambulatório da Santa Casa de São Paulo. J Vasc Bras. 2009 Sept; 8(3). [Accessed on 2018 Sept 13]. Available from http://www.scielo.br/scielo. php?pid = S16 77-54492009000 300006 &script = sci _ arttext &tlng=en
4. Capraro PA, Fisher J, Hammond DC, Grossman JA. Klippel-Trenaunay syndrome. Plast Reconstr Surg. 2002 May;109(6):2052-60; quiz 2061-2.
5. Baskerville PA, Ackroyd JS, Browse NL. The etiology of the Klippel-Trenaunay syndrome. Ann Surg. 1985 Nov;202(5):624-7.
6. Oduber CE, van der Horst CM, Hennekam RC. Klippel-Trenaunay syndrome: diagnostic criteria and hypothesis on etiology. Ann Plast Surg. 2008 Feb; 60 (2):217-23. doi: 10.1097/SAP.0b013e318062abc1.
7. Cha SH, Romeo MA, Neutze JA. Visceral manifestations of Klippel-Trénaunay syndrome. Radiographics. 2005 Nov-Dec;25(6):1694-7.
8. Sung HM, Chung HY, Lee SJ, Lee JM, Huh S, Lee JW, et al. Clinical Experience of the Klippel-Trenaunay Syndrome. Arch Plast Surg. 2015 Sep;42(5):552-8.
9. Ndzengue A, Rafal RB, Balmir S, Rai DB, Jaffe EA. Klippel–Trenaunay syndrome: an often overlooked risk factor for venous thromboembolic disease. Int J Angiol. 2012 Dec; 21(4): 233–236.
10. Kapoor A, Sarkar D, Rai GS, Anand S. Klippel-Trenaunay syndrome - a case report. Peo J Sci Res 2012; 5:51-54.

# A Case of Ebstein Anomaly with a Large Right Atrial Mass

Ray Albert R. Cabigan, MD

***Background*** --- Intracardiac masses in the setting of a congenital heart disease poses a challenging yet interesting diagnostic problem. Diagnostic dilemmas in this setting can occur making it difficult to truly define the disease entity.

***Case*** --- This is a case of a 44 year old female, diagnosed with Ebstein Anomaly, Immune Thrombocytopenia and Papillary Thyroid Cancer who developed progressive right sided heart failure and was found to have a right atrial mass that progressively enlarged to occupy almost the entirety of the right atrium. A primary neoplasm, metastasis from the thyroid cancer and a thrombus were considered but diagnostic dilemmas proved difficult to overcome.

***Conclusion*** --- A mass on cardiac imaging may represent a great variety of diseases. In an unusual case as presented above, there is not one single imaging test that could truly define the right atrial mass. When faced with a complex case involving an unidentifiable mass lesion, a biopsy should always be sought to allow early initiation of definitive management. ***Phil Heart Center J 2017;22(1):92-94.***

**Key Words: Ebstein anomaly ■ right atrial mass**

Intracardiac masses in the setting of a congenital heart disease poses a challenging yet interesting diagnostic problem.[1] This paper will present the rare clinical presentation of a large right atrial mass and the diagnostic dilemma that comes along with identifying the giant mass.

## *Case*

This is a case of a 44 year old female who had an unremarkable childhood. In 1993, she was able to give birth via normal spontaneous delivery. She was diagnosed with immune thrombocytopenic purpura (ITP) in 2006 and papillary thyroid carcinoma in 2011. It was in 2011 that the patient was found to have a -8mm apical displacement of the tricuspid valve leaflet into the atrialized right ventricle via echocardiography findings consistent with Ebstein Anomaly.

A year prior to admission, she began having bouts of anorexia, easy fatigability and bipedal pitting edema. Echocardiography now revealed the presence of a right atrial mass. This was confirmed via cardiac MRI. (*Figure 1*) A thrombus was considered and warfarin was started. An INR of 1.4-1.8 was reached. A month later, echocardiography revealed an increase in the size of the mass. Warfarin was adjusted and an INR of ~2.5 was reached. However, her symptoms persisted and gradually progressed.

She consulted at the Philippine Heart Center wheelchair borne with anasarca. Her vital signs were stable. She had no neck mass nor lymphadenopathy. She had decreased breath sounds at the base of both lungs. There were no murmurs. There was no cyanosis, bruising or signs of bleeding. She had no clubbing. Her initial INR was 3.75. Echocardiography revealed the presence of a right atrial mass attached to the interatrial septum (*Figure 2*). Similarly, a chest CT scan revealed the presence of a large mass (*Figure 3*). Both modalities could not commit whether the said mass was a neoplasm or a thrombus. Other pertinent tests revealed that the patient was persistently thrombocytopenic with counts ranging 20,000 to 123,000 since 2014. She currently has a platelet count of 47,000. Creatinine and liver enzymes were normal. Chest

*Finalist*, Poster-Case Report Presentation - Original Paper. 24th PHC Annual Research Paper Competition and Poster Presentation held on February 26, 2016 at Philippine Heart Center. Correspondence *to Dr. Ray Albert R. Cabigan.* Department of Adult Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication**  ISSN 0018-9034

x-ray was suggestive of cardiomegaly with left ventricular prominence. Additional CT scan findings revealed biapical fibrosis, bilateral pleural effusion and subpleural nodules at the right lower and left upper lobes.

Initially, a biopsy via right sided cardiac catheterization and later, surgical excision of the right atrial mass.

## DISCUSSION

The clinical case is quite unusual given the combination of illnesses and the presence of a progressively enlarging right atrial mass in the setting of an Ebstein Anomaly. Three differentials were considered- a primary neoplasm, metastasis from the thyroid cancer and a thrombus. All three are associated with right sided heart failure. The most common primary cardiac neoplasm is a cardiac myxoma.[2] Rarely, they are found at the right atrium, and even more so when associated with an Ebstein Anomaly.[3,4] The echocardiogram done in this case revealed a mass attached to the interatrial septum findings that are consistent with a myxoma.[2,3] However, there is no specific finding on echocardiography that may be able to differentiate a myxoma from a thrombus.[2]

Rarely, a papillary thyroid carcinoma may metastasize to the right atrium. Papillary thyroid cancer can have microscopic vascular invasion and tumor thrombus in the great veins of the neck and extend up to the right atrium.[5,6] Rare cases (incidence of 0-2%) showed that metastasis to the myocardium (including the right atrium) without involvement of the blood vessels may occur.[6,7] The echocardiogram revealed a mass seemingly attached at the interatrial septum and a large right atrial mass on CT scan. These findings suggests a probable metastatic/neoplastic process.[8,9]

However, on closer observation, it was noted that the borders of the mass on CT scan were separate from walls of the right atrium suggesting otherwise. A thrombus could be considered. Due to poor right ventricular contractile function, low velocity passive flow of blood from the right atrium to the right ventricular outflow tract leads

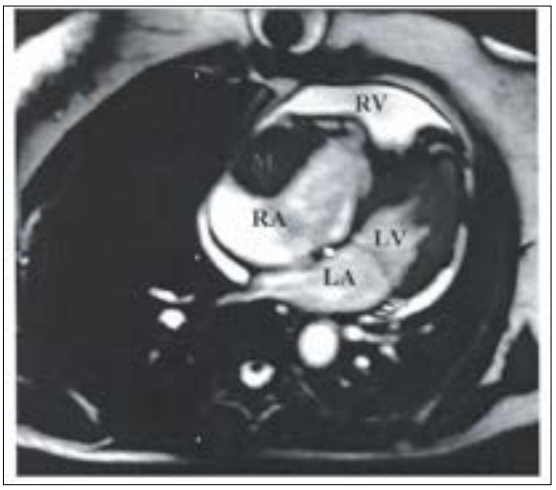


**Figure 1.** 2014 Cardiac MRI: Dilated right atrium (RA) with a 3.0 x 4.3 x 4.4cm nonenhancing filling defect at the inferolateral wall without evidence of infiltration of the myocardium. The right ventricle (RV) is noted to be small.

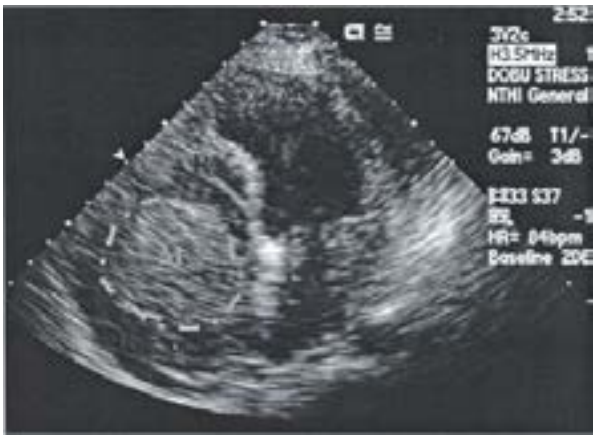

**Figure 2.** 2015 Echocardiogram: Dilated right atrium (RA) with a 6.9 x 4.8cm mass attached to the interatrial septum. M=Mass, RV=Right ventricle, LA=Left atrium, LV=Left Ventricle

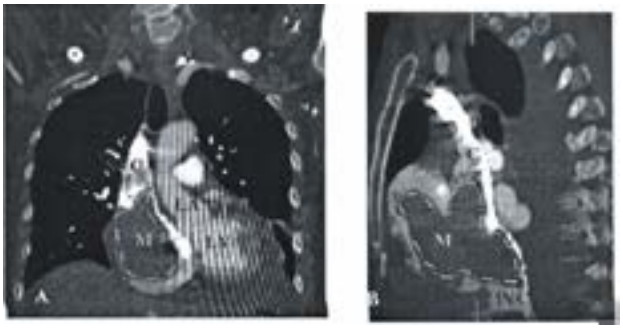

**Figure 3.** 2015 Chest CT Scan: 7.6 x 5.1 x 7.9cm mass extending to the superior and inferior vena cava. (A) Coronal view of the scan revealing a mass within the right atrium with its borders distinctly separate from the atrial wall. (B) Sagittal view of the scan revealing the right atrial mass extending from the superior vena cava (SVC) to the inferior vena cava (IVC) and occupying almost the entire dilated right atrium. The right ventricle cannot be appreciated in both views

to stasis of blood, creates a nidus for clot formation.[9] The ITP of the patient, does not necessarily protect her from thrombus formation and in a patient with risk factors, thrombus formation can still occur.[10,11] What is perplexing about this is that studies showed that ITP patients maintained on warfarin (INR was at 1.5-2.0 for a median of 3 months) demonstrated complete resolution of the thrombus.[11-13] Others showed that at an INR of 2.0 to 2.8 intracardiac thrombus resolution can occur.[14] Yet, if this were a thrombus, why did it continue to grow? The low molecular weight added to the management of the patient may help in decreasing the size of the mass if it were a thrombus - it may however take 6 weeks before an effect could be appreciated.[15]

At this point, a dilemma persists due to findings on echocardiography and on CT-scan that fail to define the right atrial mass of this patient. A biopsy of the lesion is the only means to resolve this problem. In this case, a biopsy done via cardiac catheterization revealed presence of fibrin, red blood cells, leukocytes and necrotic debris - however, this may not be representative of the actual lesion as only small amounts of "tissue" could be obtained. Surgical excision of the right atrial mass with a frozen section of similarly yielded acellular material with fibrin and necrotic debris suggestive of an old blood clot thereby definitively diagnosing the presence of a chronic thrombus.

## CONCLUSION

A mass on cardiac imaging may represent a great variety of diseases. In an unusual case as presented above, there is not one single imaging test that could truly define the right atrial mass. When faced with a complex case involving an unidentifiable mass lesion, a biopsy should always be sought so as to allow early initiation of definitive management.

## REFERENCES


1. Lobo A, Lewis JF, Conti CR. Intracardiac masses detected by echocardiography: case presentations and review of the literature. Clin Cardiol. 2000 Sep;23 (9): 702-8.
2. Leeson P, Augustine D, Mitchell A, Becher H. Oxford Echocardiography (Oxford specialist handbooks in Cardiology: 2nd ed. Oxford: UK. c2012. pg.326-327.
3. Azevedo O, Almeida J, Nolasco T, Medeiros R, Casanova J, Bartosch C, et al. Massive right atrial myxoma presenting as syncope and exertional dyspnea: case report. Cardiovasc Ultrasound. 2010 Jun 18;8:23.
4. Murayama H, Tamaki S, Kato N, Yuji N, Yokote J, Mutsuga M, et al. Right atrial myxoma associated with atrial septal defect: a case report and review of the literature. Ann Thorac Cardiovasc Surg. 2001 Jun; 7 (3):166-9.
5. Al-Jarrah Q, Abou-Foul A, Heis H. Intravascular extension of papillary thyroid carcinoma to the internal jugular vein: A case report. Int J Surg Case Rep. 2014; 5(8):551-3.
6. Portela RA, Choby GW, Manni A, Campbell D, Crist H, Goldenberg D. Unusual sites of metastasis of papillary thyroid cancer: Case series and review of the literature. Ear Nose Throat J. 2015 Aug;94(8):E43-7.
7. Bruixola G, Segura A, Caballero J, Andrés A, Reche E, Escoín C, Díaz-Beveridge R. Heart failure as first sign of development of cardiac metastases in a patient with diagnosis of papillary thyroid carcinoma on treatment with tyrosine-kinase inhibitors: differential diagnoses and clinical management. Case Rep Oncol. 2014 Aug 20;7(2):591-9.
8. Gross BH, Glazer GM, Francis IR. CT of intracardiac and intrapericardial masses. AJR Am J Roentgenol. 1983 May;140(5):903-7.
9. Kumar P, Singhal G, Sinha SK, Pandey U, Thakur R, Varma CM. Ebstein Anomaly With Right Atrial Clot. Cardiol Res. 2015 Oct;6(4-5):319-323.
10. Aledort LM, Hayward CP, Chen MG, Nichol JL, Bussel J; ITP Study Group.Prospective screening of 205 patients with ITP, including diagnosis, serological markers, and the relationship between platelet counts, endogenous thrombopoietin, and circulating antithrombopoietin antibodies. Am J Hematol. 2004 Jul;76(3):205-13.
11. Takagi S, Suzuki I, Watanabe S. Risk of thromboembolism in patients with immune thrombocytopenia. J Hematol Thrombo Dis 2015, 3:1-9.
12. Tran T, Demyttenaere SV, Polyhronopoulos G, Séguin C, Artho GP, Kaneva P, et al. Recommended timing for surveillance ultrasonography to diagnose portal splenic vein thrombosis after laparoscopic splenectomy. Surg Endosc. 2010 Jul;24(7):1670-8.
13. Ikeda M, Sekimoto M, Takiguchi S, Kubota M, Ikenaga M, Yamamoto H, et al. High incidence of thrombosis of the portal venous system after laparoscopic splenectomy: a prospective study with contrast-enhanced CT scan. Ann Surg. 2005 Feb;241(2):208-16.
14. Collins LJ, Silverman DI, Douglas PS, Manning WJ. Cardioversion of nonrheumatic atrial fibrillation. Reduced thromboembolic complications with 4 weeks of precardioversion anticoagulation are related to atrial thrombus resolution. Circulation. 1995 Jul 15;92(2):160-3.
15. Floris N, Gabriel L, Marchandise B. Successful anticoagulation for treatment of a giant left atrial thrombus. Acta Cardiol. 2010 Dec;65(6):713-5.

# Hamartoma of Mature Cardiac Myocytes: A Case Report

Randell S. Arias, MD; Arlene M. De Luna, MD

***Background*** --- Primary cardiac tumors are usually benign. Among the benign tumors, hamartomas of mature cardiac myocytes (HMCMs) are a fairly new category and are extremely rare. We describe this rare hamartoma in the heart, a first in Philippine Heart Center with regards to the clinical presentation, histopathology and differential diagnosis.

***Case*** --- The patient was a 23 year-old female who had episodes of cyanosis without difficulty of breathing or chest pain. 2D-echocardiography revealed a right ventricular mass and was admitted for surgical intervention. Diagnostic imaging (Chest CT scan and TEE) revealed a mass lesion in the right ventricle. Excision of the mass was done. The procedure was uneventful and patient was eventually discharged improved. At four month-follow up, the patient remained asymptomatic.

***Histopathologic findings*** --- On gross examination, the specimen consists of fragments of brown, firm tissue, some of which are partially lined by smooth white rubbery tissue. Microscopic sections reveal a lesion composed of fully differentiated hypertrophied myocytes with enlarged, hyperchromatic pleomorphic nuclei, occasionally with mild vacuolizations, in places variably interspersed among collagenous and scant adipose tissues. Trichrome stain highlighted the interstitial distribution of the fibrosis. A diagnosis of benign tumor of myocyte differentiation consistent with hamartoma of mature cardiac myocytes was made.

***Conclusion*** --- HMCMs are an extremely rare benign cardiac tumor of myocyte differentiation. Natural history seems to include a variety of symptoms including palpitations, exertional light-headedness, dyspnea, chest discomfort, cyanosis or even sudden death, but may present solely as by cyanosis. Surgery is an effective treatment in symptomatic cases of hamartoma of mature cardiac myocytes. To the best of the authors' knowledge this is the first case of hamartoma of mature cardiac myocytes in this institution. ***Phil Heart Center J 2017;22(1):95-99.***

**Key Words: hamartoma of mature cardiac myocytes ■ cardiac hamartoma ■ benign tumor of myocyte differentiation**

Cardiac tumors are rare, but an understanding of their histopathologic classification, clinical associations, and biologic behavior is important in the practice of surgical pathology.[1] Majority of all cardiac tumors are either metastatic to the heart or involve the heart secondarily by direct extension.[1] Primary cardiac tumors are much less common and about 80-90% of primary cardiac tumors are benign.[2] Hamartomas of mature cardiac myocytes are extremely rare with only a few of such tumors have been reported in literature.[3] We describe a 23-year old female who presented with cyanosis. Transesophageal echocardiography revealed a cystic mass in the right ventricular wall that was surgically resected. The histopathologic diagnosis was hamartoma of mature cardiac myocytes. We describe the histopathology, differential diagnosis and clinical presentation of this extremely rare primary cardiac tumor.

## *Case*

The patient was a 23 year-old female who had episodes of cyanosis without associated difficulty of breathing or chest pain. Consultation was done and 2D-echocardiography revealed a right ventricular mass. She was advised intra-operative transesophageal echocardiography (IOTEE) and surgical intervention, hence admitted in our institution. During her hospital stay, chest CT scan was done and revealed a smooth soft tissue maass lesion in the right

*Finalist*, Poster-Case Report Presentation - Original Paper. 24th PHC Annual Research Paper Competition and Poster Presentation held on February 26, 2016 at Philippine Heart Center. Correspondence *to Dr. Randell S. Arias.* Division of Laboratory Medicine. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication**  2017 ISSN 0018-9034

ventricle measuring 3.4 x 3.9 x 3.5 cm *(Figure lA & lB)*. 12-lead ECG revealed sinus rhythm, northwest axis and right ventricular hypertrophy. Transesophageal echocardiography revealed normal right ventricular dimension with normal contractility and a cystic mass with a thick capsule is seen attached from the right ventricular free wall measuring 3.0 x 4.1 cm with an area of 9 $cm^2$ *(Figure 2A & 2B)*. Excision of the mass lesion was done. Intraoperatively, the cystic mass was embedded on the right ventricular free mass and after unroofing of the cyst, there was egress of blood. The specimen was sent for histopathologic examination. The procedure was uneventful and patient was eventually discharged improved.

***Gross, histopathologic and histochemical findings.*** On gross examination, the specimen consists of five (5) fragments of brown, firm tissue, some of which are partially lined by smooth white rubbery tissue altogether measuring 4.0 x 3.8 x 1.3 cm. Due to fragmentation of the submitted specimen, the resection margin cannot be ascertained. The entire specimen is submitted in cassettes Al to A6. Microscopic sections reveal a lesion composed of hypertrophied myocytes, in places variably interspersed among collagenous and scant adipose tissues *(Figure 3A)*. The myocytes are fully differentiated with striations and contain enlarged, hyperchromatic pleomorphic nuclei, occasionally with mild cytoplasmic vacuolations *(Figure 3B)*. Dilated venules, rare thick walled vessels and interstitial fibrosis are likewise noted. The endocardium overlying the muscle fibers exhibits fibrosis with loose distribution of myofibroblasts, myxoid areas and a few calcifications *(Figure 3C, 3D)*. No definite cystic component or epithelial lining cells are identified. Special stain (Masson's trichrome) performed on block AI highlights the distribution of the fibrosis which is predominantly interstitial *(Figure 3E)*.

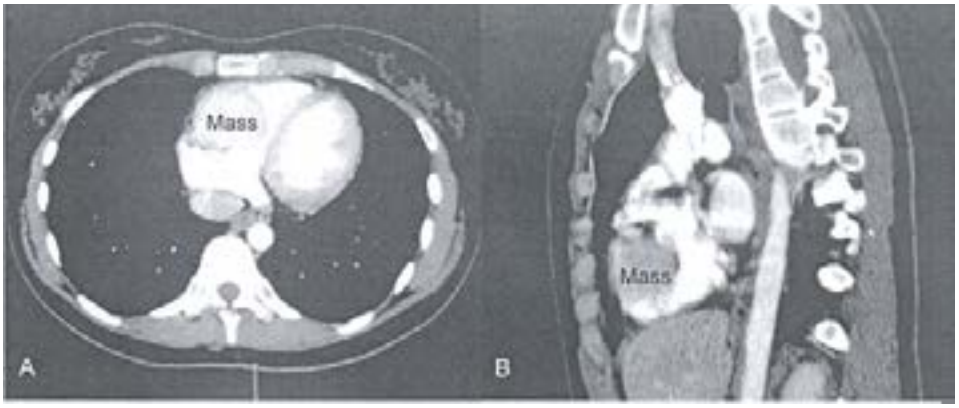


**Figure 1. Chest CT scan**. A fairly defined mass lesion located in the right ventricular region is seen in this CT scan image of axial (A) and lateral (B) views. The mass is isodense to the myocardium.

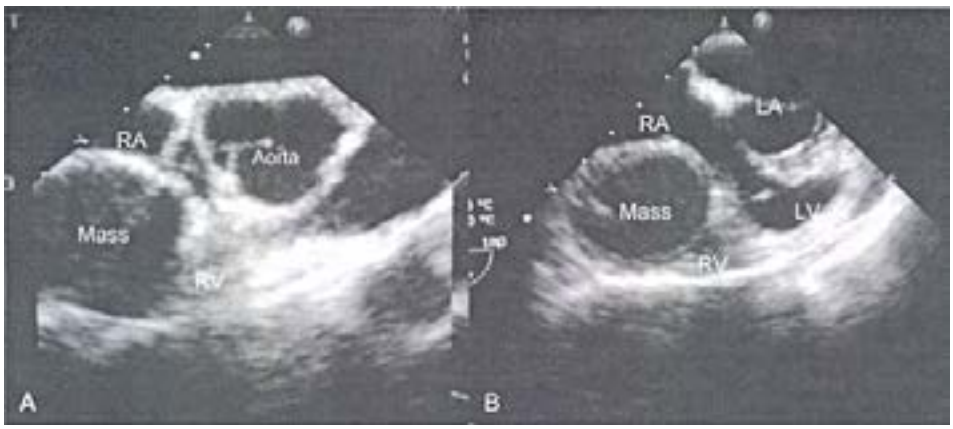


**Figure 2. Transesophageal echocardiography.** Mid-esophageal short axis view/RVOT (A) and mid-esophageal four-chamber (B) views showing a cystic mass with a thick capsule attached to the right ventricular free wall.

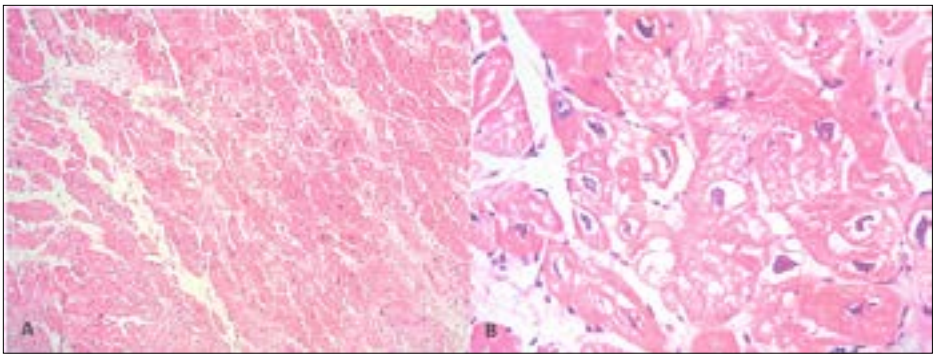


**Figure 3. A.** Microscopic sections reveal a lesion composed of hypertrophied myocytes variably interspersed among collagenous and scant adipose tissues. (H&E IOOX) **B**. The myocytes are fully differentiated with enlarged, hyperchromatic pleomorphic nuclei, occasionally with mild cytoplasmic vacuolations. (H&E 400X)

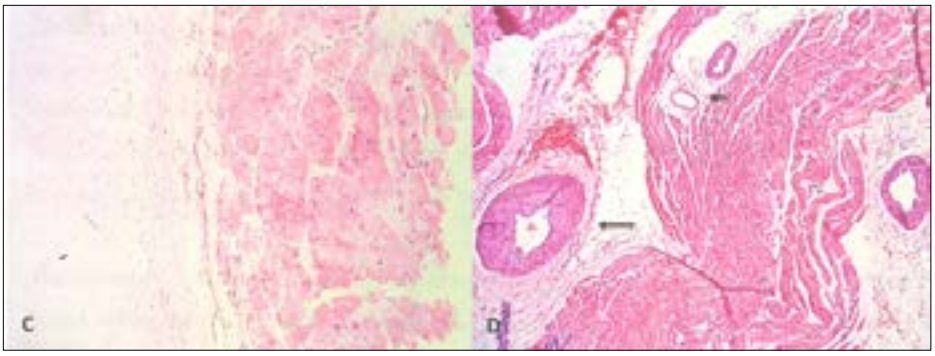


**Figure 3. C.** The endocardium overlying the muscle fibers exhibits fibrosis with loose distribution of myofibroblasts, myxoid areas and a few calcifications (not seen in this micrograph). (H&E IOOX) **D.** Dilated venules (arrowhead), rare thick walled vessels (arrow) and interstitial fibrosis are likewise **n**oted, (H&E lOOX)

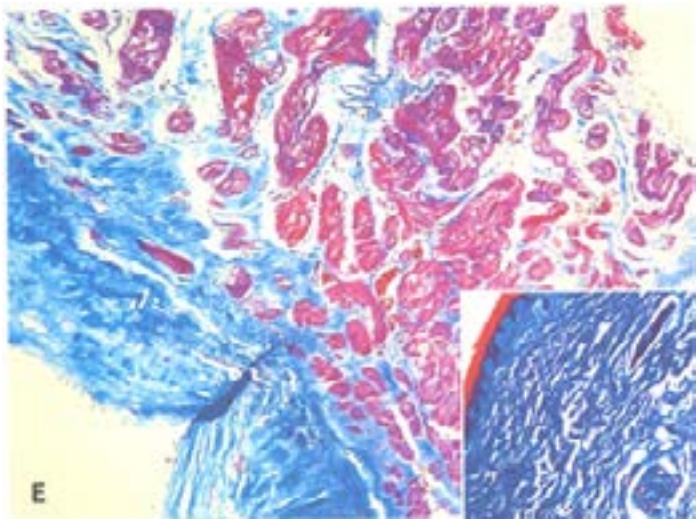


**Figure 3. E.** Special stain (Masson's trichrome) performed on block A1 highlights the distribution of the fibrosis (stained blue) which is predominantly interstitial. Inset: Positive control, skin. (Masson's trichrome (400X)

## DISCUSSION

Hamartoma of mature cardiac myocytes (HMCM) was first described by Tanimura in 1988 and since then very few cases have been reported with mode of diagnosis ranging from biopsy to surgical resection to autopsy.[3,4] Raffa et al, in a literature review of cases of hamartoma of mature cardiac myocytes, a total of only 22 cases from 1988 to 2012 were described, with an addition to the census in 2013 of this rare primary cardiac tumor with preserved contractility.[3] In the Philippines, there has been no reported cases of hamartoma of mature cardiac myocytes.

A hamartoma is defined as a mass of disorganized but mature specialized cells or tissue indigenous to the particular site.[5] In cardiac tumors, the term "hamartoma' has been loosely applied to several cardiac tumors, most commonly histiocytoid cardiomyopathy ("Purkinje cell hamartoma").[6] The term has also been applied to lesions or malformations composed of various cardiac elements, and other tumors composed primarily of a single cell type (e.g, rhabdomyoma).[6] The entity hamartoma of mature cardiac myocytes is used for a distinct tumor in adults, composed of cardiac myocytes.[6] Hamartomas are slow-growing benign tumors that usually do not involve surrounding structures. Their origin is unknown, however congenital anomalous development of embryonic cells seems most likely.[7] Although hamartomas of mature cardiac myocyte is devoid of primitive or aberrant cellular elements, their tissue architecture is abnormal and markedly enlarged myocyte forms can be observed.[8]

Hamartomas of mature cardiac myocytes may be detected at any age, but majority are found before age 20.[9] There is a male to female predominance of 4:1 and they typically are identified clinically with symptoms of palpitations, dyspnea, chest discomfort, exertional lightheadedness, or even sudden death.[9,10] They have also been found incidentally during autopsy in asymptomatic individual.[11] By ultrasound, hamartomas of mature cardiac myocytes will show high echogenecity and appear hypointense on Tl magnetic resonance imaging with only modest gadolinium enhancement.[12] In our case, the patient presented with cyanosis without associated difficulty of breathing or chest pain and the mass was only detected on 2D-echocardiography.

Grossly, HMCMs classically forms bulky intramural ventricular masses that are pale in compared to surrounding normal myocardium and often shows a fibrous texture and sheen.[1] They can resemble areas of old infarction but with increased wall thickness and distortion of surrounding ventricular wall.[1] They are generally circumscribed, but with poorly demarcated borders and range in size from 2 mm to 5 cm in greatest dimension.[6,9] In more than 90% of the time, hamartoma of mature cardiac myocytes occurs in the ventricles, usually the left ventricle, and the reported atrial occurrences have been exclusively right-sided.[9] They can be single or multiple.[11] Microscopically, these tumors are composed of enlarged myocytes with obvious cross striations and contain enlarged, irregular nuclei.[6] They are poorly demarcated and some tumor cells may interdigitate with normal-myocytes at the edge of the tumor.[6] The interstitium shows increased collagen with a few interspersed fat cells may be present.[6]

Hamartoma of mature cardiac myocytes must be differentiated from the more common rhabdomyoma and histiocytoid (oncocytic) cardiomyopathy, both of which have been referred to as "cardiac hamartoma".[13] Rhabdomyomas, often seen in the setting of tuberous sclerosis, may be multiple and are composed of mature cardiac tissue, but show extensive myocyte vacuolations, giving the characteristic appearance of 'spider cells' on histology.[13] Histiocytoid (oncocytic) cardiomyopathy is characterized by well-defined collections of myocyte showing pale granular material filling the sarcoplasm, presenting predominantly in pediatric age groups with presenting symptoms of tachyarrhythmia or sudden death and tends to regress with time.[13] Hypertrophic cardiomyopathy may share some histologic findings with a hamartoma of mature cardiac myocytes although these two can be distinguished by lack of increased vascularity, more diffuse involvement of the myocardium and characteristic septal localization of hypertrophic cardiomyopathy.[13]

Hamartoma of mature cardiac myocytes are benign neoplasms and can be excised, resulting in cure.[6] In a review conducted by Raffa, et al, surgery seems to be an effective treatment for the relief of patients with hamartoma of mature cardiac myocytes.[3] Likewise, all patients who underwent surgical excision were alive at a median follow-up of 18 months with no recurrences.[3] The patient in our case continues to be asymptomatic at four month follow-up.

## CONCLUSION

HMCMs are an extremely rare benign cardiac tumor of myocyte differentiation. Natural history seems to include a variety of symptoms including palpitations, exertional lightheadedness, dyspnea, chest discomfort, cyanosis or even sudden death. Surgery is an effective treatment in symptomatic cases of hamartoma of mature cardiac myocytes. To the best of the authors' knowledge this is the first case of hamartoma of mature cardiac myocytes in this institution.

## REFERENCES


1. Miller DV. Cardiac tumors. In: Glodblum JR, Winters GL, editors. Current concepts in cardiovascular pathology. Surgical pathology clinics. Philadelphia: WB Saunders Company, 2012; 5(2): 470-471.
2. Burke A, Virmani R. Classification and incidence of cardiac tumors. In: Burke A, Virmani R, editors. Tumors of the heart and great vessels. Washington, DC: Armed Forces Institute of Pathology; 1996, p.1-12.
3. Raffa GM, Malvindi PG, Settepani F, Melotti F, Monti L, Spaggiari P, et al. Hamartoma of mature cardiac myocytes in adults and young: case report and literature review. Int J Cardiol. 2013 Feb 20;163(2):e28-30.
4. Tanimura A, Kato M, Morimatsu M. Cardiac hamartoma. A case report. Acta Pathol Jpn. 1988 Nov; 38 (11):1481-4.
5. Kumar V, Abbas A, Fausto, N. Robbins and Cotran pathologic basis of disease. 7th ed. Philadelphia: Elsevier Saunders, 2005, p272.
6. Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC. Pathology & genetics of tumors of the lung, pleura, thymus and heart. Lyon, France: IARC Press, 2004, 251-258.
7. Menon SC, Miller DV, Cabalka AK, Hagler DJ. Hamartomas of mature cardiac myocytes. Eur J Echocardiogr. 2008 Nov;9(6):835-9.
8. Burke A, Virmani R. Tumors of the heart and great vessels. Atlas oftumor pathology. Series 3. Fascicle 16. Washington, DC: Armed Forces Institute of Pathology; 1996. p231.
9. Miller DV, Tazelaar HD. Cardiovascular pseudoneoplasms. Arch Pathol Lab Med. 2010 Mar;134(3):362-8. doi: 10.1043/1543-2165-134.3.362.
10. Fealey ME, Edwards WD, Miller DV, Menon SC, Dearani JA. Hamartomas of mature cardiac myocytes: report of 7 new cases and review of literature. Hum Pathol. 2008 Jul;39(7):1064-71.
11. Burke AP, Ribe JK, Bajaj AK, Edwards WD, Farb A, Virmani R. Hamartoma of mature cardiac myocytes. Hum Pathol. 1998 Sep;29(9):904-9.
12. Brunner-La Rocca HP, Vogt PR, Burke AP, Schneider J, Jenni R, Turina MI. A primary cardiac sarcoma with unusual histology and clinical course. Ann Thorac Surg. 2001 May;71(5):1675-7.
13. Virmani R, Burke A, Farb A, Atkinson J. Cardiovascular pathology. In major problems in pathology. 2nd ed. Philadelphia, WD Saunders Company, 2001, 40:424-68.

# *Information for Authors*

## *EDITORIAL POLICY*

### Scope of the Journal

The Philippine Heart Center Journal is devoted to the publication of original articles related to cardiovascular diseases and allied fields. The scope of articles includes original publications, editorials, current reviews, meta-analysis, critically appraisal (CATs) and case reports.

### General Policies

Contributions are reviewed by a group of cardiologists, cardiovascular surgeons and physicians of allied specialties with recognized academic and clinical expertise. Each manuscript is evaluated by at least two reviewers and may be edited for scientific accuracy and clarity. Statements and opinions expressed in articles and communications are those of the author(s) and do not necessarily reflect those of the editor or publisher. Neither the publisher nor the editor guarantee any product or service advertised in the publication. No part of the articles and communications published in the journal may be reproduced without the written permission of the publisher.

### Copyright Release and Authorship Responsibilities

All manuscripts must be accompanied by the following statements signed by all authors.

1. The undersigned author(s) transfer(s), assign(s) or otherwise convey(s) all copyright ownership of the manuscript [title of article] to the Philippine Heart Center Journal in the event the work is published. The undersigned author(s) attest(s) that the article is original in form and substance and is not under consideration by another journal.

2. The undersigned author(s) certifies (certify) that I (we) have participated to a sufficient degree in the design of this work, analysis of data, and the writing of the manuscript, and that I (we) am (are) taking responsibility for its contents.

### Conflict of Interest Disclosure Statement

All authors are requested to disclose any relationship with an individual or organization with direct financial interest in the subject matter or materials discussed in the manuscript, because a perceived or real conflict of interest may otherwise arise. Disclosure of such relationship will be held in confidence during the review process of the work if accepted for publication. Disclosure of financial interest will appear as an annotation to the published manuscript.

### MANUSCRIPT PREPARATION AND SUBMISSION

Manuscripts and all communications to the Editor should be addressed to:

***Ma. Belen O. Carisma, MD***
Editor-in-Chief
Philippine Heart Center Journal
6th Floor, Medical Arts Building
Philippine Heart Center
East Avenue, Quezon City, Philippines

Submitting the manuscript in the correct format will expedite the reviewing process and obviate undue delay in publication. Please adhere to the following requirements:

### General Guidelines

One original and two duplicate manuscripts and three full sets of tables and labelled illustrations should be submitted to the above address. The Editorial Office will be responsible for the proper handling of manuscripts so that confidentiality is preserved. Manuscripts and figures will be returned only upon the written request of the authors. Please provide a self-addressed stamped envelope for this purpose. Manuscripts should be typed double-spaced throughout (including title page, abstract, text, references, tables and legends) one side only on 22 x 28 cm (8 1/2 x 11 inches) opaque bond paper with 3 cm (1 1/4 inch) margins all around. The manuscript should be arranged as follows:

1. Title page
2. Abstract page
3. Text
4. Acknowledgement (if any)
5. References
6. Figures and legends
7. Tables

Number the pages consecutively on the upper right corner beginning with the title page.

### Title Page

The title page must contain:
1. Title of the article
2. Names of authors plus highest academic degree of each
3. Each author's official academic and/or clinical title and institutional affiliation
4. Name and address of the institution/s where the research work was conducted
5. Name, address and telephone/fax number of the author to whom correspondence should be sent

**Abstract**

All original articles must contain an abstract of not more than 250 words. The abstract should include statements on the background, objectives, method of study, results and conclusion. Abstracts for case reports should be shorter (75-80 words). Include several (3-7) keywords to assist in cross-indexing the article.

**Text**

Generally, the text should be organized as follows:
a. Introduction
b. Materials and Methods
c. Results
d. Discussion or comments
e. Conclusion

The ***Introduction*** should describe the purpose of the study and its relation to previous work in the field. It should not include an extensive literature review. The description of the ***Methods*** should be concise, but sufficiently detailed to permit repetition by other investigators. ***Results*** should present positive and relevant negative findings of the study, supported when necessary by reference to tables and figures. The ***Discussion*** should interpret the results of the study, with emphasis on their relation to the original hypothesis and to previous studies.

Abbreviations or acronyms such as CAD, AMI, LVH may be used after the terms are spelled out once each in the abstract and text followed by the abbreviation or acronym in parentheses. All measurements should use the International System (SI) of units. Alternative units may be indicated in parentheses if necessary.

Manuscripts that describe studies on humans must indicate that the study was approved by an institutional review committee and that subjects gave their written, informed consent. Studies on both humans and animals must indicate that the procedures followed were in accordance with the institutional guidelines.

**References**

References are to be cited consecutively in the text with numbers enclosed in parentheses. At the end of each article, references should be listed consecutively in the numerical order in which they were cited in the text. The form of references should be as follows

a. For Journal References: Surname and initial of author(s), title of article, name of journal, volume number, first page or inclusive pages. If there are more than three authors, list the first three authors and add et al.

*Braunwald E and Rutherford JD. Reversible ischemic left ventricular dysfunction: evidence for the "hibernating myocardium." J Am Coll Cardiol 1986;8:1467-1470.*

*Dilsizian V, Rocco TP, Freedman NM et al. Enchanted detection of ischemic but viable myocardium by the reinjection of thallium after stress -redistribution imaging. N Engl J Med 1990;323:141-146.*

b. For Books: Surname and initial of author(s), title and subtitle, editor, city, publishing house page, year as specific reference.

*Dillman WH. The Cardiovascular System in Thyrotoxicosis. In Braverman LE and Utiger RD, eds. The Thyroid - A fundamental and Clinical Text. 6th ed. Philadelphia: JB Lippincott Co; 1991,759-770.*

**Figures**

Illustrations should complement the text. The illustrations should be sharp and professionally rendered. Letters, numbers and symbols must be clear and of sufficient size to retain legibility after reduction. Glossy photographs of the original artwork, between 3-1/2 x 5 in. and 8 x 10 in. in size, should be submitted. Each illustration should be numbered and cited consecutively using Arabic numerals. Colored photographs will be considered for publication.

**Legends**

Caption for the figures must be typed, double-spaced, and must not appear in the figure. For photomicrographs, the legend should include the original magnification and the stain used.

**Tables**

Tables should be self-explanatory and should supplement, not duplicate the text. They should be numbered consecutively using Roman numerals.

**REPRINTS**

Authors will receive ten (10) copies of reprints free of charge. Individual reprints of article must be obtained from the author. The corresponding author will receive a price schedule and order form at the time of publication. Reprints in quantity must be ordered from the publisher with the author's consent.