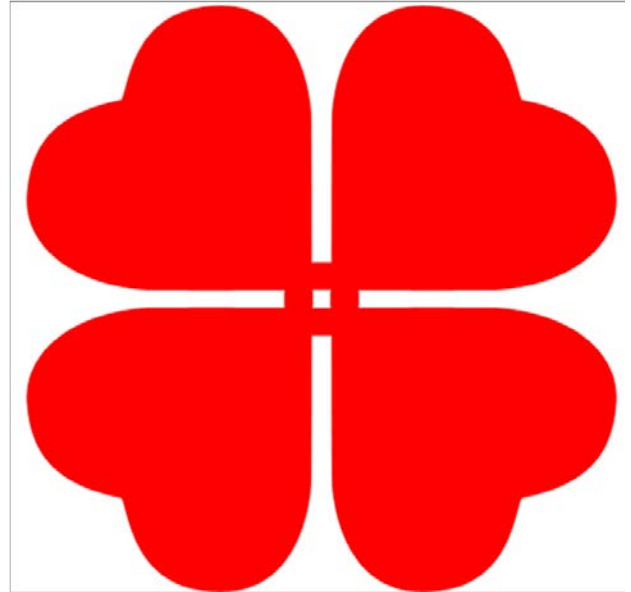


Philippine Heart Center Journal



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“Lessons from Galapagos”

Gilbert C. Vilela, MD

Change, although painful to most, is always good. Constant change is an essential part of nature. It is the foundation of moment to moment evolution. It is the gateway to progress. It defines life, and is the secret of existence. Change is the generator of evolution and dictates survival of the specie.

Someone said that most things we learned from the school were wrong. Contextually, probably those things were correct then. As time ages us, we usually know better. We know better because of experience and studying the facts. In this context, research shapes our experienced then shapes our present truths.

Ethics and the need to serve to the utmost usually drive medical practice. The papers of Benjamin C. Quito et al, Philip C. Ines et al, Ed D. Gabitoya et al, Bernadette B. Valdez et al, are fine examples. You'll read that there is something better than what we used to do. For decades, our Percutaneous Coronary Interventions were done through Trans-Femoral Approach. The paper of Philip Ines et al, says that Trans-Radial Approach is better, outcomes-wise and cost-wise. Bernadette Valdez et al, showed in their paper that Trans-catheter Device Occlusion of Isolated Ventricular Septal Defect is a finer alternative as compared to surgical closure. Helenne Brown et al, revealed in their paper that the newer risk scoring system for predicting adverse cardiovascular outcomes after PCI is better than the SYNTAX Score. These few examples written in the pages of this journal declare that research is driving the improvement of our delivery of health solutions. The contents of this journal disclose that there is something better than what we used to do and there is evidence for it.

This journal, the Philippine Heart Center, symbolizes the dreams and aspirations of the men and women who compose the institution. This journal is the proof that research is the driver to better management. Evidence-based medicine is the foundation of ethical and outstanding cardiovascular care.

I hope you enjoy this issue.

Comparison of the New Mayo Clinic Risk Scores and Clinical SYNTAX Score in Predicting Adverse Cardiovascular Outcomes Following Percutaneous Coronary Intervention at the Philippine Heart Center

Helenne Joie M. Brown, MD; James O. Ho Khe Sui, MD; Catherine C. Tan, MD; Vergel A. Ouiogue, MD

Background --- Risk stratification of patients who will undergo percutaneous coronary intervention (PCI) can help physicians, patients and their families understand the risks of the procedure, thus providing an objective basis for decision-making. This study was done to compare the prognostic value of the Clinical SYNTAX Score (CSS) and New Mayo Clinic Risk Scores (NMCRS) for in-hospital and 30-day mortality and major adverse cardiovascular and cerebrovascular events (MACCE) following PCI.

Method --- This is a prospective cohort study. The NMCRS for Predicting Mortality, NMCRS for Predicting MACE and CSS of all patients who underwent PCI at the Philippine Heart Center from April 1, 2011 to September 30, 2011 were computed. Patients were followed up for in-hospital and 30-day mortality and major adverse cardiovascular and cerebrovascular events (MACCE) following PCI.

Results --- Of the 482 patients included in the study, 22 (4.6%) died while 37 (7.7%) had the composite end-point (mortality, MI, emergency CABG, CVA) during hospitalization. Thirty days after PCI, 9 (2.0%) died while 19 (3.9%) had the composite endpoint. The prognostic value of NMCRS for predicting mortality, NMCRS for predicting MACE and CSS for in-hospital mortality, as measured by the c-statistic, is 0.827, 0.813, and 0.816 ($p < 0.05$ for all), respectively and for in-hospital composite endpoints is 0.791, 0.751, and 0.755 ($p < 0.05$ for all), respectively. Thirty days after PCI, the prognostic value of the NMCRS for predicting mortality, NMCRS for predicting MACE and CSS, as measured by c-statistic is 0.751 ($p < 0.05$), 0.760 ($p < 0.05$), and 0.651 ($p = 0.121$), respectively and for composite endpoints is 0.736 ($p < 0.05$), 0.763 ($p < 0.05$), and 0.621 ($p = 0.10$), respectively.

Conclusion --- The NMCRS for predicting mortality has better prognostic utility for in-hospital mortality and composite end-points while the NMCRS for predicting MACE better predicts 30-day mortality and composite endpoints as compared to the CSS. *Phil Heart Center J 2016;21(1):1-9.*

Key Words: New Mayo Clinic Risk Scores ■ Clinical SYNTAX Score
■ Percutaneous Coronary Intervention

Percutaneous coronary intervention (PCI) is the most commonly performed procedure for myocardial revascularization in patients with ischemic heart disease.¹ In the Philippine Heart Center alone, a total of 883 patients underwent PCI in the year 2010.² In order to optimize care of patients undergoing the procedure, risk assessment is an invaluable tool. Moreover, risk stratification ensures quality

control and cost effectiveness while allowing assessment of performance of interventional cardiologists and cardiac catheterization laboratories.³

Several risk-prediction models have been developed to help health care professionals, patients and their families comprehend the attendant risks of PCI, and thus provide an objective

basis for decision-making. These risk stratification tools or risk scores have assisted cardiologists in decision making and in accurately showing the periprocedural risk from PCI to the patient.⁴⁻⁹

In this era where the role of PCI has expanded to specific groups of patients with complex coronary artery disease^{3,10-14} newer risk scores have been developed for risk stratification in PCI.¹¹⁻¹⁴ One of these is the SYNTAX score. It is a lesion-based scoring system derived from the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial, a large randomized clinical trial which compared the use of drug-eluting stents and coronary artery bypass graft (CABG) surgery in patients with severe coronary artery disease (CAD). The use of purely angiographic variables limits the SYNTAX score in its ability to predict mortality and adverse outcomes when compared with scoring systems using clinical characteristics.⁶ The Clinical SYNTAX Score (CSS) was therefore developed to improve the ability of the SYNTAX Score to predict mortality and the risk of myocardial infarction in patients with complex CAD undergoing PCI by multiplying this score with the modified ACEF score, a simple scoring system which includes three clinical variables known to affect the risk of myocardial revascularization: age, creatinine clearance and ejection fraction.¹⁵ The CSS was shown to have greater prognostic value in predicting long-term major adverse cardiovascular and cerebrovascular events (MACCE) and mortality as compared to the SYNTAX and ACEF scores alone.¹² In the Philippine Heart Center experience, the SYNTAX score was not shown to have a significant prognostic value for mortality and MACE among patients with triple vessel CAD undergoing revascularization. However, this may be due to the limited number of subjects and short duration of follow-up.¹⁶

Another validated risk score for PCI which comprises clinical and angiographic variables is the Mayo Clinic Risk Score which has also been shown to predict mortality, MI, stroke and the need for emergency CABG surgery. It includes five clinical variables (age, congestive heart failure (CHF), New York Heart Association (NYHA) functional class $\geq$ III, urgent/emergent

PCI, chronic renal disease, and preprocedural cardiogenic shock) and three angiographic characteristics (left main stenosis $\geq$ 70% multi-vessel disease, i.e. $>$ 70% in more than one major epicardial coronary artery or in one of their major branches, and presence of thrombus in any lesion).⁶ However, because the need for angiographic variables limits the expediency of this risk model, two new clinically practical pre-PCI risk models based solely on baseline clinical and non-invasive assessments were developed from the Mayo Clinic angioplasty registry. The New Mayo Clinic Risk Scores (NMCRS) consist of two models, one for predicting procedural death and the other for predicting in-hospital MACE such as myocardial infarction (MI), stroke and emergent CABG. Points are assigned depending on the following clinical variables: age, creatinine (mg/dL), left ventricular ejection fraction [LVEF] (%), preprocedural shock, MI $\leq$ 24 hours, CHF on presentation (if without acute MI or shock) and peripheral artery disease (PAD). Despite exclusion of angiographic variables, the NMCRS discriminate well for both procedural death and MACE, emphasizing the importance of clinical variables in the determination of PCI risk.⁴

This study aims to determine which risk score has a better discriminative ability in predicting in-hospital and 30-day mortality and MACCE, one which includes both angiographic and clinical variables, i.e. the CSS or one which includes clinical variables alone thus increasing expediency of its use, i.e. the NMCRS. To the best of our knowledge, this is the first study to compare these two risk scores. Furthermore, this is the first study to determine the prognostic utility of both risk scores for adverse outcomes in the Filipino population.

METHODS

The study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki. Prior to study initiation, there was a review and approval of the study protocol and informed consent. Subsequent amendments were approved by the Philippine Heart Center Institutional Ethics Review Board (PHC-IERB). Before a subject's participation,

a written informed consent was obtained by the investigator after adequate explanation of the aims, anticipated benefits and potential risks of the study. The informed consent was signed and personally dated by the subject and the person who conducted the informed consent discussion.

This is a prospective cohort study, included were patients who underwent PCI at the Philippine Heart Center during the period of April 1, 2011 to September 30, 2011, age ≥ 18 years. Excluded in the study were patients with no baseline systolic function determination.

Sample Size. Sample size computed was $n \geq 460$ based on 95% confidence level and 80% power to detect statistical significance at assumed difference in area under the curve (AUC) of 10%. The assumption was based on the paper of Garg et.al¹² which presented an AUC of 0.89 for MACE.

Study Maneuver. All patients who underwent PCI at the Philippine Heart Center during the period of April 1, 2011 to September 30, 2011 were enrolled in the study after giving written informed consent. Cardiovascular history and risk factors were obtained. Before they underwent PCI, their coronary angiograms were reviewed by two (2) interventional cardiologists and this investigator. Prior to the PCI, points were assigned according to the NMCRS (4) variables present in the study participants, as follows:

- a. age in years
- b. serum creatinine (mg/dL)
- c. LVEF in %
- d. preprocedural shock
- e. MI ≤ 24 hours
- f. CHF on presentation (if the patient does not present with acute MI or shock)
- g. peripheral artery disease (PAD) - defined as the presence of claudication, history of peripheral vascular surgery, presence of abdominal aortic aneurysm, disease of the cranial and extracranial arteries (history of stroke or transient ischemic attack, history of carotid surgery, or presence of carotid disease documented with ultrasonography, angiography or carotid bruit)⁴

The total score (range 0-13+) was calculated separately for prediction of mortality and

following categories of risk for prediction of death: very low (0-5 points), low (6-7) moderate (8-10 points), high (11-12), and very high (13+). They were also stratified into the following categories of risk for prediction of MACCE: very low (0-2 points), low (3-5) moderate (6-9 points), high (10-13), and very high (14+).

The CSS of the study participants were also computed using the formula $CSS = [SYNTAX \text{ Score}] \times [\text{modified ACEF score}]$.¹² The SYNTAX score was calculated first by scoring all coronary lesions with a diameter stenosis $\geq 50\%$, in vessels ≥ 1.5 mm using the SYNTAX Score algorithm¹³ by two invasive cardiologists and this investigator. The modified ACEF score (ACEFCrCI) was also then computed using the formula $\text{age/ejection fraction} + 1$ point for every 10 ml/min reduction in creatinine clearance below 60 ml/min per 1.73 m^2 (up to a maximum of 6 points). The LVEF used was the value before PCI. In case multiple values were available, the lowest recorded value was used. Creatinine clearance was calculated using the Cockcroft-Gault formula¹⁹ using the patient's age, weight and serum creatinine level before the index PCI.¹² The study participants were then stratified into the following risk categories based on their CSS: low (CSS < 15.6), moderate (CSS > 15.6 but < 27.5) and high (CSS > 27.5).

The study participants were followed up after 30 days from the time of index PCI via standardized telephone/cellular phone calls and/or outpatient clinic follow-up and/or mail/email. Development of MACCE (death, MI, emergency CABG or stroke) was noted. For those who developed MI during the follow-up period and were re-admitted at the Philippine Heart Center, the investigator checked the patient's medical records for electrocardiographic changes consistent with infarction, and biomarker evidence of acute ischemic injury (elevated troponin I and/or CKMB). For those who developed MI during the follow-up period and were admitted in institutions other than the Philippine Heart Center, the researcher requested the study participant or a relative to come to our institution with a copy of his/her 12-leads electrocardiogram and cardiac biomarker results (troponin and/or CKMB) when the participant was already clinically stable.

Description of Outcomes. Outcomes include all-cause mortality and MACCE during hospital admission and 30 days after PCI, MACCE include MI (ST elevation or non-ST elevation), emergency CABG and stroke.

Data Analysis. Continuous variables were presented as mean $\pm$ SD or median (interquartile range). Categorical variables were presented as frequencies and percentages. The discriminatory abilities of the NMCRS and CSS for in-hospital and 30-day mortality and development of MACCE after PCI were measured by c-statistics, and compared using receiver-operating characteristic curves.

RESULTS

A total of 482 patients admitted for PCI at the Philippine Heart Center from April 1, 2011 to September 30, 2011 were included in the study.

Baseline Characteristics. Baseline characteristics of the study population are shown in Table 1. The mean age of the patients was 59.8 ± 11.4 years. Of the study subjects, 115 (23.9%) were female, 98 (20.3%) presented with MI within 24 hours of the PCI, and 176 (36.5%) presented with unstable angina. At the time of the procedure, 27 (5.6%) were in cardiogenic shock. Of the 64 (13.3%) patients who presented with CHF during the time of the procedure, 22 (4.6%) were in NYHA Class III or IV. In 82 (17%) patients, the PCI was done on a non-elective basis. The prevalence of hypertension was 77.4%; diabetes mellitus, 36.3%; dyslipidemia, 77.4%; PAD, 4.8% and smoking, 52.5%. Forty (8.3%) had a previous PCI while 29 (6.0%) had a previous CABG. One hundred thirty-eight (28.6%) reported a history of MI, 20 (4.1%) a history of CVA, and 86 (17.8%) a family history of ischemic heart disease. The mean serum creatinine was 1.2 ± 0.9 mg/dl; the mean creatinine clearance was 74.1 ± 29.6 ml/min, The median LVEF was $55.3 \pm 9.4\%$. Thirty-nine (8.1%) patients had unprotected left main coronary artery disease.

In-hospital and 30-day Outcomes. Table 2 outlines the in-hospital and 30-day complications. Of the in-hospital complications, there were 22

deaths (4.6%), 5 MIs (1.0%), 9 CVAs (1.9%) and one patient (0.2%) was referred for emergency CABG. At 30 days' follow-up, there were 9 deaths (2.0%), 9 MIs (2.0%) and 1 CVA (0.2%). No patient was referred for emergency CABG.

NMCRS for Predicting Mortality, NMCRS for Predicting MACE versus CSS. The ROC curve for in-hospital mortality is shown in Figure 1. The respective c-statistics for the NMCRS for predicting mortality, NMCRS for predicting MACE and CSS were 0.827, 0.813, and 0.816 ($p < 0.05$ for all), indicating that all three risk scoring systems are predictive of in-hospital mortality. The NMCRS for predicting mortality, having the largest AUC ($p = 0.000$) appears to be most predictive of in-hospital mortality.

Figure 1 shows ROC Curve for In-hospital Mortality for the New Mayo Clinic Risk Score (NMCRS) for Predicting Mortality, the NMCRS for Predicting MACE and the Clinical Syntax Score (CSS).

Figure 2 shows the ROC curve for in-hospital MI. The respective C-statistics for the NMCRS for predicting mortality, NMCRS for predicting MACE and CSS were 0.620 ($p = 0.364$), 0.499 ($p = 0.750$), and 0.656 ($p = 0.076$). The largest AUC being for the CSS suggests that this may be more predictive of in-hospital MI as compared to the NMCRS. However, all three risk scores did not show statistically significant correlation with in-hospital MI ($p > 0.05$).

Figure 3 depicts the ROC curve for in-hospital CVA. The respective c-statistics for the NMCRS for predicting mortality, NMCRS for predicting MACE and CSS were 0.612 ($p < 0.05$), 0.565 ($p < 0.05$), and 0.626 ($p = 0.196$). The NMCRS for predicting mortality with the largest AUC and with statistical significance ($p = 0.001$) appears to be most predictive of in-hospital CVA.

The ROC curve for 30-day mortality is shown in Figure 4. The respective C-statistics for the NMCRS for predicting mortality, NMCRS for predicting MACE and CSS were 0.751 ($p < 0.05$), 0.760 ($p < 0.05$), and 0.651 ($p = 0.121$), suggesting that the NMCRS for predicting MACE, with the largest AUC, is most predictive of 30-day mortality.

Figure 5 shows the ROC curve for 30-day MI. The respective c-statistics for the NMCRS for predicting mortality, NMCRS for predicting MACE and CSS were 0.751 ($p < 0.05$), 0.760 ($p < 0.05$), and 0.651 ($p = 0.121$), suggesting that the NMCRS for predicting MACE, having the largest AUC, is most predictive of 30-day MI.

ROC curves for patients sent for emergency CABG surgery during in-hospital admission as well as 30-day CVA could not be generated due to a small number of these outcomes. ROC curves for patients sent for emergency CABG surgery during 30-day follow-up likewise could not be generated because no such outcome was reported.

Figure 6 depicts the ROC curve for composite endpoints (all-cause mortality, MI, emergency CABG and CVA) during in-hospital admission for PCI. The respective c-statistics for the NMCRS for predicting mortality, NMCRS for predicting MACE and CSS were 0.791, 0.751, and 0.755 ($p < 0.05$ for all), indicating that all three risk scoring systems are predictive of in-hospital composite MACCE. The NMCRS for predicting mortality, having the largest AUC ($p = 0.000$) appears to be most predictive of in-hospital composite MACCE.

Figure 7 shows the ROC curve for composite endpoints (all-cause mortality, MI, emergency CABG and CVA) 30 days after PCI. The respective c-statistics for the NMCRS for predicting mortality, NMCRS for predicting MACE and CSS were 0.736 ($p < 0.05$), 0.763 ($p < 0.05$), and 0.621 ($p = 0.10$). The NMCRS for predicting MACE, having the largest AUC ($p = 0.000$) appears to be most predictive of 30-day composite MACCE.

Figure 8 shows the ROC curve for cumulative in-hospital and 30-day composite endpoints (all-cause mortality, MI, emergency CABG and CVA). The respective c-statistics for the NMCRS for predicting mortality, NMCRS for predicting MACE and CSS were 0.792, 0.782, and 0.730 ($p < 0.05$ for all). The NMCRS for predicting mortality, having the largest AUC ($p = 0.000$) appears to be most predictive of cumulative composite endpoints during in-hospital admission for PCI and at 30 days follow-up.

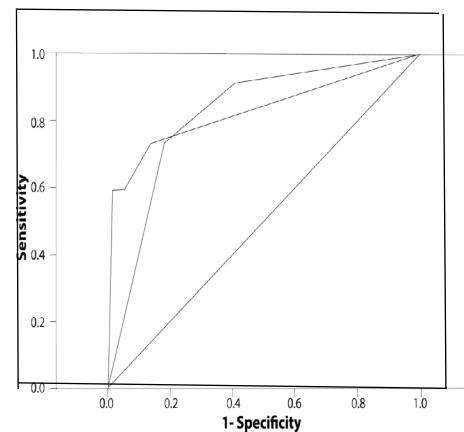


Figure 1. Comparison of Area Under the Curve (AUC) of New Mayo Clinic Risk Score (NMCRS) for Mortality, NMCRS for MACE and Clinical Syntax Score (CSS) for In-Hospital Mortality

Risk Score	Area Under the Curve (95% CI)	P-value
NMCRS for Mortality	0.827 (0.712-0.942)	0.000
NMCRS for MACE	0.813 (0.697-0.928)	0.000
CSS	0.816 (0.732-0.900)	0.000

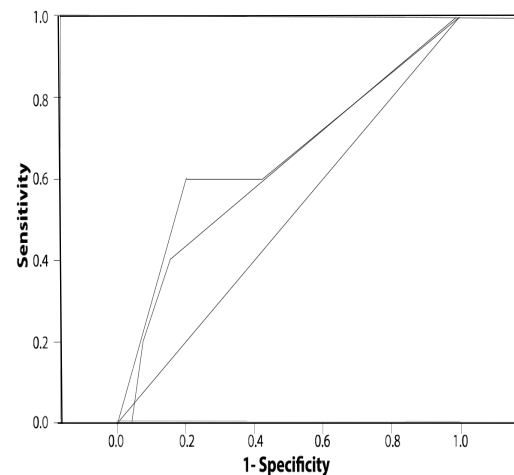


Figure 2. Comparison of Area Under the Curve (AUC) of New Mayo Clinic Risk Score (NMCRS) for Mortality, NMCRS for MACE and Clinical Syntax Score (CSS) for In-Hospital Myocardial Infarction

Risk Score	Area Under the Curve (95% CI)	P-value
NMCRS for Mortality	0.620 (0.353-0.888)	0.364
NMCRS for MACE	0.499 (0.233-0.765)	0.750
CSS	0.656 (0.374-0.937)	0.076

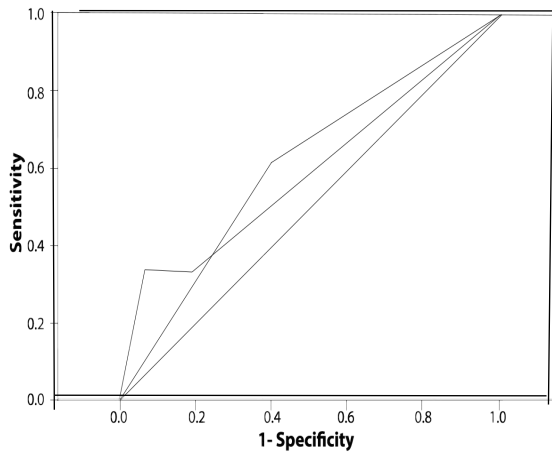


Figure 3. Comparison of Area Under the Curve (AUC) of New Mayo Clinic Risk Score (NMCRS) for Mortality, NMCRS for MACE and Clinical Syntax Score (CSS) for In-Hospital Stroke

Risk Score	Area Under the Curve (95% CI)	P-value
NMCRS for Mortality	0.612 (0.396-0.828)	0.001
NMCRS for MACE	0.565 (0.337-0.794)	0.001
CSS	0.626 (0.445-0.807)	0.196

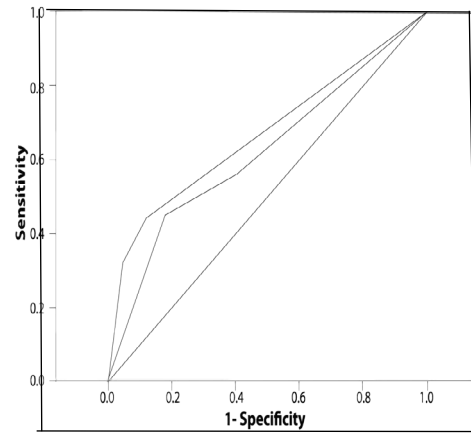


Figure 5. Comparison of Area Under the Curve (AUC) of New Mayo Clinic Risk Score (NMCRS) for Mortality, NMCRS for MACE and Clinical Syntax Score (CSS) for 30-day Myocardial Infarction

Risk Score	Area Under the Curve (95% CI)	P-value
NMCRS for Mortality	0.751 (0.578-0.925)	0.010
NMCRS for MACE	0.760 (0.614-0.906)	0.008
CSS	0.651 (0.433-0.869)	0.121

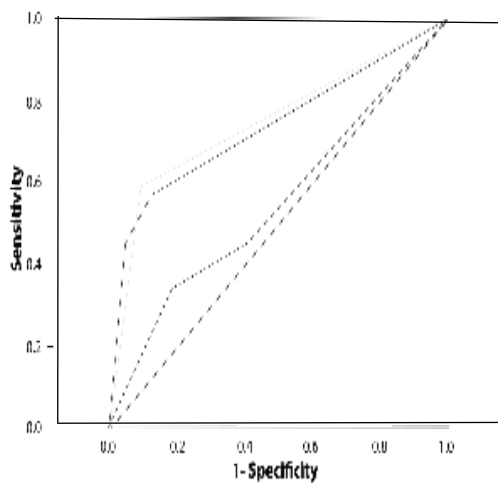


Figure 4. Comparison of Area Under the Curve (AUC) of New Mayo Clinic Risk Score (NMCRS) for Mortality, NMCRS for MACE and Clinical Syntax Score (CSS) for 30-day mortality

Risk Score	Area Under the Curve (95% CI)	P-value
NMCRS for Mortality	0.729 (0.527-0.931)	0.019
NMCRS for MACE	0.763 (0.580-0.946)	0.007
CSS	0.549 (0.342-0.755)	0.616

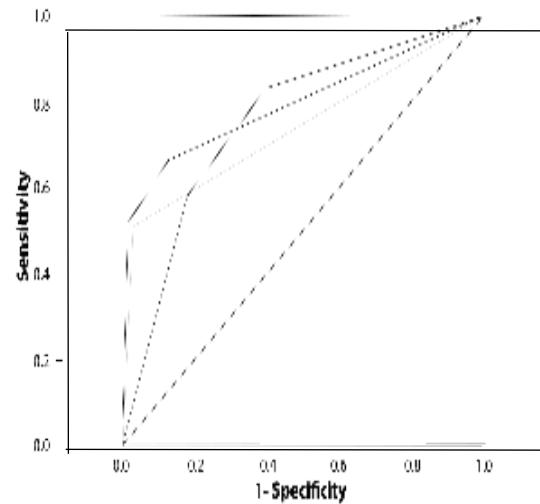


Figure 6. Comparison of Area Under the Curve (AUC) of New Mayo Clinic Risk Score (NMCRS) for Mortality, NMCRS for MACE and Clinical Syntax Score (CSS) for In-Hospital MACE

Risk Score	Area Under the Curve (95% CI)	P-value
NMCRS for Mortality	0.791 (0.683-0.900)	0.000
NMCRS for MACE	0.751 (0.636-0.865)	0.000
CSS	0.755 (0.665-0.845)	0.000

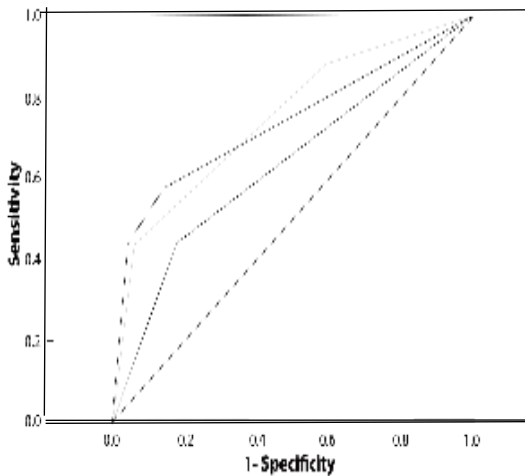


Figure 7. Comparison of Area Under the Curve (AUC) of New Mayo Clinic Risk Score (NMCRS) for Mortality, NMCRS for MACE and Clinical Syntax Score (CSS) for In-Hospital MACCE

Risk Score	Area Under the Curve (95% CI)	P-value
NMCRS for Mortality	0.736 (0.584-0.888)	0.001
NMCRS for MACE	0.763 (0.634-0.892)	0.000
CSS	(0.621 (0.466-0.776)	0.100

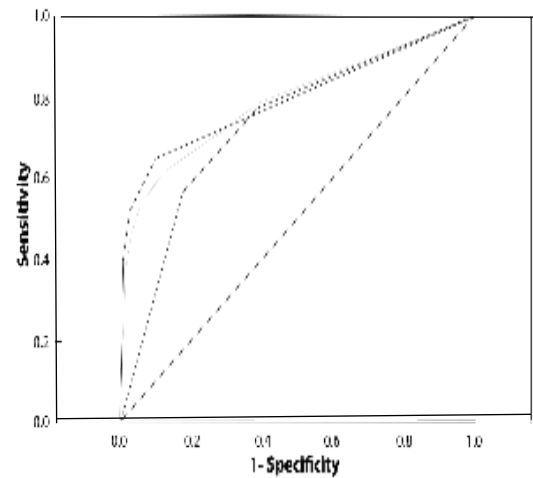


Figure 8. Comparison of Area Under the Curve (AUC) of New Mayo Clinic Risk Score (NMCRS) for Mortality, NMCRS for MACE and Clinical Syntax Score (CSS) for Cumulative In-Hospital and 30-day MACCE

Risk Score	Area Under the Curve (95% CI)	P-value
NMCRS for Mortality	0.792 (0.703-0.881)	0.000
NMCRS for MACE	0.782 (0.697-0.868)	0.000
CSS	(0.730 (0.468-0.813)	0.100

DISCUSSION

Assessment of the risks and benefits of revascularization in patients with CAD is an important aspect of decision-making, not only for the interventional cardiologist and the cardiac surgeon, but also for the patient himself, especially in choosing which form of revascularization he would undergo, whether PCI or CABG.²⁰ Risk stratification is therefore essential for the patient to give an informed decision, especially when considering the increasing complexity of coronary artery lesions being treated with PCI.^{11-13,21} Various risk scoring tools have been developed for this purpose, some of which include purely angiographic variables such as the SYNTAX score.^{11,13-14} Some include purely clinical variables such as the New Mayo Clinic Risk Score for predicting mortality, the New Mayo Clinic Risk Score for predicting MACE,⁴ the

ACEF score¹⁵ and the Modified ACEF score.¹² Some risk stratification models include both clinical and angiographic variables, an example of which is the Clinical SYNTAX Score.¹²

This study highlights the prognostic value of clinical variables alone as compared to a combination of clinical and angiographic variables for accurately estimating the periprocedural and 30-day risk from PCI. To the best of our knowledge, this is the first comparison of the prognostic value of the NMCRS and the CSS for in-hospital and 30-day adverse outcomes. This study demonstrates that the NMCRS for Predicting Mortality, the NMCRS for Predicting MACE and the CSS are all predictive of in-hospital and 30-day mortality and MACCE, with the NMCRS for Predicting Mortality faring significantly

better than the other two risk scoring systems in predicting in-hospital mortality and composite MACCE. On the other hand, the NMCRS for predicting MACE has the best prognostic value in predicting 30-day mortality and composite MACCE.

These findings are consistent with those of Singh et al.⁴ which demonstrated that despite exclusion of angiographic variables, the NMCRS can accurately estimate peri-procedural risk from PCI. The two risk models they developed, the NMCRS for Predicting Mortality and the NMCRS for Predicting MACE discriminate well for in-hospital mortality and MACCE, respectively. Our study demonstrated that the prognostic utility of these two risk models can be extended to estimation of mortality and MACCE 30 days after a patient undergoes PCI. The use of 7 clinical and laboratory variables, i.e. age, serum creatinine, LVEF, periprocedural shock, MI $\leq$ 24 hours, CHF on presentation and PAD, which can easily be obtained at bedside, makes the NMCRS a simple yet useful tool for the physician to assess the attendant risks from PCI at the time of initial contact with the patient.

The CSS, on the other hand, combines clinical and angiographic variables for predicting mortality and MACCE at 5-year follow-up.¹² It was developed to improve the ability of the SYNTAX score,¹¹⁻¹³ which includes purely angiographic variables, to predict morbidity and mortality from PCI, by combining it with the modified ACEF score,^{15,22} which by itself comprises purely clinical variables. The CSS was shown to have a superior ability to predict mortality and MACCE when compared to the individual SYNTAX and ACEF scores.¹² Our study showed similar findings for the CSS in its prognostic utility for in-hospital mortality and combined in-hospital and 30-day composite MACCE.

Our study demonstrated that both the NMCRS and CSS are predictive of adverse outcomes after PCI. One reason for this is that these two risk scoring systems have 3 clinical variables in common: age, serum creatinine and LVEF, all of which have been shown to be predictors of

adverse outcomes after revascularization.^{12,15} Furthermore, these variables are not subject to interobserver variability, thus increasing the accuracy of the 2 risk scores. However, the NMCRS for predicting mortality and the NMCRS for Predicting MACE showed statistically significant better prognostic utility than the CSS for in-hospital and 30-day mortality and MACCE in patients undergoing PCI. This can be explained by the similarity in our study population with that used in the derivation of the NMCRS, which included all patients in the Mayo Clinic angioplasty registry who underwent PCI. In contrast, the patient population used in the derivation of the CSS included those with 2- or 3-vessel CAD and excluded those with previous PCI, left main CAD, overt CHF, LVEF $< 30\%$ and a history of TIA and transmural MI in the preceding week. Our study included patients with single vessel CAD as well as those who presented with the aforementioned exclusion criteria for the CSS. Furthermore, the utility of the CSS as a risk stratification tool was for long-term adverse outcomes as compared to ours which included peri-procedural and short-term mortality and MACCE.

CONCLUSION

This study demonstrates the superior ability of a risk stratification tool which uses purely clinical variables, i.e. (1) the NMCRS for Predicting Mortality to predict in-hospital mortality and composite MACCE and (2) the NMCRS for Predicting MACE to predict 30-day mortality and composite MACCE, when compared with the CSS which uses angiographic and clinical variables. Importantly, the NMCRS becomes more expedient for both the patient as well as the physician at bedside and upon initial contact with the patient undergoing PCI for decision-making and risk stratification, being much simpler since it does not include angiographic variables. We therefore recommend the use of the NMCRS for risk stratification of patients undergoing PCI.

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Effectiveness of an Accelerated Phase II as Compared to the Standard Cardiac Rehabilitation Program in Improving Exercise Capacity and Quality of Life

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Background --- An accelerated cardiac rehabilitation program may be as beneficial as the standard program. The objective of the study was to compare the effectiveness of an accelerated Cardiac Rehabilitation with the standard program.

Method --- A prospective cohort study of 38 subjects was done in a six-month period among post cardiac surgery or intervention patients who enrolled in the 12-session Phase II or outpatient cardiac rehabilitation program. Sixteen from the original nineteen completed the accelerated program while eighteen from the original nineteen completed the standard program. The standard program was accomplished in four weeks while the accelerated program was only accomplished for two and a half weeks. Treadmill testing was done after the 6th and 12th session. An SF-36 Quality of Life Questionnaire was answered at the beginning and end of the program.

Results --- The study showed that there was no significant difference in the attained METS, VO_2 max and improvement in the quality of life between the accelerated and standard cardiac rehabilitation program. There was an increase in METS and VO_2 max from the 6th to the 12th session. The change in quality of life was greater in the accelerated than the standard program, but was not found to be statistically significant.

Conclusion --- Both accelerated and standard programs exhibited improvement in exercise capacity and quality of life. Thus, the accelerated program may be used as an alternative to the standard program. *Phil Heart Center J 2016;21(1):10-17.*

Key Words: Accelerated Program Cardiac Rehabilitation ■ Exercise Capacity ■ Quality of Life

Cardiac rehabilitation has been proven to improve exercise capacity, and has prolonged life expectancy among cardiovascular patients. It is a multifactorial process with the aim of controlling cardiac symptoms, reversing progression of the atherosclerotic process, reducing the risk of sudden death or re-infarction, and enhancing the patient's psychosocial and vocational status.¹ As a continuous program, cardiac rehabilitation should not end after the in-patient Phase I cardiac rehabilitation program, but should be continued on an outpatient basis or the so called Phase II program to attain its optimal benefits. Based on a meta-analysis of 48 randomized trials, cardiac rehabilitation reduced all-cause mortality by

20% and cardiac mortality by 26%.² Despite their evidence of benefit, there had been under-utilization of cardiac rehabilitation. What may be the cause of decreased enrolment? Lack of awareness from both physicians and patients on the long-term benefits of the program may be a major cause while another reason would be the length of the program. The typical Phase II or outpatient cardiac rehabilitation program consists of 3 sessions per week for 4 weeks for a total of 12 sessions. Some patients, particularly those who live in the provinces, would have reservations enrolling in the program for they would need to find extra accommodations in the urban area. Some patients who have had a favorable recovery would like to return to their

3rd place, Oral Presentation - Original Paper. 23rd PHC Annual Research Paper Competition and Poster Presentation held on February 26, 2015 at Philippine Heart Center. Correspondence to **Dr. Benjamin Jose C. Quito**. Department of Adult Cardiology, Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at <http://www.phc.gov.ph/journal/publication> copyright by Philippine Heart Center, 2016 ISSN 0018-9034

normal daily routine and occupation at a shorter span of time. In order to determine whether an accelerated Phase II program would be as effective as the standard Phase II program, objective data regarding improvement in exercise performance and quality of life must be presented.

The objectives of the study was to compare the effectiveness of the accelerated cardiac rehabilitation with the standard cardiac rehabilitation program in improving exercise capacity and quality of life; to compare the improvement in achieved METs and VO_2 max at the end of the 6th and 12th session in those undergoing the standard and the accelerated program; and to determine if there was a difference in the improvement of quality of life in those undergoing the standard and accelerated program.

METHODS

The study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki. Prior to study initiation, there was a review and approval of the study protocol and informed consent. Subsequent amendments were approved by the Philippine Heart Center Institutional Ethics Review Board (PHC-IERB). Before a subject's participation, a written informed consent was obtained by the investigator after adequate explanation of the aims, anticipated benefits and potential risks of the study. The informed consent was signed and personally dated by the subject and the person who conducted the informed consent discussion. The investigator preserved the confidentiality of all subjects taking part in the study. The investigator ensured that the subject's anonymity was maintained. The study was a prospective cohort done at Comprehensive Cardiac Rehabilitation Unit of the Philippine Heart Center from July 2014 to December 2014. Included in the study were adults from 19-70 year old who underwent coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), valve surgery, aneurysm repair, congenital heart disease surgery who enrolled in the Phase II cardiac rehabilitation program were included in the study.

Patients were excluded from the study if they have one or more of the following: presence of significant ECG abnormalities (sustained and non-sustained ventricular tachycardia, T wave inversions of at least 1 mm, ST segment elevation in 3 contiguous leads), unstable angina, a fall in exertion blood pressure of more than 20 mmHg, congestive heart failure (NYHA III and IV), resting systolic BP greater than 180 mmHg and diastolic BP greater than 100 mmHg, and those who would not give consent.

Subjects were withdrawn from the study if with one or more of the following conditions developed during the course of the study: those who developed significant ECG abnormalities (sustained and non-sustained ventricular tachycardia, T-wave inversions of at least 1 mm, ST segment elevation), those who developed resting or angina on exertion during the program, those who developed resting systolic blood pressure over 200 mmHg and/or diastolic blood pressure over 100 mmHg, those who had a drop in systolic blood pressure greater than 10 mmHg from resting value during exercise testing, those who had excessive increase in BP greater than 200 mmHg or a rise in diastolic blood pressure by 5 mmHg from rest, a drop in heart rate greater than 10 bpm with increase or no change in workload, or if the patient desired to stop.

Study Maneuver. Eligible participants undergoing the Phase II outpatient cardiac rehabilitation program were asked to sign an informed consent form. They were asked to choose whether they would wish to participate in the accelerated Phase II cardiac rehabilitation program, or the standard Phase II cardiac rehabilitation program. The accelerated program consisted of 5 sessions a week, amounting to 12 sessions, which lasted for two and a half weeks. The standard program consisted of 3 sessions per week amounting to 12 sessions, which lasted for four weeks. The objectives and benefits of the study were fully explained.

At the start of each session, a basic history and physical examination were obtained to assess the patient's condition. Baseline characteristics such as age, sex, BMI and other comorbidities such as hypertension, diabetes

mellitus and dyslipidemia were taken into account.

The Short Form 36 (SF-36) to assess quality of life was answered by the patients at the beginning and end of the Phase II cardiac rehabilitation sessions. A Short Form 36 (SF-36) Health Survey Scoring Demonstration program under the *sf-36.org* website was used to obtain the quality of life scores and improvement in quality of life. The following domains were evaluated: physical functions, physical problems, emotional problems, social functioning, mental health, energy/vitality, pain, general health.

Treadmill stress testing was performed after the 6th session, and 12th session of the cardiac rehabilitation program. MET levels attained and VO_2 max the end of the treadmill stress testing were recorded. The VO_2 max was computed by multiplying the attained MET level by 3.5 mL/kg/min.

The NEPTET treadmill stress test protocol was used in the study. The patient was not required to attain 85% of the target heart rate for only functional capacity was tested. If the patient reached 100% of the target heart rate, the exercise stress test was discontinued. The rate of perceived exertion (Borg Scale) was used to gauge if the effort exerted by the patient was sufficient enough to achieve a cardiovascular training effect. A rate of perceived exertion (Borg Scale) of 12 to 16 was a target range wherein patient's achieved a cardiovascular training effect.

All patients underwent brisk walking for 20-30 minutes, stretching and calisthenics during each cardiac rehabilitation session. If the patient reached less than 6 METS during treadmill stress testing, only calisthenics without weight training was performed. If more than 6 METS was achieved on treadmill, weight training of 1 to 2 pounds was incorporated to the routine. An English version of the SF-36 questionnaire was accomplished at the beginning and at the end of the rehabilitation session to assess quality of life. In case of 3 or more absences, the patient was shifted to the standard cardiac rehabilitation program.

Definition of outcomes. The standard cardiac rehabilitation program and the accelerated cardiac rehabilitation program were the independent or exposure variables of the study. Improvement in MET levels, improvement in VO_2 max, improvement in the quality of life were the dependent or outcome variables.

The confounding variables were age, sex, BMI, the presence of co-morbidities such as hypertension, diabetes or dyslipidemia, or the type of surgery or intervention. The treatment group pertained to the allocation of subjects to either standard or accelerated group.

MET (Metabolic Equivalent of Task) was a physiological measure expressing the energy cost of physical activities defined as the ratio of metabolic rate during a specific physical activity to a reference metabolic rate, set by convention to 3.5 mL O_2 $\text{kg}^{-1}\text{min}^{-1}$. Improvement in METS was measured by subtracting the post-rehabilitation METS by the baseline METS as measured during treadmill stress testing.

Sample size calculation. Using Stata SE version 13, the minimum sample size requirement was estimated to be at least 38 (19 per group) using the following parameters: alpha = 0.05, power = 0.80, mean increase in METS for the standard and accelerated cardiac rehabilitation program was 3.04 ± 1.67 and 1.52 ± 1.67 , respectively.¹⁷ Allowing for 20% drop-out rate, the minimum sample size was increased to 48 (24 per group).

Statistical analysis. Data analysis was done using Stata SE version 13. Descriptive statistics included mean and standard deviation for quantitative variables. Frequency and percent distribution was used for qualitative variables. To determine the homogeneity of variables between the intervention and control groups, independent T-test and Fisher's exact test were used for quantitative and qualitative variables, respectively. To compare the outcomes between the groups, independent T-test was used. The level of significance was set at 0.05.

RESULTS

There were a total of 38 subjects who participated in the study, 19 from the accelerated and 19 from the standard program. Only 16 out the 19 were able to complete the accelerated program, and 18 out of 19 were able to complete the standard program.

In terms of age, there was no significant difference in the mean age of the accelerated and the standard groups, though the mean age in the accelerated group was lower than the standard group (38.81 ± 4.07 versus 47.88 ± 3.22). In terms of sex, both accelerated and standard groups showed a predominance of males. There was no significant difference between the baseline BMIs of both accelerated and standard groups.

In terms of co-morbidities, there were more hypertensives in the standard (77.78%) than the accelerated group (56.25%), but was not statistically significant. There were only a small number of diabetics in both the accelerated (6.25%) and standard group (11.11%). More dyslipidemias (61.11%) were noted in the standard than the accelerated group (43.75%).

In terms of type of surgery or intervention, no statistical significance was found between the accelerated and standard groups. There were more coronary artery bypass graft (CABG) cases (55%) in the standard group than the accelerated group (31.25%). There was only one case of Percutaneous Coronary Intervention (PCI) in both the standard and accelerated group. There were four cases of valve surgeries in each of the two groups. There was one case of aneurysm repair in the standard group while there was none in the standard group. There were more congenital heart disease cases in the accelerated (37.50%), than the standard (11.10%) group.

The mean METS attained after the 6th session in the accelerated group (7.72 ± 0.48 METS) was greater than the standard group (6.53 ± 0.49 METS) but was not found to be statistically significant. The mean METS after 12th session in the accelerated group (8.15 ± 0.42 METS) was greater than the standard group, 7.59 ± 0.48 METS) but was not statistically

significant. In the accelerated group, the mean METS increased from 7.72 ± 0.48 to 8.15 ± 0.42 METS or by approximately 0.43 METS. In the standard group, the mean METS increased from 6.53 ± 0.49 METS to 7.59 ± 0.48 METS or by 1.06 METS.

The mean $\dot{V}O_2$ max attained after the 6th session in the accelerated group (27.03 ± 1.70 mL/kg/min) was greater than the standard group (22.86 ± 1.71 mL/kg/min) but was not found to be statistically significant. The mean $\dot{V}O_2$ max after the 12th session in the accelerated group (27.86 ± 1.50 mL/kg/min) was greater than the standard group, (26.58 ± 1.70 mL/kg/min) but was not statistically significant. In the accelerated group, the mean $\dot{V}O_2$ max increased from 27.03 ± 1.70 mL/kg/min to 27.86 ± 1.50 mL/kg/min with a difference of approximately 0.83 mL/kg/min. In the standard group, the mean $\dot{V}O_2$ max increased from 22.86 ± 1.71 mL/kg/min to 26.58 ± 1.70 mL/kg/min with a difference of approximately 3.72 mL/kg/min.

The change in quality of life scores was greater in the accelerated (4.55 ± 1.82) than the standard (0.58 ± 3.45) program, but was not found to be statistically significant. There was no significant change in the different components of quality of life that were assessed. The different components assessed were physical function, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. In terms of change in vitality, the accelerated program showed a greater change (3.20 ± 2.62), than the standard program (0.95 ± 1.93). Though not statistically significant, there was a far greater improvement in emotional role in the accelerated (10.52 ± 3.82) than the standard group (1.08 ± 3.48). There was a far greater improvement in the mental health in the accelerated (4.22 ± 2.23) than the standard group (0.025 ± 1.45), though was not found to be statistically significant. In the accelerated program, there were three dropouts. One experienced urinary retention during the second day of the program and had to be readmitted. One had to go back to the province soon, thus decided not to complete the sessions. One had leg pain and decided not to continue. In the standard program, there was one drop out, due to a blood pressure of 200/100 before the second treadmill.

Table 1. Baseline Characteristics of Patients Undergoing Accelerated and Standard Phase II Cardiac Rehabilitation Program

Characteristics	Accelerated (n=16) n(%)	Standard (n=18) n(%)	P-value
Age in years (mean $\pm$ SD)	38.81 $\pm$ 4.07	47.88 $\pm$ 3.22	0.09
Sex (Male)	10 (62.50)	12 (66.67)	1.00
BMI (mean $\pm$ SD)	23.73 $\pm$ 1.20	23.25 $\pm$ 0.72	0.72
Co-morbidities			
Hypertension	9 (56.25)	14 (77.78%)	0.27
Diabetes mellitus	1 (6.25%)	2 (11.11%)	1.00
Dyslipidemia	7 (43.75)	11(61.11%)	0.49
Type of Surgery or Intervention			
CABG	5 (31.25%)	10(55%)	0.31
PCI	1 (6.25%)	1 (5.56%)	1.00
Valve Surgery	4 (25.00%)	4(22.22%)	1.00
Aneurysm	0(0%)	1 (5.56%)	1.00
Congenital	6 (37.50%)	2 (11.10%)	0.11

Table 2. Outcome of Attained METS and VO_2 max and Improvement of Quality of Life Scores According to Cardiac Rehabilitation Program

Outcome	Accelerated (n=16) (mean $\pm$ SD)	Standard (n=18) (mean $\pm$ SD)	P-value
METS (after the 6th session)	7.72 $\pm$ 0.48	6.53 $\pm$ 0.49	0.09
METS (after the 12th session)	8.15 $\pm$ 0.42	7.59 $\pm$ 0.48	0.39
VO_2 max (after the 6th session)	27.03 $\pm$ 1.70	22.86 $\pm$ 1.71	0.09
VO_2 max (after the 12th session)	27.86 $\pm$ 1.50	226.58 $\pm$ 1.70	0.58
Improvement in Quality of Life	4.55 $\pm$ 1.82	0.58 $\pm$ 3.45	0.33
Physical Functioning (PF) change	9.27 $\pm$ 2.02	11.84 $\pm$ 3.99	0.58
Role- Physical (RP) change	10.08 $\pm$ 2.93	7.60 $\pm$ 2.57	0.52
Bodily Pain (BP) change	3.37 $\pm$ 2.57	4 $\pm$ 2.48	0.86
General Health (GH) change	1.98 $\pm$ 1.38	1.11 $\pm$ 2.07	0.73
Vitality (VT) change	3.20 $\pm$ 2.62	0.95 $\pm$ 1.93	0.49
Social Functioning (SF) change	4.25 $\pm$ 2.28	3.05 $\pm$ 2.04	0.69
Role-Emotional (RE) change	10.52 $\pm$ 3.82	1.08 $\pm$ 3.48	0.07
Mental Health (MH) change	4.22 $\pm$ 2.23	0.025 $\pm$ 1.45	0.15

DISCUSSION

The study showed that there was no significant difference in the attained METS, VO_2 max and improvement in the quality of life between the accelerated and standard cardiac rehabilitation program. The attained METS and VO_2 max after the 6th and 12th session was

greater in the accelerated than the standard group, though was not statistically significant. There was a greater increase in METS from the 6th to the 15th session in the standard with a difference of 1.06 METS than the accelerated group with a difference of only 0.43 group METS. Likewise, there was a greater increase in VO_2 max from the 6th to the 15th session

in the standard group with a difference of 3.72 mL/kg/min as compared to the accelerated group with a difference of 0.83 mL/kg/min. Both the standard and accelerated groups showed an improvement in quality of life. There was marked improvement in quality of life in the accelerated group than the standard group (4.55 ± 1.82 versus 0.58 ± 3.45), though no statistical significance was established. In the individual assessment of different quality of life parameters, there was marked improvement in the emotional and mental health in the accelerated than the standard group, though no statistically significance was established.

In this investigation, there was a need to establish that both standard and accelerated standards can achieve favorable endpoints of improving exercise capacity and quality of life.

In this study, exercise capacity was measured through attained METS and $\dot{V}O_{2\max}$ after treadmill stress testing on the 6th session and the 12th session. Assessment after the 6th session had been crucial, for if the patient achieved more than 6 METS, he or she would be eligible for weight training using 1 or 2 pounds weight which had been proven to be safe in a cardiac patient. The purpose of weight training was to recondition the muscles that may have weakened during prolonged surgery, bed rest, and inactivity. The Borg's scale or rate of perceived exertion was used to ensure that the patient had been exerting enough effort to achieve a cardiovascular training effect. The American College of Sports Medicine has recommended a RPE range of 12 to 16 as the perceived exertion rate with a cardiovascular training effect, roughly corresponding to 60 to 85% of the maximal heart rate.³

In a study by Myers et al, the peak exercise capacity measured in metabolic equivalents (MET) was the strongest predictor of the risk of death among normal subjects and those with cardiovascular disease as compared to other established variables such as hypertension, smoking, diabetes, as well as other test variables such as ST segment depression, peak heart rate and development of arrhythmia after exercise.⁴ The risk of death is doubled in subjects whose exercise capability is below 5 METS as

compared to those whose exercise capacity is more than 8 METS. Fortunately, in this study, the patients achieved more than 5 METS and a little less than 8 METS. It was observed that every 1-MET increase in treadmill performance is associated with a 12% improvement in survival rate of patients referred for exercise testing. There has been an inverse relationship between exercise capacity and mortality from any cause.⁴ In this study, both accelerated and standard groups showed an increase in achieved METS which had been reflective of exercise capacity.

In this study, after the 6th session, which was half way through the program, patients in the accelerated program already achieved approximately of 7.72 ± 0.48 METS as compared to the 6.53 ± 0.49 METS achieved in the standard program. One possible reason was that patients in the accelerated program might have more focus and discipline. It should be taken into account that exercise capacity could be affected by different factors such as age, gender and physical activity prior to illness. It has been an established fact that as one ages, there would be a decrease in exercise capacity and anaerobic threshold. Thus, expected METS are adjusted based on age.⁵⁻⁶

In our study, approximately more than 60 percent of the study population for both accelerated and standard groups was comprised of men. This is in congruent with literature that more men enroll than women in cardiac rehabilitation programs.⁷⁻⁸ Male sex had been an established risk factor for coronary artery disease which could lead to death.⁷⁻⁸ Based on other literature, one possible reason that deter women from enrolling had been their belief that they should stay at home to take care of their families.⁶

In terms of exercise capacity, previous data suggest that men have a greater expected exercise capacity than women, thus a special normogram was formulated for women to predict exercise capacity.⁹ Pre-morbid exercise capacity may be influenced by co-morbidities such as chronic lung disease, arthritis, and other muscular conditions. A low pre-morbid exercise capacity that would translate into a low attain-

ment in METS in the treadmill exercise test would affect prognosis and recovery in a cardiac patient.¹⁰

The researcher would like to emphasize that each patient participating in the program have different physical, medical, and psychosocial backgrounds that would affect their progression in the cardiac rehabilitation program.

The maximal oxygen uptake has been widely accepted as a measure of cardiovascular fitness and maximal aerobic power.¹¹ In an untrained healthy male, the $\dot{V}O_2$ max ranges from 30-35 mL/kg/min, while for the untrained female, the $\dot{V}O_2$ max ranges from 27-31 mL/kg/min. Exercise training and conditioning programs can improve these scores.^{12,13} Age, sex, fitness and training, changes in altitudes and action of ventilator muscles are factors that could affect oxygen uptake.¹⁴ In this study the achieved $\dot{V}O_2$ max for both accelerated and standard groups approximated 27 mL/kg/min which was near normal levels.

The SF-36 has been a validated questionnaire, which was formulated in layman's language to assess quality of life in this study. It used eight main domains mainly: physical functions, physical problems, emotional problems, social functioning, mental health, energy/vitality, pain, general health.

In this study, it may be observed that the accelerated program had a greater improvement in quality of life than the standard program, though no statistical significance was observed. Worth noting was the greater improvement in vitality, emotional, and mental health in the accelerated program as compared to the standard program, though no statistical significance was established. One possible reason would be that participants in the accelerated program may have better attitudes in recovery. They may be more determined to finish the program in a shorter span of time. Another reason was that those who consented to be in the accelerated program might have been in a better state of physical and mental health than those who opted to stay in the standard program.

This study would like to determine if

an accelerated or fast cardiac rehabilitation program would be as effective as the standard cardiac rehabilitation program.

A previous study (Boulay, et al.) entitled "risk factor management after short-term versus long-term cardiac rehabilitation program" was done involving patients with acute coronary syndrome. Short term (3 months) and long term (12 months) cardiac rehabilitation were effective in improving exercise capacity. However, long term cardiac rehabilitation was more effective in smoking cessation, and weight management.¹⁵ A previous study performed by Cheuk-Man et al, showed that both a short course (2 months) and a long course (2 years) improved the quality of life of post myocardial infarction and post percutaneous coronary intervention patients.¹⁶

There were three drop outs in the accelerated program and one drop out in the standard program. No major adverse effects were noted. Patients in both accelerated and standard programs expressed satisfaction to the programs. In establishing proof that the accelerated program can improve functional capacity and quality of life, one could recommend the accelerated program for those who would like to finish their Phase II Cardiac Rehabilitation Program in a shorter span of time. It is recommended to continue the study to achieve a greater population in order to obtain a more accurate representation of the real picture.

The study was not a randomized controlled trial due to ethical considerations. The investigators and participants in the trial were not blinded. The subjects also have different pre-morbid exercise and functional capacities that may affect individual progress in the program.

CONCLUSION

The study showed that there was no significant difference in the attained METS, $\dot{V}O_2$ max and improvement in the quality of life between the accelerated and standard cardiac rehabilitation program. Thus, the accelerated program could be an alternative in patients who would like a shorter duration of Phase II cardiac rehabilitation program.

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The Clinical and Procedural Outcome of Patients Undergoing Trans-Radial Approach vs. Trans-Femoral Approach in Percutaneous Coronary Intervention

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Background --- Trans-Radial Approach (TRA) has been slowly and steadily growing worldwide although there are still different preferences in access site between angiographers, institutions and countries. One rate-limiting step in the technical aspect would be its learning curve. This study may contribute to the local initiative for the increased utilization of the TRA. The objectives of this study is to compare the clinical and procedural outcome of patients undergoing TRA as compared with Trans-Femoral Approach (TFA) in percutaneous coronary intervention (PCI).

Methods --- Study population (n = 109) includes patients for PCI using TRA (n = 55) and TFA (n = 54) from the period of January 2013 to December 2014. The in-hospital all-cause mortality, myocardial infarction or cerebrovascular disease (Major Adverse Cardiac and Cerebrovascular Events - MACCE) among patients undergoing TRA was compared to TFA. The bleeding complications were obtained using a standardized bleeding criterion (the GUSTO Bleeding Classification - none, mild, moderate or severe I life-threatening). Univariate and multivariate logistic regression analysis (odds ratio with a 95% confidence interval) was used to determine the strength of association between the arterial access and the outcome.

Results --- There is a significant reduction the observed bleeding (hematoma) with the TRA during PCI as compared to TFA (OR = 2.66, p = 0.022). There was no statistically significant difference (p > 0.05) between MACCE, occurrence of arrhythmia, procedural time, fluoroscopy time and cross-over between access in this study.

Conclusion --- TRA offers a favorable advantage on outcomes by reducing the cost burden of bleeding and vascular complications in certain subsets as compared to the traditional TFA. The clinical and procedural outcome of TRA was comparable to TFA. *Phil Heart Center J 2016;21(1):18-25.*

Key Words: Trans-Radial Approach ■ Trans-Femoral Approach ■ Percutaneous Coronary Intervention

The first cardiac catheterization was performed by Hales¹ in 1711 on an equine ventricle using brass pipes, a glass tube and the trachea of a goose. The term “cardiac catheterization” was first coined by the French physiologist Bernard in 1844 wherein he used catheters to record intra-cardiac pressures in animals. Werner Forssmann¹ performed the first documented human cardiac catheterization in Eberswald, Germany in 1929. The first peripheral human balloon angioplasty was performed by Andreas Gruentzig¹ in 1974. His success on coronary angioplasty in animals was presented in the American Heart Association Meeting in 1976. The first human coronary balloon angioplasty

was performed intra-operatively in 1977 by Gruentzig, Myler and Hanna in San Francisco, USA. Then in Zurich, Gruentzig performed the first catheter laboratory percutaneous coronary intervention (PCI) in a conscious patient.

In 1948, Radner^{2,3} first described the trans-radial catheterization with a radial artery cut-down. In 1989, Campeau⁴ reported his work on the percutaneous entry in the distal radial artery for coronary angiography on 100 patients. The first Trans-Radial Approach (TRA) percutaneous coronary intervention was reported by Kiemeneij^{2,5-7} in Amsterdam in 1993. In the past 2 decades, the utilization of the trans-radial

approach has gained wider acceptance. TRA has been slowly and steadily growing although there are still different preferences in access site between angiographers, institutions and countries. One rate-limiting step in the technical aspect would be its learning curve. Currently, the position statement of the European Association of Percutaneous Cardiovascular Interventions and Working Groups on Acute Cardiac Care and Thrombosis of the European Society of Cardiology states that a default radial approach is feasible in routine practice after appropriate training with the inherent proficiency in the femoral approach if it may be needed as a bailout strategy.²

In the Philippines, in our large-volume cardiac center, we have yet to acquire local data regarding this operative approach. According to the 2011 Cardiac Catheterization Laboratory Census at the Philippine Heart Center (PHC), there were 3,580 patients that underwent Coronary Angiography (CA) and 891 underwent Percutaneous Coronary Intervention (PCI). In the Short Stay Unit (SSU) alone, the ward dedicated for patients who had percutaneous coronary procedures, there are 1,115 patients that underwent CA and 153 patients that underwent PCI in 2011. The in-hospital outcome study⁸ of PCI at the Philippine Heart Center (PHC) by Arenas et al., showed a 98.4% success rate (p value <0.0001 . OR = 0.06. 95% CI:0.03-0.1) for the procedure. In another PHC study,⁹ according to Rillera-Posadas et al., the success rate of PCI was 95% and 96% in patients with or without diabetes (p = NS) respectively. The increasing interest in TRA is worldwide. However, the National Cardiovascular Data Registry (NCDR) showed that of the nearly 600,000 who underwent first PCI from 2004 to 2007 in the US, only 1.32% used the trans-radial approach thus showing its under utilization. In the local setting, the Philippine Heart Center as the premier cardiovascular center of the country, this study may contribute to the local initiative for the increased utilization of the trans-radial approach.

The objective of this study is to compare the clinical and procedural outcomes of patients undergoing trans-radial as compared to trans-femoral approach in percutaneous coronary intervention.

METHODS

The study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki. Prior to study initiation, there was a review and approval of the study protocol and informed consent. Before a subject's participation, a written informed consent was obtained by the investigator after adequate explanation of the aims, anticipated benefits and potential risks of the study. The informed consent was signed and personally dated by the subject and the person who conducted the informed consent discussion.

This is a prospective cohort study. Included were adult patients for coronary angiography (CA) and percutaneous coronary intervention (PCI) using trans-radial approach (TRA) or trans-femoral approach (TFA) admitted at a large volume cardiac catheter center, the Philippine Heart Center (PHC) from the period of January 2013 to December 2014.

Sample size. The computed sample size was $n = 100$ with at least 50 patients in either the TRA or TFA based on 95% confidence level, 80% power and assumed difference in success rate of 20%. The assumption was based on 98% success rate of the procedure as published in the paper of Arenas et al.¹⁵ The total study population included in the study was 109, of which 55 underwent trans-radial approach and 54 underwent trans-femoral approach.

Study maneuver. Study population includes patients for PCI using TRA and TFA from the period of January 2013 to December 2014. Data were encoded utilizing a data collection form to facilitate improved data gathering. The list of patients were acquired from the daily patient log or the Cardiac Catheterization Laboratory (CCL), the Short Stay Unit (SSU) and the Coronary Care Unit (CCU). The independent and dependent variables were gathered by (1) chart review; (2) access to the computerized hospital database (MedTrak Integrated Hospital System Version 6) of the Philippine Heart Center; or (3) individual patient interview and physical examination.

Clinical adverse events such as in-hospital mortality, myocardial infarction or cerebrovascular disease were noted. The procedural success, procedural time, fluoroscopy time and cross-over access site were also obtained which may reflect the technical aspect of each procedure. We utilized the GUSTO Bleeding Classification,¹² a standardized bleeding criterion (none, mild, moderate or severe/life threatening) on the basis of the presence or gross hematoma or bleeding, hypotension, need for transfusion or delta (Δ) hemoglobin (Hgb) or hematocrit (Hct).

Statistical Analysis. Data were encoded in Microsoft Excel 2010 and analyzed in the STATA SE version 12 (Texas USA). Descriptive statistics included frequency and proportion for categorical variables while mean and standard deviation was used for continuous variables. To check the comparability between group (TRA and TFA) an independent t-test for continuous variables and Fisher's exact test were used. Logistic Regression Analysis (Odds Ratio with a confidence interval set at 95%) was used to determine the strength of association between arterial access and outcome. Univariate analysis was used for single predictor variables. Controlling for the effect of confounders, multivariate analysis for multiple significant predictor variables was done. A p-value of <0.5 is considered statistically significant.

RESULTS

Table 1 shows the baseline characteristics. The baseline characteristics showed that there were no significant difference between the two groups according to arterial access except for the following setting: (1) in the setting of an elective and emergency double set-up (DSU); (2) in patients with ACS, STEMI, NSTEMI and UA; and (3) in patients with totally occluded arteries either acute or chronic (>3 months). This reflects the preference of angiographers in precarious or emergency situations and their expertise for one arterial access over the other during PCI.

Table 2 shows the intraprocedural data according to the arterial access. The procedural time was found to be longer in the TFA group, which was due to the higher complexity of lesion and higher risk situations among this group. The fluoroscopy time, which is a measure of total radiation exposure, was similar for both TRA and TFA groups. This was consistent with the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) database,¹³ which found that radial access was not associated with higher radiation exposure both for coronary angiography and intervention. Crossover (or change) of arterial access was found insignificant in this study.

Table 3 shows the occurrence of MACCE according to arterial access. The occurrence of major adverse cardiac and cerebrovascular events ($p=0.197$) including death ($p=0.324$), myocardial infarction and cerebrovascular disease during the hospital stay is not significantly different between the two groups, although the proportion of events was higher among patients with TFA (Table 3). The result of the primary outcome showed that utilization of which ever access site is acceptable and did not confer any statistical significant advantage.

Table 4 shows the complications according to arterial access. Most of the study patients who developed bleeding complications (access site hematoma) were classified as Mild under the GUSTO Bleeding Classification. There were no patients observed with moderate or severe or life threatening bleeding under GUSTO Classification in this study. Using univariate logistic regression for bleeding complications, it revealed a statistically significant increase in bleeding (hematoma) with the TFA with an odds ratio (OR) of 2.66 (95% CI: 1.15 - 6.13, $p = 0.022$). This translates to a 2.66 times higher likelihood of developing significant bleeding (hematoma) in the TFA post-PCI. The occurrence of ventricular tachycardia ($p = 0.247$) and bradyarrhythmia ($p = 5.51$) seen more frequently in the TFA, although it did not achieved statistical significance.

In order to factor in the multiple predictor variables and controlling for the effect of confounders, a multivariate logistic regression analysis (Table 5) for bleeding done showed 7.28 times increased risk of bleeding with the TFA (95% CI: 1.10 - 48.22, $P = 0.040$). Bleeding complications (hematoma) was increased for the TFA in following patient subsets: (1) those undergoing emergency PCI ($p = 0.47$); (2) those with left main artery

($p = 0.021$) and right coronary artery lesion ($p = 0.41$); and (3) those with increased body mass index ($p = 0.016$). On the contrary, the TRA showed an increased bleeding complication with the following patient subsets: (1) those with Type B ($p = 0.002$) and C ($p = 0.012$) coronary artery lesion; and (2) Type 2 Diabetes Mellitus ($p = 0.002$). The result found statistically significant 50-fold, 100-fold and 25-fold increase risk of bleeding for Type B

Table 1. Baseline Characteristics of PCI Patients According to Arterial Access

Variable	Trans-Radial Approach (n = 55) n(%) or mean + SD	Trans-Femoral Approach (n = 54) n(%) or mean + SD	P-value
Age (years) Mean $\pm$ SD	39-82 59 $\pm$ 11 (95% CI: 57-62)	26-84 58 $\pm$ 11 (95% CI: 55-61)	0.395
Sex			
Male	46 (84)	48 (89)	0.580
Female	9 (16)	6 (11)	0.580
BMI (kg/m ²)	27.0 $\pm$ 4.0 (95% CI: 25.8-28.3)	26.5 $\pm$ 6.6 (95% CI: 24.3-28.6)	0.635
Co-morbidities			
HTN	45 (82)	44 (81)	1.000
DM	20 (36)	22 (41)	0.696
CVD	1 (2)	4 (7)	0.206
CKD	2 (4)	3 (6)	0.679
DSU (CA + PCI)			
Emergency	3 (5)	23 (43)	<0.001
Elective	52 (95)	31 (57)	<0.001
ACS	18 (33)	36 (67)	0.00
STEMI	4 (21)	26 (72)	<0.001
Anterior	0 (0)	9 (35)	0.417
Anterolateral	1 (25)	4 (15)	0.417
Anteroseptal	0 (0)	3 (12)	0.417
Inferior	3 (75)	8 (31)	0.417
Posterior	0 (0)	2 (7)	0.417
NSTEMI	11 (58)	10 (28)	<0.001
UA	4 (21)	0 (0)	<0.001
Diseased Vessel			
1VD	24 (44)	18 (33)	0.368
2VD	19 (35)	18 (33)	0.368
3VD	12 (22)	18 (33)	0.368
Coronary Artery Lesion			
LMA	4 (7)	5 (9)	0.742
LAD	43 (78)	46 (85)	0.459
LCx	26 (47)	29 (54)	0.567
RCA	25 (45)	30 (56)	0.340
Ramus	1 (2)	1 (2)	1.000
Type of Lesions			
Type A	27 (49)	16 (30)	0.061
Type B	23 (42)	26 (48)	0.061
Type C	5 (9)	12 (22)	0.061
Bifurcation lesion	3 (5)	6 (11)	0.320
Total occlusion			
<3 months	2 (4)	17 (31)	<0.001
$\geq$ 3 months (CTO)	2 (4)	5 (9)	<0.001

Abbreviations: BMI - Body Mass Index; HTN - Hypertension; DM - Diabetes Mellitus; CVD - Cerebrovascular Disease; CKD - Chronic Kidney Disease; PAD - Peripheral Arterial Disease; DSU - Double Set-up; ACS - Acute Coronary Syndrome; CA - Coronary Angiography; PCI - Percutaneous Coronary Intervention; TFA - Trans-femoral Approach; TRA - Trans-radial approach; CAD - Coronary Artery Disease; VD - Vessel Disease; CTO - Chronic Total Occlusion

fold, Type C coronary lesion and patients with diabetes mellitus respectively when TRA was utilized. The above characteristics with significant bleeding risk reflects the complexity of the lesion and the technicality of the operative approach during PCI.

All of the enrolled preliminary patients in both groups had achieved angiographic success (*Table 6*). The patients who achieved procedural success were 98% for TRA and

94% for the TFA. The result was comparable to the retrospective cohort study¹⁴ of the National Cardiovascular Data Registry (2007-2012). There were 2,820,874 PCI procedures in this registry from 1,381 sites in the U.S. with procedural success of 94.70% and 93.81 % for the TRA and TFA respectively. Likewise, this value was consistent with the Philippine Heart Center (PHC) data of 98% success rate⁸ for PCI procedure. Looking into each results above (*Table 5*), note that there

Table 2. Intra-procedural Data of PCI Patients According to Arterial Access

Variable	Trans-Radial Approach (n = 55)	Trans-Femoral Approach (n = 54)	P-value
Procedural time (mins) Mean ± SD	59.6 ± 30.5 (95% CI: 51.3-67.9)	71.6 ± 30.6 (95% CI: 63.3-79.9)	0.045
Fluoroscopy time (min) Mean ± SD	18.0 ± 12.5 (95% CI: 14.5 - 21.4)	21.7 ± 11.5 (95% CI: 18.6 - 24.8)	0.109
Cross-over access	2 (4)	1 (2)	1.000
Number of Stents Deployed			
1 stent	25 (45)	19 (35)	0.550
2 stents	8 (15)	16 (30)	
3 stents	8 (15)	8 (15)	
4 stents	12 (22)	3 (6)	
5 stents	1 (2)	6 (11)	
>5 stents	1 (2)	2 (3)	

Table 3. Primary Outcome - MACCE Post-PCI According to Arterial Access

Outcome	Trans-Radial Approach (n = 55)	Trans-Femoral Approach (n = 54)	OR*	95% CI	P Value
Over-all MACCE	1 (2)	4 (7)	4.32	0.47 - 39.97	0.197
Death	1 (2)	3 (7)	3.18	0.32 - 31.53	0.324
MI	0 (0)	0 (0)	-	-	-

Abbreviations: MACCE - Major Adverse Cardiac and Cerebrovascular Event; MI - Myocardial Infarction; CVD - Cerebrovascular Disease.

* Univariate Logistic Regression Analysis for TFA versus TRA was done to determine the Odds Ratio.

Table 4. Secondary Outcomes - Post-PCI According to Arterial Access

Outcome	Trans-Radial Approach (n = 55)	Trans-Femoral Approach (n = 54)	OR*	95% CI	P value
Bleeding or Vascular Complications			2.66	1.15 - 6.13	0.022
None	43 (78)	31 (57)			
Mild	12 (22)	23 (43)			
Moderate	0 (0)	0 (0)			
Severe or Life-threatening	0 (0)	0 (0)			
Arrhythmia					
Ventricular Tachycardia	2 (4)	5 (9)	2.70	0.50 - 14.6	0.247
Bradyarrhythmia	1 (2)	5 (9)	5.51	0.62 - 48.82	0.125
Temporary Pacemaker	0 (0)	5 (9)	-	-	-

* Univariate Logistic Regression Analysis for TFA versus TRA was done to determine the Odds Ratio.

is slight better procedural outcome in the TRA group, however, it must be taken into account that patients who are “sickly” (e.g. in need of emergent procedure) or have more complex lesions, there is an existing tendency for angiographers to utilize the femoral access. This may be due to the need for a larger bore catheters and size of instrumentation in these types of situations. The familiarity with the arterial access (radial or femoral approach) may also be a factor. There

were no statistically significant ($p > 0.05$) association of procedural success with each analyzed patient characteristics: (a) number of vessel diseased (1VD, 2VD or 3VD); (b) coronary artery involved (LM, LAD, LCx, RCA and Ramus); (c) number of stents deployed (1, 2, 3, 4, 5, and >5); (d) type of lesion based on the ACC/AHA (Type A, B, and C); (e) presence of total occlusions (acute or chronic > 3 months); and (f) bifurcation stenting.

Table 5. Multivariate Logistic Regression Analysis for Bleeding in TFA versus TRA

Outcome	OR*	95% CI	P value
Bleeding or Vascular Complications	7.28	1.10 - 48.22	0.040
Emergency DSU	7.19	1.03 - 50.33	0.047
Coronary Artery Lesion			
LMA	35.09	1.72 - 717.29	0.021
RCA	5.78	1.07 - 31.21	0.041
Type of Lesions			
Type B	0.02	0.001 - 0.213	0.021
Type C	0.01	0.0005 - 0.395	0.012
Body Mass Index	1.35	1.06 - 1.71	0.016
Diabetes Mellitus	0.04	0.005 - 0.314	0.002

* Multivariate Logistic Regression Analysis for TFA versus TRA was done to determine the Odds Ratio.

Table 6. Angiographic and Procedural Success According to Arterial Access

	Trans-Radial Approach (n = 55)		Trans-Femoral Approach (n = 54)		P value
Overall Angiographic Success	55 (100%)		54 (100%)		
Overall Procedural Success	54 (98%)		51 (94%)		
	N	Procedural Success	N	Procedural Success	P Value
Diseased Vessel					
1VD	24	24 (100%)	18	16 (89%)	0.178
2VD	19	19 (100%)	18	18 (100%)	-
3VD	12	11 (92%)	18	16 (89%)	1.000
Coronary Artery Lesion					
LMA	4	4 (100%)	5	5 (100%)	-
LAD	43	42 (98%)	46	42 (91%)	0.362
LCx	26	25 (96%)	29	27 (93%)	1.000
RCA	25	24 (96%)	30	28 (93%)	1.000
Ramus	1	1 (100%)	1	1 (100%)	-
Stent Deployed					
1 stent	25	25 (100%)	19	17 (89%)	0.181
2 stents	8	8 (100%)	16	14 (88%)	0.536
3 stents	8	8 (100%)	8	8 (100%)	-
4 stents	12	12 (100%)	3	3 (100%)	-
5 stents	1	1 (100%)	6	6 (100%)	-
>5 stents	1	1 (0%)	2	2 (100%)	-
Type of Lesions					
Type A	27	27 (100%)	16	16 (100%)	0.133
Type B	23	22 (96%)	26	24 (92%)	1.000
Type C	5	5 (100%)	12	12 (100%)	-
Total Occlusion					
<3 months	2	2 (100%)	17	14 (82%)	1.000
≥ 3 months (CTO)	2	2 (100%)	5	5 (100%)	-
Bifurcation stenting	3	3 (5%)	6	6 (100%)	-

DISCUSSION

The major composite complication after coronary arteriography (CA) in general, is less than 2%.^{15,16} In a study done in Cleveland Clinic¹⁷ on 4,078 patients undergoing percutaneous coronary intervention (PCI), 81 deaths (2%) occurred in 30 days. However, only 42% of this 30-day deaths were associated with the procedure. According to the American College of Cardiology - National Cardiovascular Data Registry (ACC-NCDR),¹⁸ the frequency of in-hospital myocardial infarction and death were 0.4% and 1.4% respectively. In a systematic analysis, the trans-radial approach (TRA) was associated with a 78% reduction in bleeding¹⁹ (OR 0.22, 95% CI: 0.16-0.29) and 80% reduction in blood transfusions (OR 0.2, 95% CI: 0.11-0.32) when compared to the trans-femoral approach (TFA). These findings were consistent in both randomized and observational studies. In patients with STEMI undergoing primary PCI with contemporary anti-coagulation regimens in the HORIZONS-AMI trial, the TRA compared with the TFA was associated with reduced major bleeding and improved event-free survival.²⁰ The TRA allows early ambulation after coronary angiography and reduced bleeding complications. In a multicenter trial of radial versus femoral access for coronary angiography and intervention in acute coronary syndromes (RIVAL trial),²¹ there were no statistically significant difference in the primary outcome of major cardiovascular events. However, this study showed significantly less bleeding and vascular access site complications with the radial compared to the femoral access.

In a meta-analysis and systematic review by Jang et al.²² on 21 studies involving 8,534 patients, TRA was found to have significant reduction in the major adverse cardiac events (OR of 0.56, 95% CI, $p < 0.001$), mortality (OR of 0.55, 95% CI, $p < 0.001$), and major bleeding (OR of 0.32, 95% CI, $p < 0.001$, compared to the TFA). The results translated into shorter hospital length of stay with the TRA with a weighted mean difference of 2.23 days ($p < 0.001$). The meta-analysis done by Bertrand et al.¹⁹ included 76 studies with 15 randomized trials and 61 observational studies that comprised a total of 761,919 patients. Their results revealed a 44%

reduction of mortality with TRA (OR = 0.56) early after PCI and a 78% reduction in bleeding (OR = 0.22) with 80% reduction in transfusions (OR = 0.20). Technical challenges during TRA includes a smaller lumen diameter of the radial artery, encountered arterial spasm, the inability to perform intra-aortic balloon pump insertion or to utilize large catheters (e.g. 8F catheter) in certain PCI subsets.

In the local setting, with the aim to reduce the cost of rendering cardiovascular healthcare service to Filipinos, TRA offers a favorable advantage on outcomes by reducing the cost burden of bleeding and vascular complications²³ in certain subsets as compared to the traditional TFA with shorter length of hospital stay.²²

CONCLUSION

There is a significant reduction the observed bleeding (hematoma) with the trans-radial arterial approach during percutaneous coronary intervention as compared to trans-femoral approach. There was no statistically significant difference between MACE (including in-hospital death, myocardial infarction, cerebrovascular disease), occurrence of arrhythmia, procedural time, fluoroscopy time and cross-over between access in this study. The clinical and procedural outcome of trans-radial approach was comparable to transfemoral approach.

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Association of Door-to-Balloon Time with Clinical Outcomes in Post-Primary Percutaneous Coronary Intervention Patients

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Background --- Primary percutaneous coronary intervention (PCI) is the preferred method of reperfusion for patients with ST-elevation myocardial infarction and a critical component of this management is related to the door-to balloon time. This study aimed to determine the association between door-to-balloon time and clinical outcomes among post-primary PCI patients.

Methods --- We performed a prospective cohort of 177 patients who presented at the emergency department with ST-elevation myocardial infarction and underwent primary percutaneous intervention. Outcome measures include mortality, congestive heart failure and re-infarction in-hospital (within 30 days) and within 6 months based on door-to-balloon time.

Results --- Compared with door-to-balloon time ≤ 90 minutes, door-to-balloon time of >90 minutes was associated with increased risk of in-hospital mortality (OR 5.31; 95% CI 1.52 - 18.56; p 0.009) but no significant association with in-hospital risk for congestive heart failure (OR 1.60; 95% CI 0.72 - 3.58; p 0.252). Within 6 months, door-to-balloon time of more than 90 minutes was also associated with a statistically significant increased risk for mortality (OR 4.60; 95% CI 1.51 - 14.02; p 0.006) and congestive heart failure (OR 2.28; 95% CI 1.03 - 5.03; p 0.020). When adjusted to confounders, multivariate analysis showed that door-to-balloon time more than 90 minutes is associated with increased risk for mortality in-hospital and within 6 months but not with congestive heart failure.

Conclusion --- This study showed an increased risk of mortality in-hospital and within 6 months and trend toward increased risk for congestive heart with door-to-balloon time >90 minutes. Efforts should continue to achieve a shorter door-to-balloon time to improved clinical outcomes of all patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Phil Heart Center J* 2016;21(1):26-32.

Key Words: door-to-balloon time ■ Clinical outcomes ■ Primary Percutaneous Coronary Intervention
■ ST-elevation myocardial infarction

Primary percutaneous coronary intervention (PCI) is the preferred method of reperfusion for patients with ST-elevation myocardial infarction¹ especially in PCI-capable institution like the Philippine Heart Center. A critical component of this management is related to the time upon arrival at the emergency department and the initiation of reperfusion method termed as door-to-balloon time.² As a system goal, primary percutaneous intervention should be performed within 90 minutes of medical contact. Catheter-based techniques applied early without prolonged delay have been shown to improve outcomes in patients with acute myocardial infarction.²⁻⁴ The significance of door-to-balloon time is also highlighted by its inclusion

as one of the core quality measures to improve the care of patients with acute myocardial infarction.⁵⁻⁷

The importance of a short door-to-balloon time was also associated with lower in-hospital mortality regardless of the time of onset of symptoms to presentation as reported in the US national registry of myocardial infarction.³ Therefore, efforts in reducing the door to balloon time has been studied in several centers in the western countries to improve quality of care and survival of patients who have had myocardial infarction.^{4,8} Despite these benefits, recent study in our institution revealed a decreased compliance of achieving door-to-balloon time

of less than 90 minutes.⁹ Several other registries have also reported the benefit of short door-to-balloon time to be limited with early presentation and no significant decreased in risk of mortality despite efforts of adherence to current guidelines.^{10,11} In an effort to resolve these conflicting data, this study will evaluate the institution's experience regarding relationship of door-to-balloon time with short-term outcomes in patients who presented with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention.

This study aimed to determine the association of door-to-balloon time with outcomes of in-hospital mortality, congestive heart failure and re-infarction as well as within 6 months after acute coronary syndrome. If indeed clinical outcomes are associated with door-to-balloon time, institution should make necessary measures to reduce the door-to-balloon time.

METHODS

This prospective cohort study involved ST-elevation myocardial infarction patients admitted at the Philippine Heart Center Emergency Department from March 1, 2013 to August 31, 2014. Adult patients 19 years old and above who were candidates for primary percutaneous coronary intervention for ST-elevation myocardial infarction were included in the study. Patients with symptom onset more than 12 hours associated with signs of hemodynamic and electrical instability as well as ongoing ischemia (chest pain or dynamic ECG changes), as indications for primary percutaneous coronary intervention, were also included. Patients with high-risk non-ST-elevation myocardial infarction or unstable angina requiring early invasive strategies and those who have received prior fibrinolytic therapy for STEMI (facilitated PCI) were the exclusion criteria.

Study Maneuver. This study was approved by the institutional review board and informed consent was obtained from eligible participants. The time of medical contact in the emergency department and time of PCI (balloon inflation) were determined by the investigator based on the records at the emergency department and the invasive laboratory. A pre-specified data abstraction tool

including the time of onset of symptoms, baseline characteristics such as age, sex, co-morbid illness, family history, functional class and baseline electrocardiogram were filled up. The Thrombolysis in Myocardial Infarction (TIMI) score for each subject was also determined. Medical management were left to the attending physician's discretion. Patients were monitored throughout the hospital stay and followed up to 6 months while observing for outcomes to occur. Patients who were discharged were followed up after 30 days and at 6 months in the clinics or out-patient department from onset of myocardial infarction. Outcomes in this study included mortality, congestive heart failure and re-infarction in-hospital and within 6 months. Patients were contacted through phone or were seen, interviewed and examined to determine presence of symptoms and signs of heart failure and determine their functional capacity. Patients during subsequent admissions for an elective procedure (e.g. stage procedure/revascularization) or re-hospitalization were also assessed for presence of outcome.

Door-to-balloon time was defined as the time from the arrival at the emergency department to time of first balloon inflation during percutaneous coronary intervention. In-hospital events were defined as events occurring within 30 days of hospitalization after an acute coronary event. Mortality included deaths from both cardiac and non-cardiac causes. Diagnosis of congestive heart failure was based on symptomatology and findings in physical examination as well as functional capacity evaluated using exercise stress test and/or 6 minute walk test. Re-infarction was defined as new onset chest pain associated with ECG changes and elevated myocardial biomarkers.

Statistical Analysis. Sample size (n) was computed at 196 based on 95% confidence interval, 10% relative error and mortality rate of 15% among STEMI patients as presented in the study of Limbungan et al.⁹

Data analysis was done using Stata SE version 13. Quantitative variables were summarized and presented as means and standard deviation, while qualitative variables were tabulated and presented as frequency and percent distribution. Categorical and continuous variable

were compared between groups using two-sample T test and Fisher's exact test, respectively. Univariate and multivariate logistic regression analyses were used to determine the association of door-to-balloon time with clinical outcomes (OR and 95% CI). A probability value of less than 0.05 was considered statistically significant.

RESULTS

One hundred seventy-seven (177) patients were enrolled in the study, sixty-nine (39%) has door-to-balloon time of >90 minutes and one hundred eight (61%) has door-to-balloon time ≤90 minutes. This cohort was predominantly males (78%), with a mean age 56.7 ± 10.1 . The average door-to-balloon time was 177.55 ± 61.32 minutes. Baseline characteristics were presented in Table 1. Many patients have hypertension and diabetes being the most common co-morbid illnesses in both groups; however, majority with pre-existing coronary artery disease were noted in the group with door-to-balloon of >90 minutes ($p = 0.001$). At baseline, majority of the patients were in functional class I or II presenting as anterior wall STEMI; however, significant number of patients in door-to-balloon time of >90 minutes presented with Killip III-IV during admission compared to that of patients with door-to-balloon time of less than 90 minutes ($p = 0.021$).

The Thrombolysis in Myocardial Infarction (TIMI) score was higher in patients with door-to-balloon >90 minutes ($p = 0.014$) and a significant number has onset of symptoms more than 12 hours observed in this group ($p = 0.037$).

All 177 patients were included in the analysis of association of door-to-balloon time with risk of in-hospital mortality. Fifteen (15) subjects (5 in the group with DTB ≤90, in the group with DTB >90), however, were lost to follow-up after hospitalization. The investigator was not able to contact these patients (either wrong number, no reply or no answer of calls) and there were no out-patient or clinic follow-up within 6 months after the acute coronary event. A total of 155

subjects analyzed for mortality within 6 months and, 159 and 147 subjects analyzed for congestive heart failure in-hospital and within 6 months, respectively (*Figures 1 and 2*). All patients who have the outcomes of mortality and congestive heart failure were included in the analysis at 6 months. Patients without symptoms of heart failure who have died early during hospitalization, in which the presence of heart failure is uncertain, were not included in the analysis.

Table 2 showed the association of door-to-balloon time as to in-hospital mortality. Logistic regression analysis showed significant association of door-to-balloon time of more than 90 minutes with increased risk of in-hospital mortality (OR 5.31; 95% CI 1.52 - 18.56, $p = 0.009$). Multivariate analysis revealed significant association when adjusted to confounders such as TIMI score, sex, smoking history and past medical history of diabetes mellitus (OR 13.96; 95% CI 2.14 - 90.94, $p = 0.006$). In Table 3, there was a trend towards in-hospital risk for congestive heart failure but the association is not statistically significant (OR 1.60; 95% CI 0.72 - 3.58, $p = 0.252$) and no association was determined when adjusted to confounders. Within 6 months, door-to-balloon time of more than 90 minutes was also associated with a statistically significant increased risk for mortality (OR 4.60; 95% CI 1.51 - 14.02; $p = 0.007$) and congestive heart failure (OR 2.28; 95% CI 1.03 - 5.03, $p = 0.042$) as shown in Tables 4 and 5, respectively. When adjusted to confounders such as TIMI score, sex, smoking history, past medical history of diabetes mellitus and chronic kidney disease and anterior wall STEMI, multivariate analysis showed that a door-to-balloon time >90 minutes was associated with increased risk of mortality within 6 months (OR 17.93; 95% CI 2.48 - 129.57, $p = 0.004$). However, the association with congestive heart failure within 6 months was not evident when adjusted to confounders such as TIMI score, Killip class, time onset of symptoms and past medical history of chronic kidney disease and coronary artery disease (OR 1.16; 95% CI 0.31 - 4.36, $p = 0.83$). Re-infarction occurred in only 2 patients with door-to-balloon time of more than 90 minutes and no statistical analysis was done.

Table 1. Baseline Characteristics of Post-PCI patients as to Door-to-Balloon Time

Characteristics	Door-to-balloon time ≤90 minutes (n=69)	Door-to-balloon time >90 minutes (n=108)	p value
Door-to-balloon time (in mins)	66.86 ± 16.20	149.84 ± 56.72	
Age in years	55.38 ± 9.10	57.56 ± 10.72	0.164
Sex (%)			
Male	54 (78.26)	84 (77.78)	0.547
Female	15 (21.74)	22 (22.22)	
Co-morbidities			
Hypertension	46 (66.77)	78 (72.22)	0.267
Diabetes Mellitus	22 (31.88)	35 (32.41)	0.538
Coronary Artery Disease	4 (5.8)	27 (25.00)	0.001
COPD	1 (1.45)	7 (6.48)	0.112
Cerebrovascular Disease	2 (2.90)	6 (5.56)	0.332
Chronic Kidney Disease	6 (8.70)	9 (8.33)	0.569
Family History (%)			
CAD	16 (23.19)	41 (37.96)	0.029
Hypertension	44 (63.77)	78 (72.22)	0.154
Diabetes Mellitus	16 (23.19)	25 (23.15)	0.567
Smoking History	46 (66.67)	69 (69.63)	0.416
Functional Class			
I or II	61 (88.41)	81 (75.00)	0.021
III or IV	8 (11.59)	27 (25.00)	
ECG finding			
Anterior/anterolateral wall	49 (71.01)	59 (54.69)	0.078
Inferior/posterior wall	19 (27.54)	46 (52.59)	
LBBB	1 (4.5)	3 (3.78)	
TIMI Score	3.80 ± 2.35	4.83 ± 2.84	0.014
Symptom onset >12 hours	11 (15.94)	31 (28.70)	0.037

PCI, percutaneous coronary intervention; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; LBBB, left bundle branch block; TIMI, Thrombolysis In Myocardial Infarction

Table 2. Association of door-to-balloon time with in-hospital mortality

Outcome	Door-to-balloon time ≤90 minutes (n=69)	Door-to-balloon time >90 minutes (n=108)	OR	P value
In-hospital (%)				
Mortality	3 (4.35)	21 (19.44)	5.31	0.009

Table 3. Association of door-to-balloon time with in-hospital risk for congestive heart failure

Outcome	Door-to-balloon time ≤90 minutes (n=67)	Door-to-balloon time >90 minutes (n=92)	OR	P value
In-hospital (%)				
CHF	11 (16.42)	22 (23.91)	1.60	0.252

Table 4. Association of door-to-balloon time with mortality within 6 months

Outcome	Door-to-balloon time ≤90 minutes (n=64)	Door-to-balloon time >90 minutes (n=98)	OR	P value
Within 6 months (%)				
Mortality	4 (6.25)	23 (23.47)	4.76	0.006

Table 5. Association of door-to-balloon time with risk for congestive heart failure within 6 months

Outcome	Door-to-balloon time ≤90 minutes (n=62)	Door-to-balloon time >90 minutes (n=85)	OR	P value
Within 6 months (%)				
CHF	12 (17.74)	28 (32.94)	2.28	0.032

DISCUSSION

The findings of this observational study revealed that an increased door-to-balloon time in STEMI patients undergoing primary percutaneous coronary intervention was associated with increased risk for in-hospital mortality and within 6 months with trends toward increased risk for congestive heart failure.

This observation was similar with previously reported studies and cohorts of national registries.¹⁻⁴ The large US national registry of myocardial infarction reported that short door-to-balloon time was associated with lower in-hospital mortality regardless of time of onset of symptoms to time of presentation at the emergency department.³ However, in a long-term follow up of STEMI patients undergoing primary percutaneous coronary intervention reported by Shiomi, et al.¹⁰ no significant difference was found in the incidence of composite of cardiovascular death and congestive heart failure with shorter door-to-balloon time of less than 90 minutes. The benefit of short door-to-balloon time was limited to patient who presented early at the time of symptom onset. In the same study, the analysis showed a trend toward lower risk of cardiovascular death and congestive heart failure with short symptom-to-balloon time. In our study, more patients in the door-to-balloon time more than 90 minutes have time of onset of symptoms more than 12 hours compared to those who have door-to-balloon time of 90 minutes or less, which may be associated with increased mortality in the former group. Theoretically, a short symptom-to-balloon time, meaning short ischemic time, would be expected to be associated with favorable clinical outcome because experimental studies showed that the effect of reperfusion on myocardial salvage was decreased after about two to three hours after the onset of an acute coronary event.¹² However, the uncertainty of the

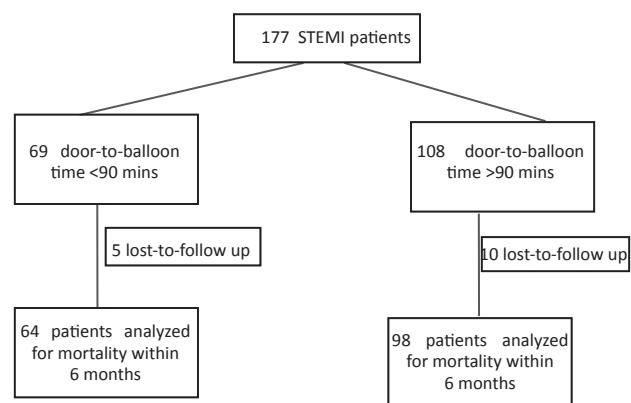


Figure 1. Flow chart for selection of study population and analysis of risk of mortality
STEMI, ST-elevation myocardial infarction

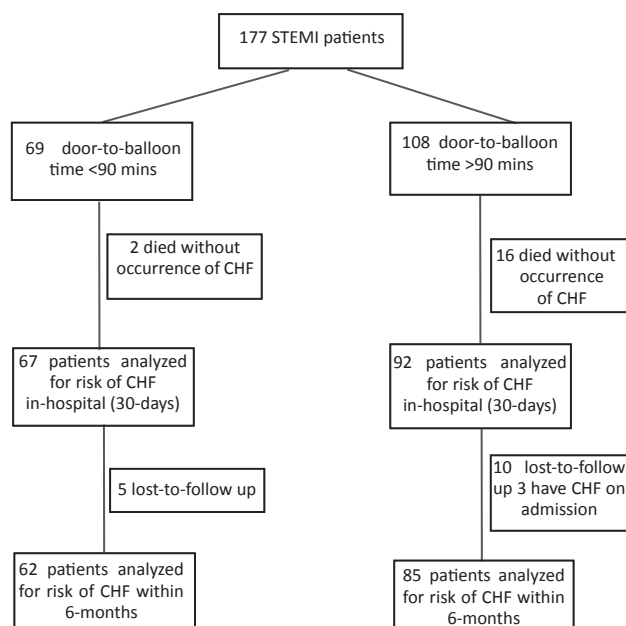


Figure 2. Flow chart for selection of study population and analysis of risk of congestive heart failure
STEMI, ST-elevation myocardial infarction; CHF, congestive heart failure

onset of symptoms because of recall bias and variation in the time course of development of myocardial necrosis, as well as differences in patient's health seeking behavior were factors affecting the relationship between clinical outcome and time of onset of symptoms in STEMI patients. Moreover, Brodie et al.¹³ showed that there was improved in-hospital survival with decreased symptom-to-balloon time in patients with cardiogenic shock, whereas symptom-to-balloon time did not affect survival in low risk patients, suggesting that early presentation and early intervention in high-risk patients will have favorable outcomes.

If compared to the study by Limbungan et al,⁹ the institution's adherence to door-to-balloon time has slightly increased to 39% from 26%, while in-hospital mortality rate for STEMI patients remained almost the same (13.55% vs. 15%). Flynn et al.¹¹ also reported that an observed reduction in door-to-balloon time did not lead to a significant reduction in in-hospital mortality, implying that efforts in reducing door-to-balloon time has not resulted in expected survival benefits. Several factors have been identified that may have an effect on the relationship between door-to-balloon time and mortality. Earlier studies supported that healthier patients with stable hemodynamics treated with shorter door-to-balloon times may strongly influence clinical outcome.¹⁴ Furthermore, multiple lines of evidence suggested a marked decline in myocardial salvage with time and identifying a critical time-dependent period for revascularization within several hours of symptom onset is important, such that, if door-to-balloon time begins outside the critical time-dependent period, decreased door-to-balloon time may not have a major impact on survival.¹¹ Another factor to be considered is the risk stratification of patients at the time of presentation. The Thrombolysis in Myocardial Infarction (TIMI) score and Killip classification predicted 30-day mortality in ST-segment elevation myocardial infarction. Antoniucci et al.¹⁵ stratified patients based on the TIMI risk criteria and showed a statistically significant increased in mortality with increased in time to treatment in high-risk group, whereas no significant effect of short door-to-balloon time in low-risk group. Similarly, our study showed a significant number of patients

in the door-to-balloon time >90 minutes having higher TIMI scores and Killip classification upon presentation, suggesting that early time to treatment may have an impact on clinical outcome in this group of patients.

One of the implications of this study focused on efforts that will continue to decrease the door-to-balloon time for all patients presenting as ST-elevation myocardial infarction undergoing primary PCI. Notably, efforts to further reduced door to balloon times, currently recommended by clinical practice guidelines, offer the potential to significantly reduce patient mortality. The degree of urgency should not depend mainly on baseline risk factors and time of symptom onset. Efforts and strategies in improving door-to-balloon time has been reported by Bradley, et al.⁸ focusing on innovative, standardized protocol development, flexibility in implementing these protocols, senior management support and collaborative interdisciplinary team management. Moreover, further improvement in outcomes of patients with STEMI could be achieved by reducing the total ischemic time with efforts on promoting awareness to patients and improving their health seeking behavior, as well as efforts that will focus in the improvement of pre-hospital care system and early referral system to PCI-capable institutions.

Limitations of the study. There were several limitations of the study. First, the computed sample size was not achieved with 9% drop-out rate, making this study less powered. Second, there were differences in the baseline characteristics between the groups, primarily on the risk stratification of patients at presentation which might limit the comparability of the outcomes. Adjustment using multivariate analysis may limit the effects of confounders in both groups. Third, we cannot exclude the influence of patients' recall bias on symptom onset and reporting of symptoms for congestive heart failure, which may affect reporting of such outcome, although these difficulties were also cited in other studies regarding symptom onset. These might partly influence the reporting of risk for congestive heart failure in-hospital and within 6 months as well as explain the discordance of observed findings compared with other studies. Fourth, the follow-up was too short due to

limited time to conduct this cohort. The impact of long-term outcomes might influence the need to further improve efforts of the institution to achieve short door-to-balloon time in the management of ST-elevation myocardial infarction. Lastly, this study did not include the determination of factors that contribute to longer door-to-balloon time. Further studies were recommended focusing on these factors that will improve the institutions quality health care assurance.

CONCLUSION

In conclusion, this study showed an increased risk for mortality in-hospital and within 6 months and trend toward increased risk for congestive heart failure with door-to-balloon time of more than 90 minutes. Efforts should continue to achieve a shorter door-to-balloon time to improve clinical outcomes of all patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention.

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Outcome of Pediatric Patients Who Underwent Tetralogy of Fallot Correction in relation to the Surgical Technique Used in Relieving Right Ventricular Outflow Obstruction

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Background --- Before the advent of surgical intervention, about 50% of patients with Tetralogy of Fallot died in the first few years of life. Surgical repair, which includes closure of the VSD and relief of right ventricular outflow tract (RVOT) obstruction has greatly improved the long-term survival of TOF patients. Potential complications have been reported in operated TOF patients even if they remain asymptomatic. The objective of this study is to determine the outcome of pediatric patients who underwent tetralogy of fallot correction in relation to the surgical technique used in relieving right ventricular outflow tract obstruction.

Method --- In this prospective study, 63 patients who underwent tetralogy of fallot correction were included. Postoperative complications of residual pulmonary stenosis, pulmonary regurgitation, and right ventricle systolic and diastolic dysfunction were determined and analyzed in relation to the surgical technique used to relieve right ventricular outflow tract obstruction.

Results --- Residual pulmonary stenosis was observed on all patients for both groups. Right ventricular dilatation was still evident on most patients in both groups, with transannular patching group at 60.9% and pulmonary valve sparing group at 60%. RV systolic dysfunction was more common in transannular patching group, accounting for 56.5% of the group while in pulmonary valve sparing group, it was present in 19 patients, accounting for 25% of the group. RV diastolic dysfunction was present in 91.3% of transannular patching group and 85% in pulmonary valve sparing group. With regards to the distance travelled in 6 minute walk test, transannular patching group showed a mean of 297 ± 71.3 m while in pulmonary valve sparing group, it was 215.3 ± 69.2 m. 96.7% and 97.5% of transannular patching group and pulmonary valve sparing group respectively, were in functional class II, while there was 1 (4.3%) from each group who were in functional class III. There was no significant statistical difference that was noted in all the outcomes that were determined for both group.

Conclusion --- Both RV systolic and diastolic dysfunction are present in the early postoperative period. Diastolic dysfunction was more common among patients who had transannular patching while systolic dysfunction was more common among patients who had pulmonary valve sparing. Pulmonary incompetence was more common among the transannular patching group. Most patients in both groups were in functional class II and had sub-optimal distance travelled in six minute walk test. *Phil Heart Center J 2016;21(1):33-40.*

Key Words: Tetralogy of Fallot ■ Postoperative Outcome ■ Surgical Technique
■ Right Ventricular Dysfunction

Tetralogy of Fallot is the most common cyanotic congenital heart disease with an incidence of approximately 0.5/1000 live births (5% to 7% of congenital heart lesions).¹ Before the advent of surgical intervention, about 50% of patients with Tetralogy of Fallot died in the first few years of life, and it was unusual for a patient to survive more than 30 years.² Most patients die in childhood with a survival rate of 66% at 1

year of age, 40% at 3 years, 11% at 20 years and 3% at 40 years.^{1,2} Nowadays, in the advent of surgical repair, which includes closure of the VSD and relief of right ventricular outflow tract (RVOT) obstruction, there is a great improvement in the long-term survival of TOF patients.¹

Nevertheless, a myriad of potential complications have been reported in operated TOF

2nd place, Oral Presentation - Original Paper. 23rd PHC Annual Research Paper Competition and Poster Presentation held on February 26, 2015 at Philippine Heart Center. 1st place - Young Investigators Award - Philippine Heart Association, May 2016. Correspondence to **Dr. Lorielyn G. Mandigma**. Department of Pediatric Cardiovascular Medicine. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at <http://www.phc.gov.ph/journal/publication> copyright by Philippine Heart Center, 2016 ISSN 0018-9034

patients that underlie the importance of follow-up after surgery, even if they remain asymptomatic.¹ These complications include rhythm and conduction disorders, such as sudden cardiac deaths, pulmonary regurgitation (PR) with RV dilatation and dysfunction, and residual RVOT obstruction. These will lead to subsequent hospitalizations, repeat operations, arrhythmias, heart failure as well as death following the initial corrective surgery.¹ These relevant postoperative events, bring about limitation in the right ventricular function, and quality of life and life expectancy.

Reparative surgery for tetralogy of fallot should ideally result in complete closure of the ventricular septal defect, preservation of right ventricular form and function, with an unobstructed right ventricular outflow tract incorporating a competent pulmonary valve.³ Successful repair through a right ventriculotomy was first achieved by Lillehei and Varco, using 'controlled cross-circulation' in 1954.⁴ Kirklin et al was the first to use a pump oxygenator for the repair of TOF one year later.⁵ Improvements in cardiopulmonary bypass technology as well as in surgical technique and perioperative care made early repair feasible with low morbidity and mortality.⁶ Transatrial/transpulmonary repair of TOF, which was first reported in 1963 by Hudspeth et al. has been an important step in the evolution of TOF surgery.⁷ It was reintroduced by Edmunds et al. in 1976 and popularized in recent years. The benefits of the transatrial/transpulmonary approach are believed to derive from eliminating a right ventriculotomy, which may lead to late right ventricular (RV) dilatation and dysfunction as well as increased risk of ventricular ectopic activity.⁸ At our center, tetralogy of fallot correction has been performed since 1975 when the center became operational. In a local study of Bote-Nunez et al., they showed that both transannular patch technique and valve sparing technique are already being performed since 1980 and had excellent late survival with only three known late deaths due to cardiac-related causes.⁹ Subjects included in the study belong to functional class I and II. Residual pulmonary

stenosis was also noted on 2D-echocardiogram in 60% of the subjects.⁹

The study of Murphy et al. on the long-term outcome in patients undergoing surgical repair of tetralogy of fallot showed that the overall survival rate of 95 % 5 years after operation, 92 % after 10 and 15 years, 91% after 20 years, 87% after 25 years and 86 % after 32 years.¹⁰ According to age at the time of operation, the 30 years survival was 90% for less than 5 years old, 93% for 5 to 7 years old, 91% for 8 to 11 years old, and 76% for more than 12 years old.¹⁰ According to patching of pulmonary annulus, the 30 years survival was 87 % for those without pulmonary outflow patch, 85% for those who had patching through the annulus and 88% for those who had patching up to the annulus.¹⁰

Despite the high favorable outcome as shown in several studies, several potential complications have been identified and warrant the need for long-term follow-up.

In the study of Cardoso et al., restrictive RV physiology was seen on follow-up of most patients.¹¹ Incidence varied from 50-70% in the study of Gatzolius et al. Restrictive physiology increases the chance of ventricular arrhythmia and sudden cardiac death.¹²

Pulmonary regurgitation (PR) complicating surgical repair of TOF is common in all patients, with over 80% having at least moderate-to-severe PR. PR has been shown to be related to the use of transannular patch during RVOT reconstruction and aggressive infundibulectomy involving the pulmonary valve annulus. The adverse effects of PR include progressive dilatation of RV, reduced exercise capacity, arrhythmia and sudden death.¹³ Impaired exercise capacity after complete repair of tetralogy of fallot is directly related to the degree of residual pulmonary regurgitation.¹⁴

This study aimed to provide current data on the surgical outcome of tetralogy of fallot patients who underwent repair at our institution. It also aimed to help establish a guideline on post-operative monitoring and follow-up.

METHODS

This is a prospective cohort study done at the Philippine Heart Center from November 2012 to October 2014. Included in the study were patients with tetralogy of fallot (TOF) whose age at the time of surgery was from 3-18 years old. Excluded were TOF patients with pulmonary valve atresia, associated complex congenital heart disease, TOF patients with genetic abnormalities, have clinical signs of right-sided failure (jaundice, hepatomegaly, pulmonary venous congestion) prior to surgery, and Tetralogy of Fallot patients who have echocardiographic findings of RV dysfunction prior to surgery.

Sample Size. The sample size computed is $n = 45$ based on 95% confidence level, maximum tolerable error of 10%, assumed rate of RV diastolic dysfunction of 72.5%¹⁴ and assumed census of tetralogy of fallot correction.¹¹

After approval of the IERB, eligible subjects for the study were recruited, informed consent were secured from parents/guardians of all subjects and assent form was also secured for patients 7-18 years old. The eligible subjects were further grouped depending on the surgical technique used in relieving their RVOT obstruction (Group A-TOF patients who underwent transannular patching and Group B-TOF patients who underwent valve sparing procedure). The demographic characteristics, and preoperative clinical data (hematocrit, oxygen saturation, pulmonary arteries and pulmonary valve z score, previous palliative procedure) were obtained. The presence and degree of residual pulmonary stenosis, presence and degree of pulmonary regurgitation, right ventricular dilatation, and RV dysfunction (systolic and diastolic) were determined by echocardiographic assessment prior to hospital discharge of subject (at least one week up to one month postoperation). Transthoracic 2-dimensional echocardiography were performed and interpreted on the eligible subjects by three echocardiographers to avoid bias. RV diastolic dysfunction

was determined by the presence of any of the following signs of diastolic dysfunction by 2D echocardiography: a.) presence of shortened isovolumic relaxation time; b.) E/A reversal; c) E/A ratio >1 ; d.) E/Ea > 10 ; or e.) presence RV restrictive physiology. Determination was done by M-mode imaging of the right ventricular cavity, followed by detailed pulsed doppler echocardiography: transtricuspid and characteristics at the level of the tips of the valve leaflets in apical 4 chamber view. The antegrade diastolic PA flow, E:A ratio, and right ventricular isovolumic relaxation time were measured. Tissue doppler imaging was used to measure RV diastolic dysfunction. For RV systolic function determination, the parameters that were determined were RV ejection fraction, and tricuspid annular plane systolic excursion (TAPSE). Tricuspid annular plane systolic excursion was used to arrive at a quantitative measurement of RV systolic function by directing M-mode cursor from apex to the medial tricuspid annulus during systole or when RV shortens from base to apex. Tissue doppler imaging was also used to measure RV systolic dysfunction.

Six minute walk test (6MWT) was used to predict the functional capacity of the subjects. Functional status classification was done using the modified Ross classification for heart failure in children. Six minute walk test was done on OPD follow-up (at least two weeks post-operation). For subjects aged three to six years old, psychological conditioning regarding six minute walk test was done prior to hospital discharge and prior to the test on follow-up. If any of the subjects, regardless of their age and reason, failed to finish the test, he/she was rescheduled at another time within a month, until he/she was able to complete the test. The data that were determined were distance walked in six minutes, oxygen saturation and heart rate during the six minutes and during a three minutes recovery period. The patient's functional status was assessed using the modified Ross classification for heart failure in children, which was done through patient and parent/guardian interview.

Plan for Analysis. Data analysis was done in Stata SE version 13. Continuous variables were calculated as means $\pm$ standard deviation while categorical variables were expressed as frequency and percentages. The two groups were compared by Fisher's exact tests for dichotomous variables and student's t tests for continuous variables. The level of significance was set at 0.05.

RESULTS

Table 1 shows the baseline characteristics of the two groups being compared in this study. Results show that the subjects in Group A were older and had a greater weight compared to Group B although there was no significant difference between the two groups.

Table 2 shows the outcome of patients in the two groups during the immediate post-operative pulmonary regurgitation was more common among the transannular patch group (Group A) at 30.4% compared to the valve-sparing group (Group B) at 27.5%. All patients who had pulmonary regurgitation in both groups have mild severity.

In terms of residual pulmonary stenosis, all patients on both group had residual pulmonary stenosis. Patients from the valve-sparing group (Group B) had greater severity with 15 having moderate pulmonary stenosis and 5 having severe pulmonary stenosis. This finding did not yield statistical significance.

Right ventricular dilatation was still present on most patients on both groups, with Group A at 60.9% and Group B at 60%.

RV systolic dysfunction was more common in Group A, accounting for 56.5% of the group while in Group B, it was present in 19 patients, accounting for 25% of the group.

RV diastolic dysfunction was present in 91.3% of Group A and 85% in Group B. Specifically, stage 3 diastolic dysfunction, which connote restrictive physiology is present in 33% of the patients in Group A and 20% in Group B.

With regards to the distance travelled in 6 minute walk test, Group A has a greater distance travelled at a mean of $297 \pm 71.3\text{m}$ as compared to Group B, at $215.3 \pm 69.2\text{m}$.

Table 1. Pre-operative Clinical Data of Patients Who Underwent TOF Correction

	*Group A N = 23 (%)	**Group A N = 40 (%)	P-value
Sex			
Male	13 (56.5%)	23 (57.5%)	1.00
Female	10 (43.5%)	17 (42.5%)	
Age (years $\pm$ SD)	7.5 $\pm$ 3.5	7.0 $\pm$ 3.8	0.64
Weight (kg $\pm$ SD)	22.5 $\pm$ 10.64	19.5 $\pm$ 9.89	0.27
Hematocrit (SI unit $\pm$ SD)	0.56 $\pm$ 0.08	0.53 $\pm$.09	0.27
Oxygen Saturation (% $\pm$ SD)	77.7 $\pm$ 7.0	77.6 $\pm$ 7.4	0.94
Previous palliative surgery	3 (13%)	1 (2%)	0.13
Z score			
Right pulmonary artery (z score $\pm$ SD)	-0.95 $\pm$ 0.93	0.79 $\pm$ 0.86	0.49
Left pulmonary artery (z score $\pm$ SD)	-1.1 $\pm$ 1	-0.75 $\pm$ 0.78	0.17
Pulmonary valve annulus (z score $\pm$ SD)	-2.5 $\pm$ 1.7	-2.1 $\pm$ 1.1	0.27

* Group A - Transannular Patch Group

**Group B - Valve-sparing Group

Table 2: Post-operative Outcome of Patients Who Underwent TOF Correction

	*Group A N = 23 (%)	**Group A N = 40 (%)	P-value
Presence and degree of pulmonary regurgitation			
None	16 (69.6%)	26 (65%)	0.798
Mild	7 (30.4%)	11 (27.5%)	
Moderate	0 (0%)	0 (0%)	
Severe	0 (9%)	0 (0%)	
Presence and degree of residual pulmonary stenosis			
Mild	23 (100%)	20 (50%)	0.229
Moderate	0 (0%)	15 (37.5%)	
Severe	0 (0%)	5 (12.5%)	
Presence of right ventricular dilatation	14 (60.9%)	24 (60%)	1.00
Presence of RV dysfunction			
Systolic	13 (56.5%)	19 (47.5%)	0.6
Diastolic	21 (91.3%)	34 (85%)	0.51
Distance travelled in six minutes (meters $\pm$ SD)	297 $\pm$ 71.3	215.3 $\pm$ 69.2	0.081

* Group A - Transannular Patch Group

**Group B - Valve-sparing Group

Table 3: Functional Assessment by Modified Ross Classification for Heart Failure in Children in Patients Who Underwent TOF Correction

	*Group A N = 23 (%)	**Group A N = 40 (%)	P-value
Class I	0	0	1.0
Class II	22 (96.7%)	39 (97.5%)	
Class III	1 (4.3%)	1 (2.5%)	
Class IV	0	0	

* Group A - Transannular Patch Group

**Group B - Valve-sparing Group

Table 3 shows the functional classification of the patients who underwent tetralogy of fallot correction. Most patients at Group A (96.7%) is in functional class II, while there was only 1 (4.3%) who was in functional class III. This patient had a prolonged hospital stay due to chylothorax and right ventricle failure. This patient was subsequently diagnosed with absent left pulmonary artery on hemodynamic studies that was done postoperatively. In Group B, 97.5% were in functional class II while 1 patient was in functional class III. This patient had previous BTS surgery, which was patent but was not able to be taken down intraoperatively due to technical difficulties. This patient

subsequently had a reoperation after 8 months, and was subsequently discharged; however, the patient died after 4 months.

All the results that were gathered did not yield any statistical significance.

DISCUSSION

Surgical repair by means of ventricular septal defect closure and relief of right ventricular outflow obstruction is the definitive management for tetralogy of fallot. Over the years, there

has been consistent progress to refine the surgical techniques and improve in anesthetic and critical care management to achieve this goal. This evolution has provided better postoperative outcomes and has led to improvement in the quality of life of repaired TOF patients as they reach adulthood.

Postoperative complications of pulmonary incompetence and right ventricular dysfunction can be attributed to many factors. Among which, the surgical technique used to relieve right ventricular outflow tract dysfunction has been implied as one of the many causes.

In our study, pulmonary incompetence was already seen among patients in both groups with the transannular group having a greater incidence at 30.4% as compared to the pulmonary valve sparing group at 27.5%. Both groups had mild severity. Not long ago, pulmonary incompetence was regarded as an inevitable, but unimportant late sequelae of repair. During then, much emphasis was placed on the need for complete relief of obstruction, often at the expense of a freely regurgitant and ever-dilating outflow tract.³ This misguided assertions of investigators can be understood when the time course of the effects of postoperative pulmonary incompetence is considered. Problems from pulmonary incompetence however occur decades after repair;³ and is due to progressive RV dilatation and pressure overload.

Both groups had residual pulmonary stenosis. All patients in the transannular group had mild severity. In the pulmonary valve sparing group, 50% had mild, 7.5% had moderate and 2.5% had severe severity. In the past 20 years, a shift from the need for complete relief of obstruction¹⁵ towards a policy to preserve the pulmonary valve, even at the expense of a modest residual stenosis, has occurred.¹⁶ This shift might keep adverse late effects of pulmonary incompetence to a minimum and retain the integrity of the outflow tract, avoiding late aneurysmal dilation.³

Findings of both diastolic and systolic RV dysfunction were noted at the early postoperative period. Of which, there were more patients in the transannular patching group who diastolic dysfunction (91.3%), compared to the

valve-sparing group (85%). In the study of Cardoso and Miyague,¹¹ RV restrictive physiology, which connotes diastolic dysfunction, was seen in 63.3% of their patients who underwent tetralogy of fallot correction. In their particular study, most of their subjects underwent¹⁷⁻¹⁹ transannular patching. Authors of previous studies have found a correlation between this technique (transannular patching) and the appearance of anterograde diastolic flow in the pulmonary artery, which is seen in 2D-echocardiography of patients with restrictive physiology. Restrictive right ventricular physiology can occur both early and late after repair. Norgard et al. found in their study that the anatomical substrate requiring a transannular patch repair is the most important determinant for early restriction, and midterm restriction is most likely to occur if early restriction is present.¹⁷ Restrictive physiology may relate to a process of endomyocardial fibrosis intrinsic to the disease itself and intensified as time goes by;²⁰ to the ventriculotomy; and to the interposition of patches in the interventricular septum and in the infundibulum.¹⁷ It also seems to be influenced by immaturity of the right ventricle, which adapts to the aggressions of extracorporeal circulation, cardioplegia, and hypothermia.²¹ In the study done by Cardoso and Miyague,¹¹ they have concluded that early postoperative restrictive right ventricular physiology (diastolic dysfunction) may be a transient phenomenon of incomplete adaptation of that ventricle to volume and pressure modifications.

RV systolic dysfunction was more common in the pulmonary valve sparing group at 52.5% compared to the transannular group 43.5%. These findings were contrary to the findings of Nair et al wherein RV dysfunction was more common in patients who needed a transannular patch. They also found that this remarkable decrease in systolic wall motion velocity occurred despite the presence of volume overload in all of our patients, because of the concomitant pulmonary regurgitation.²² This difference may be explained by the timing of follow-up. Findings in our study was during the early postoperative period as compared to the study of Nair et al wherein their findings were noted at least 10 years postoperatively.

Almost all patients on both group belongs to functional class II. This finding is expected to improve after full recovery from surgery. There was only 1 patient from both groups who were in functional class III. This patient from the transannular group had systolic and diastolic RV dysfunction postoperatively and suffered from RV failure. He needed prolonged inotropic support and several failure medications to relieve his symptoms. Subsequent cardiac catheterization data revealed that an absent left pulmonary artery was the etiology of the patient's RV failure. In the pulmonary valve sparing group, the patient who was in functional class III was already 12 years old and had underwent previous palliative surgery. Technical difficulties were encountered during her surgery and the patent shunt from the previous palliative surgery was not removed. Postoperatively, she had RV systolic dysfunction and was noted to have a significant VSD leak causing volume overload and pulmonary congestion.

Results of the six minute walk test for both groups were sub-optimal at a mean of $297 \pm 71.3\text{m}$ for Group A, and $215.3 \pm 69.2\text{m}$ for Group B as compared to the normal value by age which is $470 \pm 57\text{m}$.²³ Like functional class, these results are expected to improve after full recovery from surgery.

The results of this study did not show statistical difference between the two groups as compared to previous published studies but it has confirmed the presence of RV dysfunction in the early postoperative period. The implications of these findings suggest a well catalogued and continuous follow-up of repaired TOF patients. As shown in the study done by Remotigue et al., both RV systolic and diastolic dysfunction was present among repaired TOF patients after one to two years on follow-up and transannular patching technique was associated with the occurrence of restrictive physiology. These findings shows that complications at the early postoperative period, although may be a transient phenomenon may still persist during the midterm follow-up.

Limitations of the Study. Most subjects of this study were preoperatively risk stratified as low risk. There were only 13 patients who had addi-

tional risk factors for surgery. Ten of which are adolescents and 4 of which underwent previous palliative surgery. This variable may have affected the findings of this study since the results may not be a true reflection of the TOF patients undergoing TOF correction.

CONCLUSION

Both RV systolic and diastolic dysfunction are present in both groups in the early postoperative period. Diastolic dysfunction was more common among patients who had transannular patching while systolic dysfunction was more common among patients who had pulmonary valve sparing.

Our study showed that the surgical technique used to relieve the right ventricular outflow obstruction, is not, by itself, associated with the development of right ventricular dysfunction.

Pulmonary incompetence was a more common finding among patients who underwent transannular patching.

Most patients on both groups were in functional class II and had sub-optimal distance travelled in six minute walk test.

RECOMMENDATIONS

1. Continuous monitoring should be done for those patients who were identified to have RV dysfunction in order to prevent the sequelae of the dysfunction.
2. A follow-up study must be done to check for persistence of RV dysfunction and the evolution of pulmonary incompetence on mid-term and long-term follow-up.
3. A prospective study that would equally include TOF patients with pre-operative moderate and high-risk stratification per group should be done in order to evaluate the true incidence of right ventricular dysfunction among post-op tetralogy of fallot patients.

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Comparison of the Clinical Outcome and Cost of Transcatheter Device Occlusion and Surgical Closure of Isolated Ventricular Septal Defect

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Background --- The most common congenital heart disease in childhood is ventricular septal defect (VSD) and the standard mode of treatment for defects that needs correction is surgical closure under cardiopulmonary bypass. Advancements in technology leads us into the era of percutaneous closure of VSDs. The current trend in the correction of congenital heart disease is to use techniques that would allow early hospital discharge and with the least morbidity possible. The general objective of this study is to compare the cost and the clinical outcome of transcatheter device occlusion and surgical closure of isolated ventricular septal defect among pediatric patients of this institution.

Method --- This is a prospective cohort study of pediatric patients (<19yo) who underwent either device or surgical closure of uncomplicated VSD in this institution from January to December 2014. Complications that occurred immediately after the procedure, during the hospital stay and 1 month after discharge were compared. The length of the post procedural hospital stay were likewise compared. Actual in-hospital charges and costs of complications during the hospital stay were noted.

Results --- All cases of VSDs that were included in the study was closed successfully with no residual shunts for both groups. The only complications noted were blood loss requiring blood transfusion (22.6 % for the surgical group and 12.9% for the device group), procedure-related infection (12.9%) and pneumothorax (12.9%). The only complication seen in the device group was blood loss requiring blood transfusion. The mean post procedural days in the surgical group is 4.7 days and 1.2 days for the device group ($p < 0.001$). The mean post procedural days for patients with complications in the surgical group is about 7 days. There was a significant difference in the hospital and procedural costs between the 2 groups. The surgical group was more expensive by Php. 75,200.00 ($p < 0.001$).

Conclusion --- The results of this study support the continued use of transcatheter occlusion as treatment option for closure of isolated VSD. *Phil Heart Center J 2016;21(1):41-46.*

Key Words: Ventricular Septal Defect ■ Transcatheter Closure of VSD

The most common congenital heart disease in childhood is ventricular septal defect (VSD) and the standard mode of treatment for defects that does not close spontaneously and does not respond to medical management is surgical closure under cardiopulmonary bypass. The first successful closure of VSD using cardiopulmonary bypass was at the Mayo Clinic by Dushane and Kirklin in 1856.¹ Surgical closure has been the traditional approach to closing the defect until 1967 when Porstmann et al introduced the first non-surgical closure of congenital

heart disease (CHD) with the use of occluders.² Advancements in technology are leading us into the era of percutaneous closure of VSDs. The current trend in the correction of congenital heart disease is to use techniques that would allow early hospital discharge and with the least morbidity possible. The benefits of avoiding bypass are definitely attractive.

In a study by Xunmin et al of China, 48 VSD patients who were treated surgically and 73 patients who were treated with treated with per-

cutaneous amplatzer occluder were compared. They concluded that the closure rate was similar in the amplatzer VSD closure and surgical closure and that there were more complications in the surgical group but the majority of these was minor and did not require any change in management. Hospital stay and home convalescent times were significantly shorter after amplatzer closure. The cost of both techniques was similar.³ Another study by Liu et al in China compared the results and did an economic analysis on surgical and transcatheter closure of perimembranous ventricular septal defect. They concluded that the superior clinical outcomes and economic benefits of percutaneous closure are inspiring and that percutaneous closure is a valuable alternative to surgery and allows more patients to be effectively treated in China.⁴ In a large institutional study on outcomes and complications after transcatheter closure of a perimembranous-type ventricular septal defect in 890 cases in Taiwan, the incidence of serious complication was 1.12% (10/890), including five cases of third-degree atrioventricular block, two cases of severe tricuspid valve regurgitation, one with of cerebral infarction in the basal ganglia area, and two with femoral artery thrombosis. Nevertheless, no death was reported during patient follow-up and they concluded that transcatheter closure of perimembranous VSDs in selected patients was effective and safe. After a thorough literature search, no local study on VSD device and surgical closure was reviewed.

In this institution, almost all patients with VSD that need correction is done under cardiopulmonary bypass. Transcatheter closure using implantable devices has only been started around 7 years ago and is recently gaining popularity. When explaining therapeutic options to patients or parents with VSD, outcome goals and adverse events need to be fully explained. Since transcatheter device closure is a relatively new procedure here, data on effectiveness, cost and complications comparing these procedures are currently lacking, hence this research was formulated.

The purpose of the this study was to compare the cost and the clinical outcome of transcatheter device occlusion and surgical closure of isolated ventricular septal defect among pediatric patients; to determine the incidence of pediatric

patients with isolated ventricular septal defect who will undergo surgical and device closure; to compare the incidence of clinical outcomes of VSD closure through device occlusion and through surgical correction; and to determine and compare the actual in-hospital costs of these procedures.

METHODS

This research has been reviewed and approved by the institutional ethics review board. Informed consent and assent were obtained from the parents or legal guardian and the subjects prior to inclusion in the study.

This is a prospective cohort study of pediatric patients (<19yo) who underwent either device or surgical closure of uncomplicated VSD in this institution from January to December 2014. Uncomplicated VSD means isolated VSD with no other associated congenital anomalies nor co-morbid conditions.

Patients were included in the study if they had isolated VSD, either muscular or perimembranous type who were qualified to undergo either of the 2 treatment modalities. The choice of surgical or transcatheter closure was based on the preference of the family after thorough explanation by the physician-in-charge. The choice of the device brand to be used depends on the preference of the patient and the physician-in-charge. The 2 local brands of VSD device available in our market are SearcareTM and SanareTM.

Subjects were excluded if they had co-existing cardiac or noncardiac problems that may affect the clinical course and the hospital stay of the patient. They were likewise excluded if they had severe pulmonary hypertension as determined by physical examination and echocardiographic findings.

Subjects were labelled into 2 groups: those who underwent VSD surgical closure and those who underwent VSD transcatheter device closure.

Demographic data such as age, sex, weight, defect size and VSD type were recorded and compared. The length of the post procedural hos-

pital stay were likewise compared.

Complications that occurred immediately after the procedure, during the hospital stay and 1 month after discharge were recorded.

Complications that were noted include residual shunts defined as persistence of VSD murmur and the presence in color-doppler flow mapping of a left to right shunt across the interventricular septum. Residual shunt were classified as follows; trivial (1-2 mm colour jet width), small (1-2 mm colour jet width), moderate (2-4 mm colour jet width), or large (>4 mm colour jet width).⁵

Other complications that were noted include bleeding, infections, arrhythmia, complete heart block requiring intervention, device embolization requiring surgery, device embolization with percutaneous retrieval, loss of peripheral pulse and even death resulting from the procedure. Echocardiographic findings such as the pulmonary artery pressure, change in LVED and new or worsening valvular regurgitations were likewise assessed.

Successful VSD closure was defined as the absence of residual shunts as confirmed by 2D echocardiography, which was done prior to the discharge of each subject.

In the computation of the cost for both procedures, only actual in-hospital charges were included. Costs of complications during the hospital stay were also noted. The actual in-hospital charges were gathered through the computer-generated medical records (MEDTRAK™) of this institution. The professional charges and the additional diagnostic studies on follow up were not included. Indirect costs, such as parental work absence, lost of income, social and psychologic costs of puncture pain and thoracotomy scar and radiation exposure were not quantified in the analysis. Social costs such as transportation and food were likewise not quantified.

Statistical data analysis was done using STATA SE version 13. The quantitative variables were summarized and presented as mean and standard deviation, while qualitative variables were tabulated and presented as frequency and and percent distribution. Homogeneity of charac-

teristics between the 2 groups were tested using the *t* test for quantitative variables and Fisher's exact test for qualitative variables. Comparison of outcome between the 2 groups were determined and tested using independent Hest for the cost and length of hospital stay while Fisher's exact test for specific outcomes. A *p* value less than or equal to 0.05 was considered significant. Furthermore, logistic regression analysis was used to compare surgical and device group in terms of developing at least one complication.

Using PASS (Power Analysis and Sample Size) 2008 software, the minimum sample size requirement was computed using the parameters for logistic regression analysis: alpha (0.)= 0.05, power (1-β) = 80%, PO (success rate among patients undergoing PCI)= 0.26, P1 (success rate among patients undergoing surgery)=0.02. The computed 47 minimum sample size was increased to 60 or 30 subjects per group, accounting for possible 20% drop-out rate. With the exception of alpha and power levels which were set by the reseacher, all other parameters were taken from the study of Thompson and colleagues.⁸

RESULTS

Table 1 shows the characteristic data of pediatric patients with ventricular septal defect according to their respective mode of correction. The surgical group had a significantly younger age group with a mean of 4.8 years, the youngest was 1 year old. The device group had bigger patients with a mean age of 10.48 years and the youngest was 2 years old. There were more female patients in the surgical group while there were more male patients in the device group. There was a significant difference between the weight of the patients in both age group. The lowest weight in the surgical group is 9 kg and 11 kg for the device group. There was also a significant difference on the VSD size between the 2 groups. The surgical group had a mean VSD size of 0.67 cm and 0.45 cm for the device group. Both groups mostly had the perimembranous type of VSD, only the surgical group had subpulmonic VSD and only the device group had muscular VSD. Most patients on both groups had normal pulmonary artery pressure (PAP) and most had left ventricular hypertrophy (LVH).

Table 1. Characteristic Data of Pediatric Patients with Ventricular Septal Defect According to their Mode of Correction

Characteristics	Surgical Group (n = 31)	Device Group (n = 31)	P-value
AGE (years), mean $\pm$ SD	4.83 $\pm$ 3.11	7.59 $\pm$ 0.48	<0.001
SEX			0.440
Male (%)	11 (35.48)	16 (51.61)	
Female (%)	20 (64.52)	15 (48.39)	
WEIGHT (Kg)	21.7 (21.56)	34.15 (16.65)	0.0135
Echocardiographic Parameters			
VSD size (cm)	0.67 $\pm$ 0.05	0.45 $\pm$ 0.12	<0.001
VSD Type			
Perimembranous (%)	25 (80.65)	29 (93.55)	0.012
Subpulmonic (%)	6 (19.35)	0	
Muscular (%)	0	2 (6.45)	
Pulmonary Artery Pressure			
Normal (%)	25 (80.65)	29 (93.55)	0.012
Mild PAH (%)	6 (19.35)	0	
Moderate PAH (%)	0	2 (6.45)	
LVED size			0.001
Normal (%)	10 (32.26)	0	
LVH (%)	21 (67.74)	31 (100.0)	

Table 2. Complications after VSD Closure According to the Mode of Correction

Complications	Surgical Group (n = 31)	Device Group (n = 31)	P-value
Residual Shunt	0	0	
Blood loss requiring blood transfusion	7 (22.58)	4 (12.90)	0.508
Infection related to the procedure	4 (12.9)	0	0.113
Pneumothorax	4 (12.9)	0	0.113

Table 3. Complications after VSD Closure According to the Mode of Correction

Group	With Complications (n = 15)	No Complications (n = 47)	Odds Ratio	P Value
Surgery	11 (73.33)	20 (42.55)	3.75	0.045
Device	4 (26.67)	27 (57.45)		

Table 2 shows the complications after VSD closure according to the mode of correction. The only complications observed with the device group were blood loss requiring blood transfusion and infection related to the procedure. Most patients who needed blood transfusion were from the surgical group and all patients who developed infection and pneumothorax were seen in the surgical group.

Table 3 shows the comparison of the outcome according to the mode of correction. The odds of complication is 3.75 times higher in the surgical group as compared to the device group ($p = 0.045$).

Table 4 shows the postprocedural days in relation to clinical outcomes according to the mode of correction. There was a significant difference in the number of post-operative days between the two groups among the patients with no complications. The mean postprocedural days in the surgical group is 4.65 days and 1.4 days for the device group. The mean post procedural days for patients with complications in the surgical group is about 5 days for those who needed blood transfusion and for those who were treated for infection and 5 days for those who developed pneumothorax. For the device group, patients who needed blood transfusion had 1.25 post procedural days.

Table 4. Post-procedural Days in Relation to Clinical Outcomes According to the Mode of Correction of VSD

Complications	Surgical Group (n = 31)	Device Group (n = 31)	P Value
Residual Shunt	-	-	
Blood loss requiring blood transfusion	4.8 ± 0.87	1.25 ± 0.5	<0.001
Procedure related infection	4.3 ± 1.65	-	
pneumothorax	5	-	

Table 5. Average Cost of Uncomplicated Procedures According to Mode of Correction of VSD

	Surgical Group (n = 31)	Device Group (n = 31)	P Value
Hospital and procedure cost	Php 296,621.54 ± 158,573.02	Php 221,420.65 ± 49,969.67	<0.001

Table 5 shows the average cost according to mode of correction. There was a significant difference in the hospital and procedural cost between the 2 groups regardless of the outcome. The surgical group was more expensive by Php 75,200.00.

DISCUSSION

In this study, the cost and the clinical outcome of transcatheter device occlusion and surgical closure of isolated ventricular septal defect among pediatric patients in this institution were compared. All cases of VSD that were included in the study were closed successfully with no residual shunts for both groups. The only complications noted for both groups was blood loss requiring packed RBC transfusion (25.8% for the surgical group and 12.9 % for the device group). Procedure related infection (12.9 %) and pneumothorax (12.9%) were only seen in the surgical group. The mean post procedural days in the surgical group is 4.6 days and 1.2 days for the device group. The mean post procedural days for patients with complications in the surgical group is about 5-7 days. There was a significant difference in the hospital and procedural costs between the 2 groups. The surgical group was more expensive by Php 75,200.00.

Postprocedural residual shunt is the main factor that is indicative of a successful VSD closure, either through surgery or transcatheter closure. The incidence of successful VSD closure in the single institutional study of Liu et al. in Changhai hospital, wherein 345 patients were included in the study, was recorded at 99.4% in the transcatheter group and 98.9% in the surgical group.⁵ In this research, the incidence of residual shunt was 0% as confirmed by angiography and 2D echocardiography. Some literatures would report higher incidence of residual shunts in the surgical group as compared to the transcatheter group. This is probably because in the transcatheter group, the VSD leaks or residual shunts can be checked immediately after positioning the device in the ventricular septum. If the closure of the defect is inappropriate, the device can be withdrawn and reimplanted to ensure satisfactory closure of the defect. Another important determinant in the success of transcatheter closure is the proper occluder specification selection.

The complications seen in the surgical group were mostly blood loss requiring blood transfusion resulting from the technical difficulty of undergoing open heart surgery. Other complications in the surgical group were related to the tracheal intubation and the use of cardiopulmonary bypass, which were not seen in the transcatheter group. Other significant reported complications in the transcatheter group that is

not seen in the surgical group include device embolization and loss of peripheral pulses. None of these complications were seen in our subjects.

Based on the results of this study, the largest cost difference between the two modes of correction is that of the requirement for cardiopulmonary bypass and longer hospital stay in the surgical group. The majority of the surgical patients are discharged in almost 5 days and 7 days at most for the patients who develop procedure-related infection during their hospital stay. Transcatheter closure eliminates the cardiopulmonary bypass complications and the thoracotomy scar associated with surgical closure, and postprocedure recovery is shortened considerably, hence a lower hospital cost is incurred.

LIMITATIONS OF THE STUDY/ RECOMMENDATIONS

Since this is a short term study, a follow through to include long term efficacy and morbidity of transcatheter closure is worth venturing on for the promotion of better modality selection in the closure of isolated uncomplicated VSDs.

For a more accurate cost benefit study, indirect costs, such as parental absence from work and psychologic and social costs of pain from the procedure needs to be quantified to establish a more cost-effective treatment option for VSD closure.

This study is limited to only one institution and one cost allocating accounting system. Other institutions may have different cost relationships between the two methods of VSD correction, probably because of different incurred costs or different clinical protocols, hence it is limited by institutional differences.

CONCLUSION

In this institution, there are more VSD patients who are undergoing surgical closure than transcatheter closure.

For both groups, no residual shunts were reported. The only complications observed were blood loss requiring blood transfusion, infection related to the procedure and pneumothorax.

The only complication seen in the device group is blood loss requiring blood transfusion. There was a significant difference in the hospital and procedural cost between the 2 groups. The surgical group was more expensive by Php 75,200.00.

The results of this study support the continued use of transcatheter occlusion as a treatment option for closure of isolated VSDs.

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Association of Nutritional Status Using Mini Nutritional Assessment Short Form (MNA®-SF) with Risk of Exacerbation Among Elderly COPD Patients

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Background --- Malnutrition is a common extrapulmonary systemic effect of COPD. It has been shown that malnutrition is correlated with frequency of hospital visits and an independent risk factor for mortality among COPD patients. This study aims to correlate COPD exacerbation with the nutritional status of the elderly patient aged ≥ 65 years old using anthropometric measurements and MNA®-SF.

Methods --- This is a cross-sectional study involving 131 elderly COPD patients who were newly or already diagnosed with COPD confirmed by Pulmonary Function Testing (PFT) at Philippine Heart Center pulmonary laboratory. Nutritional status using Mini Nutritional Assessment short form (MNA®-SF), Body Mass Index, and Anthropometric measurements (mid arm circumference, calf circumference) were measured. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD Combine Assessment Tool was used to evaluate rate of exacerbation. Nutritional status was correlated with the risk of exacerbation using the Pearson's product-moment correlation.

Results --- One hundred thirty one (131) COPD patients participated in the study. Patients who were categorized as at risk of malnutrition and malnourished based on MNA®-SF have ≥ 1 episodes of exacerbation per year ($r = 0.7041$, $p = 0.000$). BMI and MAC showed significantly negative correlation with risk of exacerbation ($r = -0.3873$, $p = 0.000$; $r = -0.2555$, $p = 0.0039$).

Conclusion --- There is a strong correlation between malnutrition and risk of COPD exacerbation using the MNA®-SF as a nutritional assessment tool. *Phil Heart Center J* 2016;21(1):47-52.

Key Words: COPD exacerbation ■ Malnutrition ■ Mini Nutritional Status Short Form

Chronic Obstructive Pulmonary Disease (COPD) is a global health concern. It is characterized by progressive airflow limitation and associated with enhanced chronic inflammatory in the airways and lungs.¹ It is a leading cause of mortality and morbidity worldwide and has a strong impact on the economy. By 2020, it will be the third cause of death and the fifth cause of disability worldwide.² COPD is frequently associated with systemic effects and among them, malnutrition is very common.³ Weight loss, depletion of fat free mass, and loss of fat mass are frequent findings. These abnormalities leads to peripheral muscle weakness, decrease muscle

weakness, decrease muscle mass, impaired functional and exercise capacity, increased hospital stay, and worsening of disease symptoms and quality of life.⁴

A number of nutritional tools have been developed to assess nutritional status. For the elderly aged ≥ 65 years old, the modified Mini Nutritional Assessment Short Form (MNA®-SF) questionnaire was developed to provide a rapid assessment of malnutrition in an acute care setting. This revised questionnaire included an option to use the calf circumference if Body Mass Index (BMI) is not available. According to

Kaiser MJ et al., MNA®-SF is a valid and sensitive rapid nutrition screening instrument that retains the validity and accuracy of the original full Mini Nutritional Assessment (MNA) questionnaire.⁵ In this assessment tool, patients are categorized as 1) normal nutritional status, 2) at risk of malnutrition, and 3) malnourished. According to Landbo et al., a low (BMI) is an independent risk factor for mortality in patients with COPD and with strongest association in subjects with severe COPD.⁶ On the other hand, a study made by Yazdanpanah et al., suggested that in addition to BMI, other nutritional indices like Mid-arm Muscle Circumference (MAMC), Fat Free Mass (FFM), Fat Mass (FM) index should be used for early diagnosis of malnutrition before weight loss occurs.³ Gupta et al., showed that BMI and mid upper arm circumferences were significant predictor of severity of illness and important determinants of hospital outcome. They have found out that those with lower BMI will take longer time to recover, or improve symptomatically, hence having a longer hospital stay.⁷

This study aims to correlate risk of COPD exacerbation with the nutritional status of elderly patient's aged ≥ 65 years old using anthropometric measurements (BMI, MAC, and CC) and MNA®-SF. To our knowledge, this is the first study to use MNA®-SF as a nutritional assessment tool in elderly Filipino COPD patients.

METHODS

This is a cross sectional study involving elderly COPD patients, aged ≥ 65 years old. All subjects were diagnosed to have COPD by Pulmonary Function Testing (PFT) at Philippine Heart Center pulmonary laboratory. A post-bronchodilator FEV1/FVC < 0.70 confirms the presence of airflow limitation. Patients under the nutrition support team, with history of recent major surgery and trauma or with concomitant disease that might alter nutritional status (cirrhosis, uncontrolled diabetes, chronic renal failure, cor pulmonale, cancer, decompensated CHF,

concomitant bronchiectasis, and active pulmonary tuberculosis) were excluded in the study.

Demographic data such as age, sex, comorbidities, smoking history, medications used and their GOLD COPD classification were obtained in a given questionnaire. Smoking status was labeled according to pack years. It was calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked.⁸

The association between symptoms, spirometric classifications, and rate of exacerbations was assessed using the GOLD's COPD Combined Assessment Tool. As defined by the 2014 GOLD COPD guidelines, exacerbation is an acute event characterized by a worsening of the patient's respiratory symptoms (increased in symptoms of dyspnea, cough, and sputum production) that is beyond normal day-to-day variations and leads to a change in medication.⁹

Nutritional Assessment. Nutritional anthropometric indices were measured. Height was measured in meters using a stadiometer and weight in kilograms using a reliable weighing scale. Body Mass Index (BMI) was calculated as a ratio of weight and square of height (kg/m^2). Mid arm circumference (MAC) was measured midway between acromion and olecranon using a measuring tape. Calf circumference (CC) was measured by wrapping a measuring tape around the calf at the widest part. It can be done on sitting or supine position. The MNA®-SF was used to screen the nutritional status of older (≥ 65 years old) COPD patients. It is composed of 6 items: 1) questioning declined food intake and weight loss during the last 3 months 2) mobility 3) psychological stress or acute disease 4) neuropsychological problems and 5) BMI. In the end, each patient was categorized as a) Normal Nutrition status, B) At risk of malnutrition, and C) malnourished, based on the score that they have obtained. Scores of 12-14 are considered normal nutritional status; 8-11 indicate at risk of malnutrition; 0-7 indicates malnutrition. The MNA®-SF was performed only by the principal author. Patient's nutritional status and other anthropometric indices were correlated with the rate of history of exacerbation in a year.

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. Correlation between MNA®-SF and risk of exacerbation and other anthropometric measurements was determined and tested using Pearson's product-moment correlation, and was graphically presented using scatterplot. The level of significance was set at 0.05.

RESULTS

Baseline characters of the 131 COPD patients included in the study are shown in Table 1. There were 118 (90.08%) males and 13(9.92%) females with a mean age of 72.59 ± 6.4 years. Mean average BMI of the subjects was 22.22 ± 4.44 kg/m². Of the 133 subjects, calf circumference was used in 20 subjects in lieu of BMI. Mean mid arm circumference of the subjects were 26.01 ± 17.18 . The subjects averaged 44.48 ± 17.18 pack year's smoking history. The subjects based on the GOLD criteria were divided into four groups: 11.45% were classified in Class A, 19.855 % were classified in Class B, 29.77% in Class C, and 38.93 in Class D. Among the medications that the patients maintained, the three most common were combination of LABA + ICS (64.12%), SAMA + SABA (64.12%), and LAMA (56.49%).

Table 2 presents the association of nutritional status based on MNA®-SF with risk of exacerbation per year. There is a significant association of nutrition categories with the risk of exacerbation ($p=0.000$). Subjects who have a normal nutritional status significantly have no episodes of exacerbation in a year ($p=0.000$). Those who are at risk of malnutrition, noted to have at least one episode of exacerbation per year. However, 2 or more exacerbations was observed for those who are malnourished ($p=0.000$).

Correlation between different nutritional categories according to MNA®-SF and risk of exacerbation was demonstrated significantly in Figure 1. Malnourished patients are likely to have 2 or more exacerbations in a year ($r=0.7041$, $p<0.001$). Body Mass Index (BMI) was nega-

tively correlated ($r = -0.3873$, $p < 0.000$) with risk of exacerbation (Figure 2) suggesting that patients with lower BMI have more exacerbations per year. Mid Arm Circumference (MAC) also showed negative correlation with risk of exacerbation (Figure 3). The smaller the MAC, the higher is the risk of having more than 1 exacerbation in a year.

Table 1. Baseline Characteristics of the COPD Patients Included in the Study.

Demographics (N = 131)	MEAN $\pm$ SD / N (%)
Age in years	72.59 $\pm$ 6.4
BMI (kg/cm ²)	22.22 $\pm$ 4.44
Mid Arm Circumference (cm)	26.01 $\pm$ 5.28
Calf Circumference (cm)	27.25 $\pm$ 6.09
Smoking History (pack/year)	44.48 $\pm$ 27.18
Sex	
Male	118 (90.08)
Female	13 (9.92)
Co-morbidities	
Hypertension	131 (100.0)
Diabetes Mellitus	131 (100.0)
GOLD COPD Class	
Class A	15 (11.45)
Class B	26 (19.85)
Class C	39 (29.77)
Class D	51 (38.93)
Medications	
SABA	59 (45.38)
SAMA	2 (1.53)
SAMA + SABA	84 (64.12)
LABA + ICS	112 (85.00)
LABA	8 (5.11)
LAMA	74 (56.49)

Table 2. Association of MNA®-SF with History of Exacerbation Among Subjects with COPD Included in the Study

History of Exacerbation per year	MNA®-SF			P-Value
	Normal Nutritional status (N%)	At Risk of Mal-nutrition (N%)	Mal-nourished (N%)	
0	25 (71)	3 (6)	0 (0)	0.000
1	7 (20)	26 (51)	6 (13)	0.000
2 or more	3 (9)	22 (43)	39 (87)	0.000

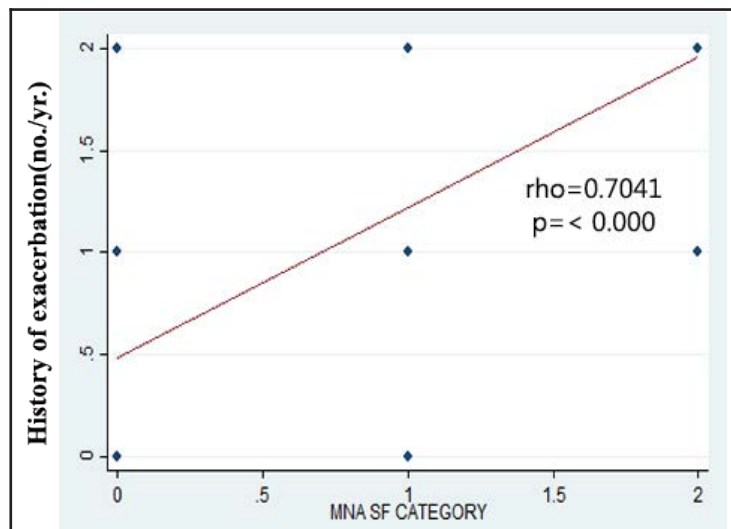


Figure 1. Correlation between MNA® SF and history of exacerbation

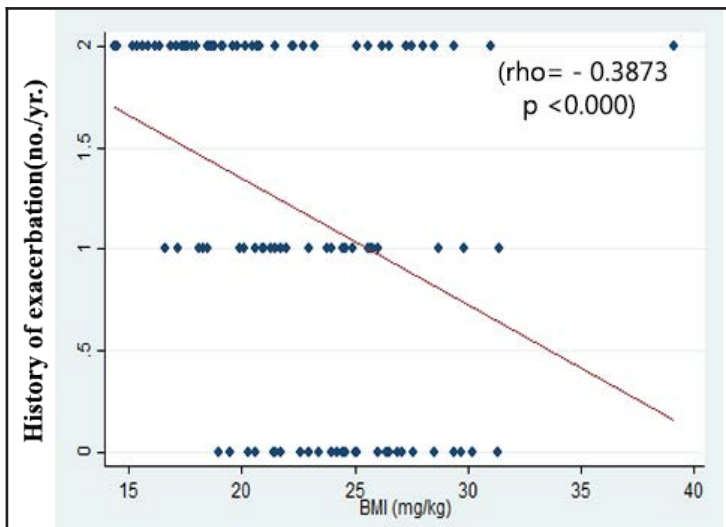


Figure 2. Correlation between BMI and history of exacerbation per year

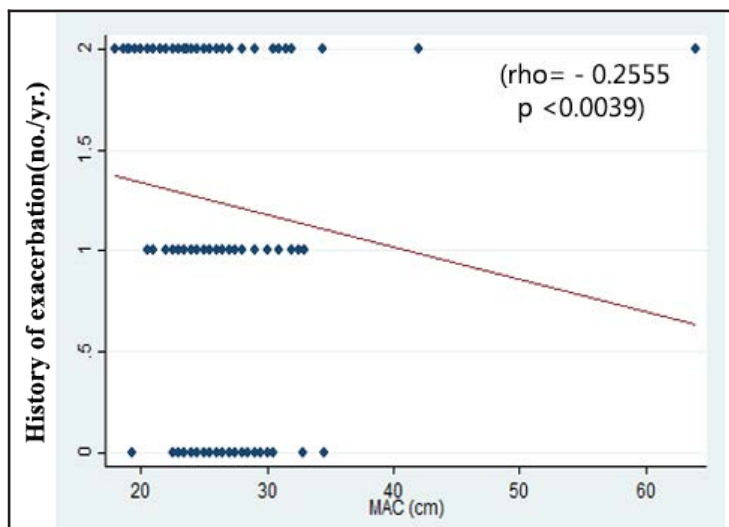


Figure 3. Correlation between MAC and history of exacerbation per year

DISCUSSION

Nutritional abnormalities, weight loss, and skeletal muscle dysfunction (SMD) are significant extrapulmonary systemic effects of COPD.¹⁰ The identification of weight loss and SMD as systemic effects of COPD has drawn attention to the importance of nutritional support, often combined with exercise programs for the improvement of quality of life and prognosis in these patients.¹¹ Malnutrition may be harmful in COPD patients due to decreased respiratory muscle mass and muscle strength.¹² The loss of skeletal muscle mass is the main cause of weight loss in COPD, whereas loss of fat mass contributes to a lesser extent.¹³ Possible pathogenetic mechanism has been variously suggested to result from the following: 1) energy imbalance; 2) disuse atrophy; 3) tissue hypoxia from arterial hypoxemia; 4) systemic inflammation; and 5) anabolic hormonal insufficiency.¹⁴ The causes of these nutritional abnormalities are still unclear. COPD patients are observed to exhibit an increased basal metabolic rate and because this increased metabolic requirement is not met by a parallel increase in caloric intake, weight loss ensues.¹⁵ Several mechanisms could possibly contribute to the increased metabolic rate in COPD. First, drugs commonly used in the treatment of COPD (e.g. B2-agonists) can increase metabolic rate.¹⁶ Secondly, systemic inflammation could also play a significant role, as shown by the relationship between metabolic derangement and increased levels of inflammatory mediators in COPD.¹⁷ Thirdly, tissue hypoxia may also has a role, since other diseases characterized by tissue hypoxia, such as

congestive heart failure, also shows an increased metabolic rate.¹⁸ Furthermore, it was found that there is a direct relationship between the activity of cytochrome oxidase, the mitochondrial enzyme that consumes oxygen, in skeletal muscle and the degree of arterial hypoxemia present in COPD.¹⁹ Similar regulation of cytochrome oxidase was also found in circulating lymphocytes harvested from patients with COPD²⁰ suggesting that this bioenergetics abnormality may affect tissues other than skeletal muscle. Muscle malfunction may be secondary to either intrinsic muscle alterations (mitochondrial abnormalities and loss of contractile proteins) or alterations in the external milieu in which the muscle works (hypoxia, hypercapnia and acidosis), resulting from the abnormalities of pulmonary gas exchange that characterize COPD.²¹ These systemic effects increase the predisposition of exacerbation and respiratory failure. Hence, it is important to identify and correct this problem.

The main findings in this study showed that there is a significant correlation between degree of malnutrition and rates of exacerbation with elderly COPD patient who belongs to MNA®-SF categories of who are at risk of malnutrition and malnourished having higher rates of exacerbation per year. There were also a significant negative correlation of BMI and MAC with the risk of exacerbation with patients having lower BMI and MAC values having more exacerbations per year. The increased risk of exacerbations in malnourished patients observed in our study is consistent with other reports that have found an increased need of medical care, increased number of hospitalization and a higher mortality in underweight COPD patients.¹⁴⁻¹⁵ Pouw et al., reported that patients who lost weight during an exacerbation-related hospitalization, had a higher risk of early non-elective re-admission.¹⁴

Limitations in this study were the small population size and the study being conducted in a single institution. Therefore, this study recommends bigger sample size and inclusion of patients from different medical centers.

CONCLUSION

Assessment of nutritional status of elderly COPD patients using the MNA®-SF can help categorize patients who are at risk for more frequent episodes of exacerbation per year. There is a strong correlation between malnutrition and risk of COPD exacerbation using the MNA®-SF as a nutritional assessment tool.

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A Cohort Study on the Use of Absorbable Sutures Versus Steel Wires in Sternal Closure in Pediatric Patients After Cardiovascular Surgery: a Philippine Heart Center Experience

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Background --- Sternal closure after cardiothoracic surgery has traditionally been with the use of stainless steel wires. Various international papers have been published vouching for the comparability of absorbable sutures with regards to stability and complication rates. This alternative method of closure is being offered at the Philippine Heart Center although no study has been done to document the results, hence this paper came into creation.

Methods --- This is a cohort study on the incidence of complications of sternal closure among pediatric post cardiac surgery patients whose sternotomies were closed using the conventional wires versus those patients whose sternum were closed with polydioxanone sutures.

Results --- There were a total of 246 patients, with 82 the absorbable suture group and 164 in the wire group. There was no significant difference in the gender distribution $p=0.89$. The wire group is heavier ($p=0.01$) and older ($p=0.01$) as compared to the absorbable suture group. The wire group has higher incidence of infections; however the results is not statistically significant ($p=0.67$).

Conclusion --- Sternal closure with absorbable sutures is a safe alternative to the traditional sternal wire closure, with comparable rates of complications between the two groups. *Phil Heart Center J 2016;21(1):53-57.*

Key Words: Sternal Closure ■ Absorbable Sutures

Over ninety percent of the annual operative census of the Philippine Heart Center is comprised of cardiac surgery and almost all of these procedures are done via a median sternotomy approach. Sternal closure is mainly through the use of stainless wires that are sewn through the sternum. Absorbable sutures, like polydioxanone sutures (PDS) and vicryl sutures are not commonly utilized in place of wires. Chances are, these few patients would belong to the pediatric group and most are neonates. There is currently no data on how many cardiac cases are being closed using absorbable sutures after a median sternotomy, specifically for pediatric cases. Part of the objective of this study would be to address this lack of available data.

There are several complications of using wires: adult patients complaining of discomfort

and pain, and erosion onto the skin in patients with thin dermis and subcutaneous tissue leading to chronic sinus tract with or without the development of infection.¹⁻³ Another disadvantage is that the sternal wire are not compatible with magnetic resonance imaging. Should these complications appear, removal of wires would most likely be required. In addition, the PDS would be easier to remove during emergency sternal reopening.

In a study done by Isik et al.⁴ in 1999, 153 post-sternotomy patients were subjected to sternal closure using polydioxanone sutures (PDS), only two of the 153 had sternal dehiscence which led the investigators to conclude that PDS was a safe alternative for sternal closure. Complete hydrolysis of PDS was

a safe alternative for sternal closure. Complete hydrolysis of PDS was approximately at six months, which was longer than the three month bone healing duration. PDS has the longest absorption rate in comparison to other absorbable sutures, hence we use PDS in our institution.

In 1992, in the Department of Pediatric Cardiac Surgery, Hopital de la Timone, Marseille, France, in a series of 50 patients ages 5 months to 16 years and weight 5 to 27 kilograms, PDS was used with no complications noted.⁵

In yet another study done by Schwab et. al⁶ in 1994, 59 children weighing up to 30 kilograms, the use of resorbable suture such as PDS allowed a complication-free stability of the sternum and good wound healing.

In 1999, Keceligil et. al⁷ used PDS for sternal closure in 264 consecutive sternotomies in pediatric patients. Complications like sternal wound infection, dehiscence and mediastinitis occurred in 1.51% (3/264). They concluded that the use of absorbable suture is a safe alternative to standard sternotomy closure.

Based on the results of the aforementioned studies, it is high time that there is a documentation of the results of this alternative intervention at the Philippine Heart Center.

The objectives of this study were to compare the effects of sternal closure using sternal wires and absorbable sutures on post-operative outcomes in pediatric post-cardiac surgery patients and to determine and compare the incidence of post-operative complications.

METHODS

This is a cohort study on the incidence of complications of sternal closure among pediatric post cardiac surgery patients whose sternotomies were closed using the conventional wires versus those patients whose sternum were closed with polydioxanone sutures. The study protocol was approved by the Institutional Ethics Review Board (IERB) and consent and assent forms were obtained prior to participation.

Study Population. The study included pediatric patients who underwent cardiothoracic surgery at the Philippine Heart Center from October 2012 to September 2013. Also included were pediatric patients weighing 2 to 30 kilograms who underwent cardiothoracic surgery using the sternal approach, either electively or as emergency. Excluded in the study were patients with known hypersensitivity to polydioxanone sutures, patients on chronic steroids and with delayed sternal closure patients.

Sample size computed was $n=214$, with 107 per group at 95% confidence level, 80% power and the assumed difference in the rate infection of 10 percent. The basis for assumption was the paper Mulch et. al,⁸ entitled "closure of longitudinal sternotomy with absorbable sutures" in 1986 with one percent infection rate with absorbable suture.

Study Maneuver. Once the patient is deemed eligible in the study as per fulfillment of the inclusion criteria, informed consent from the parent/guardian was obtained. It was specifically mentioned that traditionally, wires were used and that absorbable sutures were innovatively new in the field. Permission from the attending physician was also sought before the patient's inclusion.

The parent at any time, with or without reason, can opt to voluntarily withdraw from the study. The study, on the other hand, was terminated if in the preliminary reports there was an incidence of complications in the either group of more than ten percent (10%).

After the usual conduct of the planned procedure, sternal closure was done by the surgeon and the material depends on his or her preference. Four or five simple interrupted wires or absorbable suture was passed through the parasternal interspaces. The wires would be twisted and cut the standard way, while the absorbable sutures was tied in five knots. Subcutaneous tissue and skin closure was done routinely using continuous 3/0 absorbable sutures and the skin with 4/0 absorbable sutures.

The patient's demographic data, preoperative and postoperative diagnosis, procedure and its

duration was collected and collated.

The immediate post-operative/in-hospital status of the sternotomy was monitored in terms of the occurrence of complications as defined.

The parents together with the patients were instructed to report for follow-up at the out-patient department a week after discharge as part of this ongoing study. The surgery fellow-on-duty at the out-patient recorded the data of the included subjects in a specifically labeled logbook. Any noted complication was addressed appropriately either with antibiotics given orally or intravenous and/or scheduled for debridement.

Post-operative surveillance for complications was set at the first out-patient follow-up which is at one week after discharge and at one month after discharge. The parents were instructed to follow-up at anytime should any of the aforementioned complications arise within the period of prescribed observation. A complete indexed list of patients and their contact numbers was stationed at the out-patient department and whoever was assigned at the OPD recorded his or her assessment of the condition of the sternal incision. Assessment of complications was based on the definitions used in this study.

Analysis of Data. Quantitative data was described as mean $\pm$ standard deviation and qualitative data in frequency and percent distribution. To determine the homogeneity of the patients' characteristics, T-test and chi-square test were applied to the data. To compare the outcome of the two groups, chi-square test was used if there no probable confounders. Multiple logistic regression was used to determine the independent effect of interventions to outcome. A p value of ≤ 0.05 was considered significant.

RESULTS

This study was able to reach its total target sample size of 214 patients, with 82 patients included in the absorbable suture group and 164 in the wire group. Baseline characteristics of the two intervention groups are as stated in Table 1.

Although more males were included in either group (57% for the suture group and 55% for the wire group) gender distribution between the two intervention groups showed no significant difference (p value 0.89).

The mean age and mean weight of the patients between the two groups showed a significantly heavier and older group in the wire group. The wire group (n= 164) had a mean age of almost six years compared to the suture group's (n= 82) mean age of a year and a half. The mean weight of the wire group was 18 kilograms as compared to almost eight kilograms in the suture group. Both difference in the age and weight had a p value of 0.01.

With regards to the outcome of interest, which is infection, those with infection tended to be younger and lighter as compared to the patients who did not contract an infection. This is evident in Table 2 which shows the mean age of those with infection was a year and a half compared to almost five years in the no infection group (p value 0.16). Also the weight of those patients with infection was 8 kilograms compared to almost double their weight for the no infection group (p value 0.22). Both differences were however not significant as evident with the corresponding p values.

Table 1. Baseline Characteristics of Pediatric Patients According to Sternal Closure Material Used

Characteristics	Sternal Closure Material		p-value
	Suture (n=82)	Wire (n=164)	
Gender			
Male	47 (57%)	91 (55%)	0.89
Female	35 (43%)	73 (45%)	
Age (in years)	1.55 $\pm$ 2.24	5.82 $\pm$ 4.59	0.01
Weight (in kilograms)	7.48 $\pm$ 6.05	18.05 $\pm$ 12.47	0.01

Table 2. Rates of Infection Associated with Mean Age and Mean Weight

Characteristics	Infection		p-value
	With Infection	No Infection	
Age (in years)	1.62 ± 2.00	4.46 ± 4.46	0.16
Weight (in kilograms)	8.04 ± 4.08	14.65 ± 11.92	0.22

Table 3. Rates of Infection Among Pediatric Patients according to Sternal Closure Material Used

Infection	Sternal Closure Material		p-value
	Wire (n=64)	Suture (N=82)	
With infection	4 (2%)	1 (1.23%)	0.67
Without infection	160 (98%)	81 (98.78%)	

Finally, Table 3 shows the rate of infection comparing the two intervention groups. Actual figures show that there were more infections in the wire group (4), compared to only one in the suture group, however this was not statistically significant.

DISCUSSION

Traditional closure of the sternum entails using sewing stainless steel wires through the sternum. This was not without complications.¹⁻³ These include patients complaining of discomfort and pain, erosion onto the skin in patients with thin dermis and subcutaneous tissue leading to chronic sinus tract with or without the development of infection. The aforementioned authors proposed the use of absorbable sutures particularly polydioxanone as a safe alternative to stainless steel wire with minimal incidence of complications.

At the Philippine Heart Center, this alternative method of sternal closure is already being offered to a select group of patients, particularly the pediatric group. A study on the incidence of complications has not been done as of yet, much less, a randomized trial. This study started out as a randomized clinical trial, however, due to lack of consent from both the attending physicians

and the parents, this study was converted into a prospective cohort study of two intervention groups.

The study population was comparable with the aforementioned studies in the past literature. The same can be said of the mean age and weight of the patients. Although in the study by Isik et. al⁴ their study had an older age inclusion which was up to 71 years and heavier weight range which was up to 75 kilograms. The infection rate from their study was at 1.3% compared to the author's study which was at 1.23%. In yet another study done by Keceligil et. al,⁷ they had 1.5% complication rate.

Finally, in the series done by Mulch,⁸ there was one complication out of 150 patients with an infection rate of 1.54%.

Due to lack of randomization and matching, several variables have not been controlled such as the weight and age of the patients. This lack of randomization is the primary limitation of this study.

As compared with the aforementioned studies, it can be concluded that the author's study is at par with international studies as regards the incidence of complications particularly of infection with the use of absorbable sutures in the closure of sternotomies.

CONCLUSION

Sternal closure after cardiac procedures is a safe alternative to using stainless steel wires in the pediatric age group. The experience at the Philippine Heart Center yielded comparable incidence of complications compared with studies done in the international fora.

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The Correlation of Epicardial Adipose Tissue (EAT) Thickness and Radiodensity with CT Coronary Artery Calcium Score

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Background --- Interest on epicardial adipose tissue as a measure of cardiovascular risk has recently been emerging. CT coronary artery calcium score has been regarded as a standard of reference for cardiac event risk determination. This research aims to determine the correlation between epicardial adipose tissue (EAT) thickness and radiodensity with coronary artery calcium score (CACS).

Methods --- 146 patients, 40 years of age and above with CT calcium scores were included in this study. CACS were calculated by a calcium analysis software. EAT thickness were measured on the right ventricular anterior free wall at the 25%, 50% and 75% levels of the wall and subsequently averaged. EAT radiodensity were evaluated at the same levels, averaged and expressed in Hounsfield units. Pearson's Product-Moment correlation was used to determine the correlation between EAT thickness and EAT radiodensity with the CACS.

Result --- The mean EAT thickness was 2.39 ± 1.51 mm while mean EAT radiodensity was -93.76 ± 22.99 HU. The mean coronary artery calcium score calculated was 310.38. There was moderate positive correlation between the EAT thickness and CACS, as well as between EAT radiodensity and CACS, with a Pearson's r of 0.691 ($p < 0.001$) and 0.433 ($p < 0.001$) respectively.

Conclusion --- Epicardial adipose tissue thickness and radiodensity showed moderate positive correlation with coronary artery calcium score. Further studies, possibly those that will be able to follow through with clinical outcome, is recommended to be able to establish its role as a non-invasive quantitative parameter for cardiovascular risk of adverse coronary event. *Phil Heart Center J 2016;21(1):58-62.*

Key Words: epicardial adipose tissue thickness ■ epicardial adipose tissue radiodensity ■ CT coronary artery calcium score ■ cardiovascular risk

Coronary heart disease is a leading cause of mortality in industrialized countries. Various tools comprising of clinical, chemical and imaging have been continuously evolving with a primary purpose of preventing such outcome. Systemic arterial calcification is one of the manifestations of cardiovascular disease (CVD). It has been suggested that calcified plaques in the coronary artery wall detected through CT coronary artery calcium score (CACS) may indicate coronary artery disease (CAD) and its extent.¹ Several researches support the role of CACS in predicting myocardial infarction and in cardiovascular risk stratification.² The review article by Shabestari,¹ which included a significant number of researches on CACS, concluded that this procedure is generally accepted as a standard of reference for cardiac event risk

determination.

Interest on the association of epicardial adipose tissue as a measure of cardiovascular risk has recently been emerging. A study by Toczylowski³ has discussed the effects of epicardial adipose tissue (EAT) on cardiac metabolism and function, including its role in CVD. Hypothesis on the paracrine effect of epicardial fat and its possible role as a valuable determinant of coronary plaque development and progression has been discussed. Fat, having distinct low attenuation values on CT scan, can be readily identified and easily measured. One of the parameters studied in a number of researches is epicardial fat volume. Epicardial fat volume was shown to be associated with increased incidence of high risk plaques on coronary CT angiogram

and on coronary artery disease.⁴ One research sought to examine epicardial fat radiodensity using Hounsfield units and argued that the atherosclerotic property of epicardial fat results in increased radiodensity.⁵

This research aims to determine the correlation between the coronary artery calcium score and EAT thickness and EAT radiodensity. Epicardial fat tissue as a marker of cardiovascular risk has not been extensively studied. It is readily seen in CT images of the chest but often disregarded and not included in the reports because of the lack of information regarding its significance. The clinical importance of this study will be that epicardial adipose thickness and radiodensity may provide an alternative measure of cardiovascular and coronary artery disease risk and not be simply overlooked. Another benefit would be its relative ease and accessibility in estimating cardiovascular risk especially in circumstances where coronary artery calcium score software is not available. Grading of cardiovascular risk using EAT thickness or volume and EAT radiodensity has not been established. This research also aims to initiate a cardiovascular risk score in correspondence with the CACS and possibly arrive with an appropriate recommendation of actions.

The objectives of this study were to determine the correlation between epicardial adipose tissue thickness and radiodensity with coronary artery calcium score; to determine cardiovascular risk using coronary artery calcium score; to measure epicardial adipose tissue thickness and epicardial adipose tissue radiodensity in multi-detector CT scan, and; to determine the correlation between epicardial fat thickness and radiodensity with coronary artery calcium score.

METHODS

This study was reviewed and approved by the Philippine Heart Center Institutional Ethics Review Board (PHC-IERB). Waiver of consent was requested from the PHC-IERB. This is a cross-sectional study done at the Philippine Heart Center from January 2009 to June 2014. Included in the study were in-patients and out-patients who are 40 years of age and above referred for

coronary artery calcium score or coronary CT angiogram with calcium scores and with acceptable images for interpretation. Excluded from the study were patients with previous percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, implanted pacemaker, artificial valves or any other artifact-generating metal objects.

Study Maneuver: ECG gated non-contrast MDCT scans at a slice thickness of 3 mm and intervals of 1.5 mm were obtained using Philips Brilliance 40-slice channel configuration. Subjects were scanned in supine position during a single inspiratory breath hold.

Coronary artery calcium score were assessed on a dedicated post-processing workstation using calcium analysis software (Philips Heartbeat-CS). CACS were quantified using the Agatston score. Calcification was defined as an area $\geq 1 \text{ mm}^2$ in the axial plane of a coronary artery with an attenuation threshold of ≥ 130 Hounsfield units (HU). Regions of interest were drawn and CACS were automatically calculated by the software. Total CACS were obtained by summing the weighted scores from each coronary artery.

Epicardial adipose tissue is defined as the adipose tissue between the surface of the heart and the visceral epicardium surrounding the main coronary arteries. To determine the epicardial adipose thickness, measurements were made on the right ventricular anterior free wall along the axial plane. Three measurements were obtained at the 25%, 50% and 75% levels of the wall. EAT was measured from the visceral epicardium to the outer aspect of the myocardium and perpendicular to the surface of the heart. The mean of these measurements were used for analysis.

Epicardial adipose radiodensity measurements were evaluated at the same levels. Mean epicardial adipose tissue density were computed and expressed on a HU scale.

Above measurements were done by the investigator. After which, 20 randomly selected cases were re-assessed by another radiologist. T-test was done to the values taken to establish inter-observer variability.

Sample Size Calculation. Using NCSS-PASS 2008 statistical software, the minimum sample size requirement was 146 as computed using the following parameters: alpha (α) = 0.05, power ($1-\beta$) = 80% and $r = 0.23$ (5).

Statistical Analysis. Mean $\pm$ SD were used for quantitative variables while frequency and percent distribution were utilized for qualitative variables. Pearson's Product-Moment correlation were applied to determine the correlation between the coronary artery calcium score and the epicardial adipose thickness and radiodensity.

RESULTS

A total of 146 subjects were included in the study consisting of 93 males (63.7%) and 53 females (36.3%) with a minimum age of 42 and maximum age of 82 (mean $\pm$ SD, 57.08 ± 10.57). A significant number of subjects had undisclosed information on the presence of co-morbidities namely diabetes mellitus, hypertension, hyperlipidemia and smoking history. Table 1 demonstrates the demographic profile of the subjects.

T-test done on the quantification of epicardial adipose thickness and radiodensity by two radiologists showed no significant interobserver variability with p-value of 0.211 and 0.228 respectively.

The mean EAT thickness measured for the sample entire population was 2.39 ± 1.51 mm with range from 0.37 mm to 8 mm. The mean coronary artery calcium score calculated was 310.38. The EAT showed moderate positive correlation with the CACS with a Pearson's r of 0.691 ($p < 0.001$) as illustrated in the scatterplot provided below. (Figure 1)

The epicardial adipose radiodensity for the entire sample population has a mean of -93.76 ± 22.99 HU. The EAT radiodensity also revealed a moderate positive correlation with CACS with a Pearson's r of 0.433 ($p < 0.001$). Higher attenuation or density values expressed as Hounsfield units were obtained with higher calcium scores. Figure 2 demonstrates the relationship between

the EAT radiodensity and CACS.

Table 1. Demographic Characteristics of Patients in the Study

Characteristics (N = 146)	mean $\pm$ SD or n(%)
Subjects	
Age (years)	57.08 $\pm$ 10.57
Gender	
Male	93 (63.7)
Female	53 (36.3)
Co-morbidities	
Diabetes Mellitus (n=57)	22 (38.6)
Hypertension (n=67)	45 (67.2)
History of smoking (n=51)	26 (51)

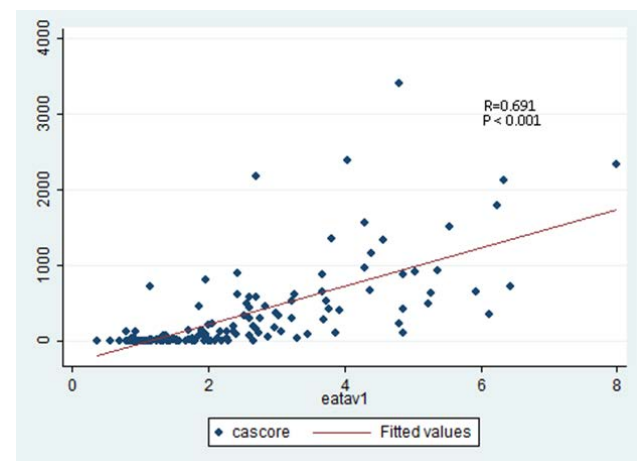


Figure 1. Scatterplot of correlation of epicardial adipose thickness with coronary artery calcium score

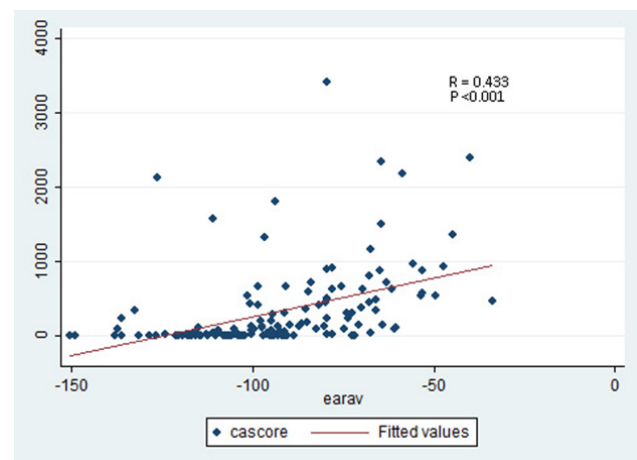


Figure 2. Scatterplot of correlation between of epicardial adipose radiodensity with coronary artery calcium score

DISCUSSION

This research showed positive correlation between the epicardial adipose tissue thickness and radiodensity with the CT coronary artery calcium score.

The mean epicardial adipose thickness in this study was 2.39 ± 1.51 mm comparable with the study by Bachar⁶ which gathered a mean EAT thickness of 2.39 ± 1.59 mm. Both these studies utilized the same method of measuring the EAT thickness on the right ventricular anterior free wall at three levels (25%, 50% and 75%) from the visceral epicardium to the outer myocardial surface. Measurement over the RV wall has also been used in other imaging modalities such as echocardiography⁷ as an indicator of cardiac adiposity. Other studies have opted volumetric quantification of epicardial fat and was proven to be more reproducible than thickness. However, similar to Bachar, CT measurement of thickness was chosen due to its straightforwardness with less time and intensive labor spent in measurement; thus, potentially is more clinically applicable.

Moderate positive correlation between EAT thickness and CACS was seen in this study with a Pearson's r of 0.691 ($p < 0.001$). The accumulation of epicardial fat was shown to be related to increasing coronary plaque burden manifested by increased calcium score. This supports the previous research by Bachar which presented patients in whom coronary artery disease (CAD) had significantly thicker EAT than those without CAD.⁶ Furthermore, that study suggested that increased EAT thickness may serve as a marker for severe atherosclerosis and possibly be a risk factor for significant CAD. Other researches have used CT volumetric quantification of epicardial fat. Such studies also yielded a significant association between the amount of epicardial fat tissue and CACS.⁸ It has been hypothesized that the presence of fat surrounding the heart may contribute with the advancement of coronary atherosclerosis in an outside-inside fashion. Increased deposition of epicardial adipose tissue was postulated to initiate a vascular inflammation, contributing to atherogenesis as previously investigated by Verhagen.⁹

The association of EAT radiodensity with cardiovascular disease is far less explored compared to studies done on EAT thickness or volume. In this research, a moderate positive correlation between EAT radiodensity and CACS was identified with $r = 0.433$ ($p < 0.001$). Despite differences in method of measuring CT attenuation of epicardial fat, this study had similar results gathered by Pracon.⁵ In addition, his research also noted that patients with CAD had significantly higher CT attenuation of epicardial fat tissue. Another finding of Pracon was the association between EAT volume and EAT radiodensity which is somewhat parallel to the incidental finding of correlation between EAT thickness and radiodensity in this research.

Most of the patients included were likely referred for presence of cardiovascular disease or for prediction of possible adverse cardiac event. Thus, selection bias may have overestimated the results obtained in this research. The clinical information on pre-existing comorbidities such as hypertension, diabetes mellitus, hyperlipidemia, smoking and family history of CAD were incomplete and posed as a limitation to this study. A larger sample population with more extensive clinical data in a prospective setting or with follow-through on clinical outcome is recommended in further studies to be able to establish its role as a non-invasive quantitative parameter for cardiovascular risk or adverse coronary event.

CONCLUSION

Epicardial adipose tissue thickness and radiodensity showed moderate positive correlation with coronary artery calcium score. Further studies, possibly those that will be able to follow through with clinical outcome are recommended to be able to establish its role as a non-invasive quantitative parameter for cardiovascular risk or adverse coronary event.

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Prognostic Value of Coronary Flow Reserve by Dipyridamole SPECT Sestamibi Imaging in Predicting Future Cardiac Events

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Background --- Impairment of coronary flow reserve (CFR) precedes preclinical atherosclerosis. However, its prognostic utility using SPECT imaging is least explored. Thus, this study aimed to determine the clinical utility of CFR by sestamibi imaging in predicting future cardiac events in patients with normal and abnormal myocardial perfusion scan (MPS).

Method --- This was a prospective cohort study of 54 consecutive patients who underwent 2-day protocol of dipyridamole Tc-99m sestamibi MPS with first-pass acquisition of the pulmonary artery. CFR was computed as quotient of myocardial blood flow (MBF) at stress and at rest. MBF was calculated from global tissue perfusion divided by arterial input function. All subjects were followed-up for any major adverse cardiac events (MACE) 4 to 17 months after MPS (mean follow-up 9 ± 3 months) through review of hospital record and phone interview.

Results --- Abnormal MPI revealed significantly lower CFR (1.64 ± 0.47 vs 1.19 ± 0.36 $p=0.005$). In Kaplan-Meier analysis, patients with abnormal perfusion revealed significantly higher incidence of cardiac events compared with normal perfusion (chi-square 4.93, $p=0.027$). While based on the CFR data, there was a trend towards increased incidence of cardiac events in patients with abnormal CFR; however, this did not reach statistical significance (chi-square 0.61, $p = 0.434$).

Conclusion --- With abnormal perfusion, there was significantly reduced CFR and higher incidence of MACE. Also, with abnormal CFR, a trend towards increased incidence of MACE was noted, however, this did not reach statistical significance most likely due to short-term follow-up period. *Phil Heart Center J* 2016;21(1):63-71.

Key Words: Coronary Flow Reserve ■ Dipyridamole ■ SPECT ■ Prognostication

The factors assessed by single photon emission computed tomography (SPECT) that determines patient prognosis includes the extent of infarction and magnitude of jeopardized myocardium.² However, additional important factor in prognostic assessment is the stability or instability of the CAD process. Unstable plaque is associated with abnormal endothelial function, resulting in a vasoconstrictive response to acetylcholine stimulation, whereas stable mild coronary lesions respond with vasodilation.³ This earliest stages of atherogenesis and precedes identifiable perfusion deficits and wall motion abnormalities with traditional imaging methods.⁴

Coronary flow reserve (CFR), expressed as the ratio of maximally vasodilated flow to corres-

ponding resting flow, quantifies the ability of myocardial blood flow to increase above resting level.⁵ It is best assessed through intracoronary doppler techniques and noninvasively PET is the gold standard. But these techniques are limited due to its high costs, complexity, and relative inaccessibility.⁶ Thus, heralded the investigation of CFR using SPECT imaging, which is more widely available. Further studies even validated CFR by sestamibi imaging to be as comparable to that of intracoronary doppler⁷ and PET⁸ imaging, despite its inability to correct for scatter, attenuation and partial volume effect.

As concept on CFR has been cultivated, its clinical applicability was extended on its possible prognostic utility. Italian investigators

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spearheaded the prognostication value of SPECT estimated CFR, which showed promising results.⁹ However, no data are currently available on the prognostic value of SPECT estimated CFR in the Philippine setting and presently nuclear cardiology procedure does not have routine evaluation of CFR as basis for pre-clinical atherosclerosis, hence this study.

This study aimed to determine the clinical utility of estimated coronary flow reserve by sestamibi imaging in predicting future cardiac events in patients with normal and abnormal myocardial perfusion scan; to determine the coronary flow reserve in patients with normal and abnormal myocardial perfusion scan; to determine and compare the occurrence of cardiac events based on perfusion status; to determine and compare the occurrence of cardiac events according to coronary flow reserve; to determine and compare the occurrence of cardiac events based on perfusion and coronary flow reserve.

METHODS

This was a prospective cohort study of 54 consecutive adult patients referred to Nuclear Medicine Division, Philippine Heart Center for dipyridamole Technetium-99m sestamibi SPECT myocardial perfusion imaging (MPI) from August 2012 to September 2013. Patients with normal and abnormal myocardial perfusion scintigraphy were enrolled in the study. Eligible subjects were excluded if with history of myocardial infarction and revascularization procedures. Follow-up for major adverse cardiac events (MACE) was done at least 6 months from MPI. The institutional ethics review board approved this study and informed consent was obtained from each subject.

The minimum sample size requirement was 60 (30 per group) based on the following parameters: $\alpha = 0.05$, power 0.80, and assumed event rate of 42% and 36% among patients with normal and abnormal CFR, respectively based on the paper of Daniele et al.⁹

All adult patients referred in the Nuclear Medicine Division of the Philippine Heart Center for evaluation of coronary artery disease (CAD) using Technetium-99m sestamibi dipyridamole were included in the study. Smoking and caffeine containing food or beverages were refrained for 24 hours prior to the study. A four-hour fasting period and temporary discontinuation of certain maintenance medications (beta-adrenergic blockers and calcium channel blockers for 24 hours, long acting nitrates for 4 hours, and short acting nitrates for 1 hour) were advised. Presence of traditional risk factors for CAD was considered or patients diagnosed with hypertension, diabetes mellitus, dyslipidemia, and smoker. Request for 2D-echo was upon the discretion of the referring physician.

On day 1, pharmacologic stress was performed with dipyridamole (0.56 mg/kg, maximum of 40 mg) infused intravenously at a rate of 0.142 mg/kg/min for 4 minutes with monitoring of symptoms, blood pressure, and 12-lead electrocardiography. Tc-99m sestamibi 1110 MBq (30 mCi) was injected intravenously as a bolus on the 8th minute of the study. Simultaneous with radiopharmaceutical injection, dynamic planar images were acquired for 60 seconds (4 frames per second) in the anterior view to measure the first transit counts in the main pulmonary artery using a low energy general purpose collimator. Aminophylline 50-100 mg was given intravenously on the 10th minute of the procedure as needed for any side effects. SPECT imaging was performed 30 minutes post-sestamibi injection.

Data were acquired using a rotating dual-head gamma camera Jetstream Auto SPECT Plus software (Philips Medical Systems, Andover, MA, USA) equipped with a low energy general-purpose collimator and connected to a dedicated computer system. Thirty-two projections (30 seconds per projection) were obtained over a semicircular 180° arc, from 30° right anterior oblique to 30° left posterior oblique position in a step-and-shoot acquisition. A 20% symmetric energy window centered on the 140-keV peak was used. Filtered back projection was then performed with a low resolution Butterworth filter, with cut-off frequency of 0.5

and order 5. No attenuation or scatter correction was applied. Rest imaging was done the following day using the same acquisition protocol.

For first-pass analysis, default rectangular region of interest (ROI) was placed on the image with the best view of the main pulmonary artery, which avoids spill over from the bordering cardiac structures. The above-mentioned ROI was propagated on all first-pass images to generate the time-activity curve (TAC). The mean counts/pixel of the area under the curve represented the input function that constituted the denominator of global myocardial counts to compute for the myocardial blood flow ($MBF = \text{global myocardial counts} / \text{arterial input function}$). Global myocardial counts were derived from average of the mean counts/pixel of 2 representative short-axis tomograms at the mediobasal and medioapical views. Estimated coronary flow reserve (CFR) appeared from the ratio of dipyridamole MBF/rest MBF.

For the assessment of myocardial perfusion in each patient, a 17-myocardial segment scoring system was used with five-point scoring per myocardial segment (0, normal; 1, slight; 2, moderate; 3, severe; and 4, absence of radioactive tracer uptake). A nuclear medicine expert analyzed the radionuclide studies. Scintigraphic variables in incorporating the extent and severity of perfusion defects were manually calculated [summed stress score (SSS), summed difference score (SRS) and summed difference score SDS)] based on the official reading.

Patients were then grouped according to their myocardial perfusion scan result. Those with an SSS of ≤ 3 and an official result of no inducible ischemia were considered normal, while those with an SSS > 4 and with findings of inducible ischemia were in the abnormal group. Patients having normal and abnormal myocardial scan were further subdivided based on their coronary flow reserve whether normal ($CFR \geq 2$ or abnormal ($CFR < 2$).

Patients were monitored for major adverse cardiac events (MACE) through phone contact by patient and by review of hospital or

physician's record six months after the study. MACE include cardiac death (death due to acute myocardial infarction, ventricular arrhythmias, refractory heart failure or cardiogenic shock), acute coronary syndrome (new onset or worsening angina that required hospitalization and was associated with ischemic ST abnormalities, any elevation of cardiac troponin or both), unstable angina (angina at rest or change in pattern of existing angina requiring hospitalization but without ischemia ST-segment abnormalities and cardiac troponin elevation), and revascularization (coronary artery bypass graft, percutaneous coronary intervention).

Dichotomous data were described as frequency and percent distribution and continuous data as mean $\pm$ standard deviation. Kaplan-Meier analysis with log-rank test was used to determine association of coronary flow reserve with cardiac events.

RESULTS

There were 63 patients enrolled in the study, however, nine of them were eliminated (five (5) was due to technical problems, three (3) had poor first-pass boluses, and one (1) with tracer extravasation). Based on perfusion status, there were 43 patients with normal findings and 11 had abnormal result. Among those with normal MPI, only six (6) had normal CFR. For patients with abnormal MPI, all exhibited abnormal CFR.

Other than age and mean CFR, there was no significant difference in the rest of the baseline parameters including risk factors for CAD and certain medications.

For the hemodynamic response during pharmacologic stress, there was significant increase in mean heart rate (>10 beats/min), rate-pressure product (RPP), and myocardial blood flow in both normal and abnormal CFR groups. These implied adequate vasodilatory response from dipyridamole. There was no significant difference in the mean systolic and diastolic blood pressures at rest and at stress in patients with normal CFR.

CFR and Magnitude of Perfusion Abnormalities. Forty-three patients had normal perfusion study with a mean estimated coronary flow reserve of 1.64 ± 0.47 .

There were only 11 patients with a normal perfusion scans. Mild to moderate inducible ischemia (SDS 2.26 ± 5.87) was present in nine (9) subjects. The other two patients with no evident inducible ischemia had partial thickness fibrosis but with viable myocardium.

The mean coronary flow reserve was significantly lower at 1.19 ± 0.36 in patients with abnormal perfusion as compared to those with normal perfusion scan as shown in table 3 ($p = 0.005$). Among patients with normal perfusion, there was high proportion (89%) with reduced CFR.

Data outcome. All 54 subjects were all followed-up for any cardiac event 4 to 17 months after myocardial perfusion scintigraphy (mean follow-up 9 ± 3 months) through review of hospital record and phone interview.

One (1) patient had myocardial infarction 11 months after MPI, two (2) experienced unstable angina with consequent coronary artery bypass graft surgery 1 and 5 months post-MPI. All these three patients had abnormal MPI and reduced CFR. For those with normal MPI but with abnormal CFR, two (2) patients had unstable angina 4 days and 2 months after MPI. Due to persistent chest pain, the former under

went coronary angiogram, which showed normal coronaries. No cardiac event was noted in patients with both normal MPI and CFR.

The number of cardiac events and the annual cardiac event rate increased in the presence of reduced CFR in spite normal MPI and was even higher when both MPI and CFR were abnormal, as shown in Figure 1.

Survival Analysis. In Kaplan-Meier analysis, patients with abnormal perfusion revealed significantly higher incidence of cardiac events compared with normal perfusion (Log-rank chi-square 4.93, $p=0.027$). (Figure 2) While based on the CFR data alone, there was a trend towards increased incidence of cardiac events in patients with abnormal CFR; however, this did not reach statistical significance (Log-rank chi-square 0.61, $p=0.434$). (Figure 3) Likewise, there was trend towards decreased survival when both MPI and CFR were abnormal (Log-rank chi-square 5.09, $p = 0.079$). (Figure 4)

Intraobserver and interobserver variabilities. Since the computation of coronary flow reserve entailed meticulous post acquisition processing, we investigated for the intra-observer and inter-observer agreements of all the 54 patients for reproducibility of results. The primary investigator and an observer evaluated each of the radionuclide studies blinded to the patient's clinical data and to each other's result. There was no significant difference in the inter and intra-observer CFR estimation. (Table 4)

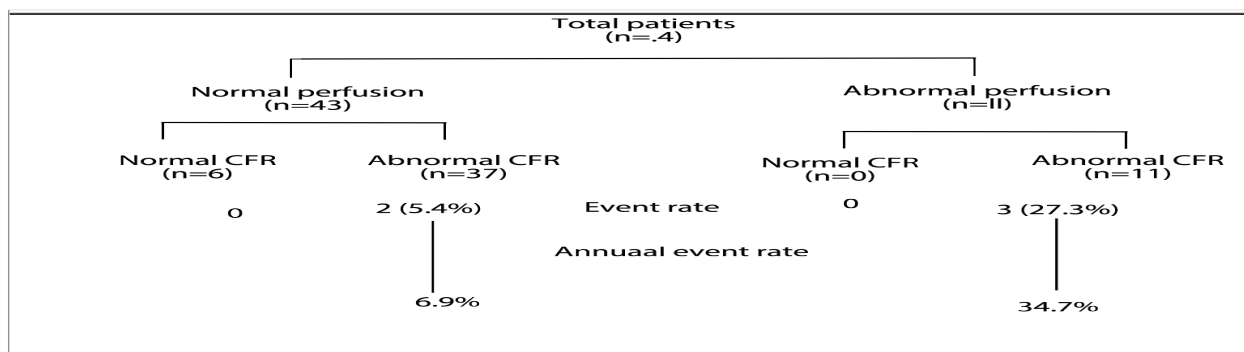


Figure 1. Flow diagram illustrating the number of cardiac events and annual cardiac event rate based on perfusion and CFR results.

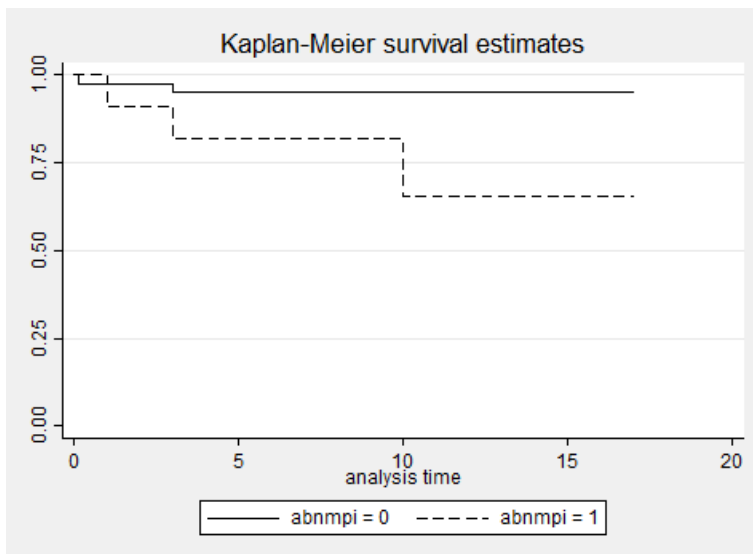


Figure 2. Event-free survival curve' in patients with normal (continuous) and abnormal (dashed) MPI.

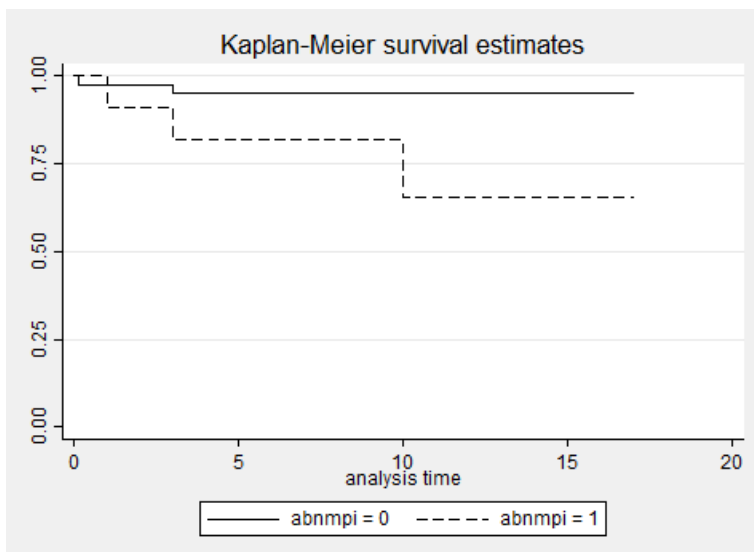


Figure 3. Event-free survival curve' in patients with normal (continuous) and abnormal (dashed) CFR.

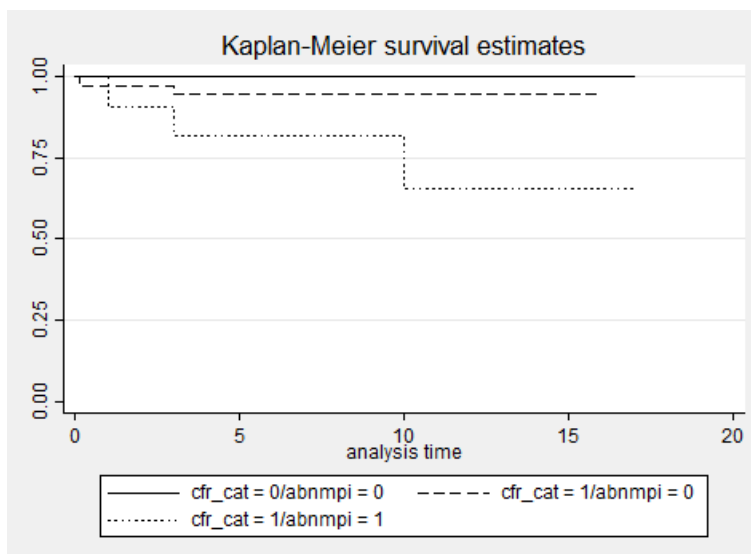


Figure 4. Event-free survival curves in patients with both normal MPI and CFR (straight line), normal MPI abnormal CFR (dashed), and both abnormal MPI and CFR (black).

Table 1. Baseline Characteristics of Patients According to Coronary Flow Reserve (CFR)

Characteristics	Normal CFR (n=6)	Abnormal CFR (n=48)	p-value
Age, years	45.67 ± 10.80	56.98 ± 13.22	0.050
Female	2 (33%)	20 (42%)	1.000
Co-morbidity			
Body mass index (kg/m ²)	26.92 ± 7.10	25.77 ± 4.80	0.601
Angina	3 (50%)	23 (48%)	1.000
Previous stroke	0	5 (11 %)	1.000
Peripheral artery disease	0	2 (4%)	1.000
Pacemaker	0	3 (6%)	1.000
Risk factors			
Hypertension	5 (83%)	37 (77%)	1.000
Diabetes mellitus	1 (17%)	14 (29%)	1.000
Dyslipidemia	4 (67%)	32 (67%)	1.000
Smoking	2 (33%)	13 (27%)	1.000
Medications			
ACE inhibitors	1 (17%)	10 (21%)	1.000
Angiotensin receptor blocker	2 (33%)	20 (42%)	1.000
Nitrates	1 (17%)	8 (17%)	1.000
Statins	3 (50%)	32 (67%)	0.653
Summed Stress Score	0.67 ± 1.21	3.85 ± 8.01	0.339
CFR	2.58 ± 0.44	1.42 ± 0.31	0.000

Table 2. Hemodynamic Parameters of Patients Before and After Dipyridamole Administration

Hemodynamic parameter	Normal CFR (n=6)	p-value	Abnormal CFR (n=48)	p-value
Heart rate				
rest	66.17 ± 9.09	0.002	72.92 ± 14.90	0.000
stress	92.83 ± 11.99		91.17 ± 15.67	
Systolic BP				
rest	126.67 ± 24.22	0.695	140.54 ± 30.69	0.018
stress	123.33 ± 16.33		128.75 ± 21.30	
Diastolic BP				
rest	76.67 ± 12.11	0.100	86.67 ± 11.73	0.000
stress	76.77 ± 17.51		77.08 ± 13.04	
Rate-pressure Product (RPP)				
rest	8405.00 ± 2106.27	0.001	10304.00 ± 3161.27	0.000
stress	11445.00 ± 2052.61		11793.13 ± 3020.67	

Table 3. Mean Coronary Flow Reserve in Patients with Normal and Abnormal Myocardial Perfusion Scan

Myocardial perfusion scintigraphy Results	Coronary flow reserve (mean± SD)	p-value
Normal (n= 43)	1.64 ± 0.47	0.005
Abnormal (n=11)	1.19±0.36	

Table 4. Intra/Interobserver variability of CFR estimation

Variability	1 st observation (mean ± SD)	2 nd observation (mean ± SD)	p-value
Intraobserver	1.55 ± 0.55	1.59 ± 0.49	0.457
Interobserver	1.58 ± 0.49	1.56 ± 0.46	0.633

DISCUSSION

This study demonstrated that with abnormal perfusion, there was significantly reduced CFR and higher incidence of MACE. Also, with abnormal CFR, a trend towards increased incidence of MACE was noted; however, this did not reach statistical significance.

Association of Perfusion with CFR. Our findings conform to the cut-off value of CFR less than 2, which generally correlates with stress-induced ischemia on SPECT⁵ doppler technique⁷, and with PET imaging.⁸ Although dipyridamole administration mainly induces vascular smooth muscle relaxation (endothelium-independent), about 20% - 40% of the maximal vasodilation is mediated by the release of the maximal vasodilation is mediated by the release of nitric oxide (NO) from endothelial cells.¹⁰ Blunting of CFR may be related to impaired nitric oxide-mediated vasodilation by superoxide anion, which is generated in response to oxidative stress. This predisposes the vessel wall to vasoconstriction. Impaired nitric oxide-mediated vasodilation is the hallmark in atherosclerosis, hypertension, and diabetes.¹

A number of studies had been conducted, using the same validated protocol that evaluated the effects of risk factors like diabetes mellitus¹² (1.36 ± 0.8) and peripheral arterial disease¹³ (1.0 ± 0.4) but with normal coronary angiogram, all have shown significant decrease in CFR compared to their controls (2.40 ± 0.3). Furthermore, a paper was published by Vicario et al¹⁴ on the influence of risk factors on CFR in 48 patients with 1-vessel CAD. Patients with intermediate lesions and with multiple coronary risk factors exhibited CFR values (1.25 ± 0.05) similar to those observed in patients with more severe coronary narrowing but without coronary risk factors (1.16 ± 1.18).

Prognostic Utility of CFR. In terms of the prognostic utility of CFR, there was only one study published using dipyridamole SPECT sestamibi at the time of investigation. According to Daniele et al,⁹ the time to achieve 2% risk of events was >60 months for those with normal CFR and <12 months for abnormal CFR with a mean follow-up period of 5.8 ± 2.1 years. This may explain the trend towards increased incidence of MACE with abnormal CFR in our study. Furthermore, they concluded that in patients with normal perfusion abnormal CFR, there was an associated higher annual event rate compared with normal CFR (5.2% vs 0.7%; $p < 0.05$). In another study using rubidium-82 PET, for cardiac death as the primary end point, in patients with CFR <1.5 there was an associated 5.6-fold increase in the risk of cardiac death with an overall 3-year cardiac mortality of 8.0%.

Likewise with dipyridamole rubidium-82 PET (median follow-up of 1.9 years), at any level of SSS (summed stress score, >4 to >8), the prevalence of MACE is higher in patients with the lowest CFR <1.5 and statistically different compared with myocardial flow reserve (MFR) >2 among patients with overt ischemia.¹⁵ The addition of MFR had data independent prognostic value to their model.

Halcox¹⁶ on mean follow-up of 3.8 ± 3 years, the event-free survival from cardiovascular events was significantly worse in patients with epicardial vasoconstrictive response to acetylcholine ($p=0.0001$). Moreso, Heitzer et al,¹⁷ in his 4.5 years of follow-up reported that the incidence of cardiovascular events increased significantly with decreasing vasodilator response to acetylcholine ($p < 0.001$) and sodium nitroprusside ($p < 0.05$). Endothelial dysfunction (attenuated acetylcholine-induced vasodilation) and increased vascular oxidative stress were

independent predictors of risk for cardiovascular events in patients with CAD. A more long-term prognostication (median 7.7 years) by Schachinger¹⁸ revealed that patients with cardiovascular events had significantly increased vasoconstrictor responses to acetylcholine infusion ($p=0.009$) and cold pressor testing ($p = 0.002$), as well as significantly blunted vasodilator responses to increased blood flow and an intracoronary injection of nitroglycerin ($p < 0.001$).

On the other hand, Meimoun et al¹⁹ assessed the usefulness of non-invasive coronary flow reserve (CFR) in predicting LV recovery and in-hospital adverse cardiac events after acute myocardial infarction. Patients without LV recovery had more severely impaired CFR compared to those with LV recovery (2.1 ± 0.55 vs. 1.46 ± 0.2 , $p < 0.001$). Furthermore, CFR was significantly correlated with 3-month LVEF and regional wall motion score (both p -values < 0.01).

Endothelium-independent microvascular dysfunction has also prognostic importance for determination of left ventricular function in cardiac transplant recipient without angiographically visible coronary artery stenosis. After 24 months, patients with CFR to dipyridamole < 2.5 showed significant decline in ejection fraction ($-7 \pm 5\%$) during exercise (versus $1.1 \pm 5\%$ in CFR > 2.5 , $p = .003$).²⁰

Microvascular dysfunction. There were 2 particular patients who presented with typical angina with normal perfusion and coronaries but with diminished CFR. Microvascular dysfunction may be the culprit because ultimately, the main clinical consequence of the inability of microvessels to match coronary blood flow to increased myocardial demand is the predominant development of subendocardial ischemia.²¹ As such, patients may experience chest pain in the absence of angiographic stenosis. In a study by Storto et al²², in patients with typical angina (1.54 ± 0.3) but with normal coronary angiogram, there was significant decrease in CFR compare with the controls (2.40 ± 0.3 , $p < 0.0001$).

CONCLUSION

With abnormal perfusion, there was significantly reduced coronary flow reserve and higher incidence of MACE. Also, with abnormal CFR, a trend towards increased incidence of MACE was noted; however, this did not reach statistical significance most likely due to short-term follow-up period.

LIMITATION AND RECOMMENDATION

Only a short-term follow-up study was done. There was unequal proportion of subjects based on perfusion and coronary flow reserve status. Independent predictor of reduced coronary flow reserve was not assessed. Longer follow-up period on larger patient cohort is suggested.

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Case Report - Adult Cardiology

Hypertrophic Cardiomyopathy with Absent Major Septal Perforator Coronary Artery Successfully Treated with Dual Chamber Pacing as an Alternate Strategy to Alcohol Septal Ablation and Surgical Myectomy

Bernard Benjamin P. Albano, MD; Erdie C. Fadreguilan, MD; Ed Gabitoa, MD; Jeffrey M. Chua, MD; James Ho, MD; Ana Beatrice Medrano, MD

Background --- Hypertrophic Cardiomyopathy (HCM) is the most common of the genetic cardiovascular disease characterized by a thickened non-dilated ventricle in the absence of another cardiac or systemic condition. Its most important hemodynamic consequence is left ventricular outflow tract (LVOT) obstruction. Its primary management strategy is surgical septal myectomy, but an acceptable alternative treatment in patients who are not suitable for (or who refuse) surgery is alcohol septal ablation (ASA). However, in patients with unfavorable coronary anatomy which precludes ASA (i.e. absence of major septal perforator branch of the left anterior descending artery), another reasonable option is dual chamber pacemaker implantation to decrease LVOT outflow gradient.

Case --- A 77 year-old female, known hypertensive, diabetic with a history of coronary artery disease presented with one week history of worsening chest pain and shortness of breath. She was admitted as a case of acute coronary syndrome and pneumonia. On work-up, 2DED revealed hypertrophic obstructive cardiomyopathy (HCM) with a demonstrated systolic anterior motion (SAM) of the mitral valve with a peak instantaneous gradient of 194 mmHg across the basal left ventricular cavity. The patient refused surgical myectomy, and alcohol septal ablation was the preferred treatment option. On coronary angiography, there was incidental finding of absent major septal perforator branch of the left anterior descending coronary artery (LAD), rendering her unsuitable for septal ablation. She was referred to electrophysiology for evaluation. She underwent dual chamber pacemaker implantation and documented significant decrease in the peak instantaneous gradient from 194 mmHg to 37 mmHg; with complete obliteration of systolic anterior motion (SAM) and improvement in overall wall motion. She remained stable and asymptomatic after pacemaker insertion until her recent outpatient follow-up (5 months post implantation).

Conclusion --- We present a case of hypertrophic cardiomyopathy with congenitally-absent major septal perforator branch coronary artery treated with dual chamber pacemaker implantation. To our knowledge, this is the first reported angiographically-absent first (major) septal perforator coronary anatomy in the setting of hypertrophic cardiomyopathy, and also the first description of dual chamber pacemaker implantation to relieve the LVOT obstruction. Although the role of dual-chamber pacing has become limited in HCM because surgical myectomy and septal ablation has resulted to better decrease in LV outflow gradient and symptom improvement, this modality remains essential and may still be considered as the treatment strategy-of-choice in patients who are unsuitable for surgical myectomy and alcohol septal ablation. *Phil Heart Center J 2016;21(1):72-78.*

Key Words: Hypertrophic cardiomyopathy ■ hypertrophic obstructive cardiomyopathy ■ surgical myectomy ■ alcohol septal ablation ■ dual chamber pacemaker implantation

Hypertrophic Cardiomyopathy (HCM) is the most common genetic cardiovascular disease characterized by a thickened non-dilated ventricle in the absence of other cardiac or

systemic condition.¹ It is a global disease with a reported prevalence of 0.2% in the general population.² Its clinical diagnosis is made by imaging with two-dimensional echocardiogra-

Finalist, Poster Presentation - Case Report. 23rd PHC Annual Research Paper Competition and Poster Presentation held on February 26, 2015 at Philippine Heart Center. Correspondence to Dr. Bernard Benjamin P. Albano. Department of Adult Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at <http://www.phc.gov.ph/journal/publication> copyright by

phy. The most important hemodynamic consequence of this condition is left ventricular outflow tract (LVOT) obstruction in which 70% of patients develop dynamic LV outflow gradient of 30 mmHg or greater. In the obstructive form, there is subaortic mechanical impedance to LV outflow, producing markedly increased intraventricular pressures that, over time, may be detrimental to LV function as a result of increased myocardial wall stress and oxygen demand. Most common obstructive mechanism (90%) is the systolic anterior motion (SAM) of the mitral valve, the remaining cause (10%) include intraventricular obstruction caused by systolic contact of septum with a papillary muscle that is anomalously positioned and may insert directly into anterior mitral leaflet.

In patients with severe drug-refractory NYHA class III and IV symptoms, the preferred primary management is surgical septal myomectomy.^{2,3} In patients who are not candidates for surgery, an alternative treatment option is alcohol septal ablation (ASA).^{1,4,5} This modality involves injection of alcohol into a major septal perforator coronary artery to create necrosis and permanent transmural myocardial infarction localized to the proximal ventricular septum which results in progressive thinning of the LV wall and a resultant decrease in LV outflow gradient.⁶ However, in patients with congenitally-absent major septal perforator branches of the left anterior descending (LAD) coronary artery, the performance of ASA may be ineffective. Implantation of a dual-chamber pacemaker was proposed as an alternate treatment for these patients with severe symptomatic obstructive HCM.^{7,8,9} By pacing the right ventricular apex with maintenance of atrioventricular synchrony, this results in a decrease in the LVOT gradient and improvement of symptoms. Importantly, however, its role in HCM has become limited due to lack of evidence of efficacy.¹⁰

This is a case of a symptomatic HCM in an elderly who refused surgical myectomy, and was planned for alcohol septal ablation but did not push through due to incidental finding of absent major septal perforator branch of the left anterior descending artery (LAD). Due to persistent refusal of surgery, she was referred to electrophysiology and underwent dual chamber pace-

maker implantation. There was noted significant improvement of symptoms and she was discharged hemodynamically stable. To our knowledge, this is the first reported case of congenital absence of septal perforator artery in the setting of HCM and also the first description of successful treatment of LVOT gradient using dual chamber pacing.

Case

This is a case of a 77 year-old Filipino, female, diabetic, hypertensive with a history of coronary artery disease who underwent percutaneous coronary angioplasty of the right coronary artery (RCA) in 2000. One week prior to consult, she complained of occasional chest heaviness aggravated by effort and worsening shortness of breath. She was admitted in the wards and initially managed as a case of acute coronary syndrome and community-acquired pneumonia. Pertinent physical examination findings include the following: BP 100/60 mmHg, CR 77 bpm, RR 22, no neck vein engorgement, bibasal rales, with a systolic ejection murmur heard over the lower left sternal border with no radiation to the carotids. 12-lead electrocardiography showed sinus rhythm, normal axis, with left atrial abnormality, and LV hypertrophy with secondary ST-T wave abnormalities; chest radiography revealed enlarged heart with LV prominence with mild congestion. Two-dimensional transthoracic echocardiogram was done which showed markedly thickened walls of the left ventricle (*Figures 1 and 2*) with a peak instantaneous continuous wave doppler gradient across the basal left ventricular segment of 194 mmHg; concentric left ventricular remodeling with segmental wall motion abnormality with preserved systolic function and presence of systolic anterior motion (SAM) of the mitral valve with an LV ejection fraction of 57% by Simpson's. Surgical myectomy was advised but she refused any surgical treatment. Alcohol septal ablation was then the treatment option.

On the second hospital day, she underwent coronary angiogram which showed patent stent on the right coronary artery (RCA) with absence of a major septal perforator branch of the left anterior descending artery (LAD) (*Figures 3-5*). Septal ablation was deferred and she was referred

to electrophysiology for evaluation. On the third day, electrophysiologic/ventricular tachycardia (VT) studies was done which revealed a sinus rhythm, with a cardiac rate of 77 bpm, and a maximum rate of 140 bpm; no significant sinus pause, atrioventricular blocks, intraventricular conduction delays; on isoproterenol infusion, she had atrial tachycardia and atrial fibrillation with rapid ventricular response and developed congestion and hypoxia. She was given with one shock of synchronized cardioversion, 150J and was transferred to coronary care unit for close monitoring. Electrolytes were corrected accordingly. After she was stabilized, she was transferred to regular room and was scheduled for dual chamber (DDD) pacemaker implanta-

tion. After implantation of pacemaker, she remained stable and symptom-free. A repeat transthoracic echocardiogram was done which revealed significant decrease in peak instantaneous gradient basal left ventricular segment from 197 mmHg to 37 mmHg, the systolic anterior motion of the mitral valve shown before was no longer appreciated, and there was overall improvement in wall motion. The presence of pacemaker lead in place was identified. She was discharged on the 10th hospital day stable and asymptomatic.

She had regular outpatient follow-up and up to 5-months post-pacemaker implantation, she remained asymptomatic.

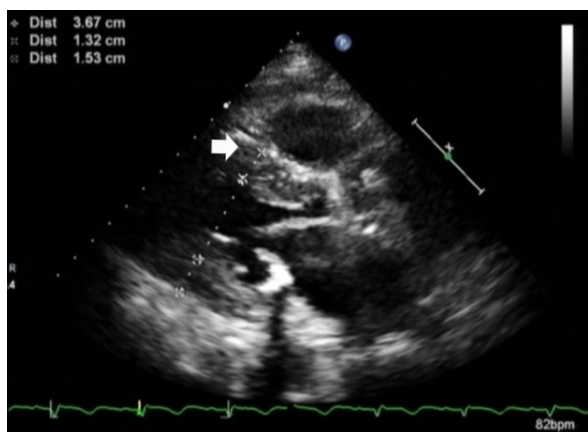


Figure 1. Parasternal long axis echocardiographic image of the patient showing hypertrophied septum (arrow) and reduced left ventricular cavity size.

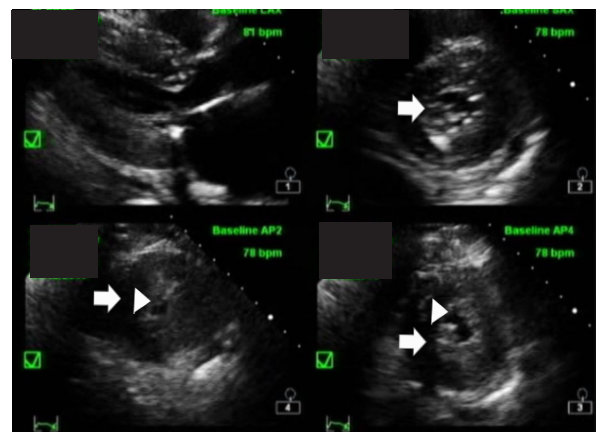


Figure 2. Short axis echocardiographic image of the patient showing concentric hypertrophy of the left ventricular wall and reduced LV cavity.

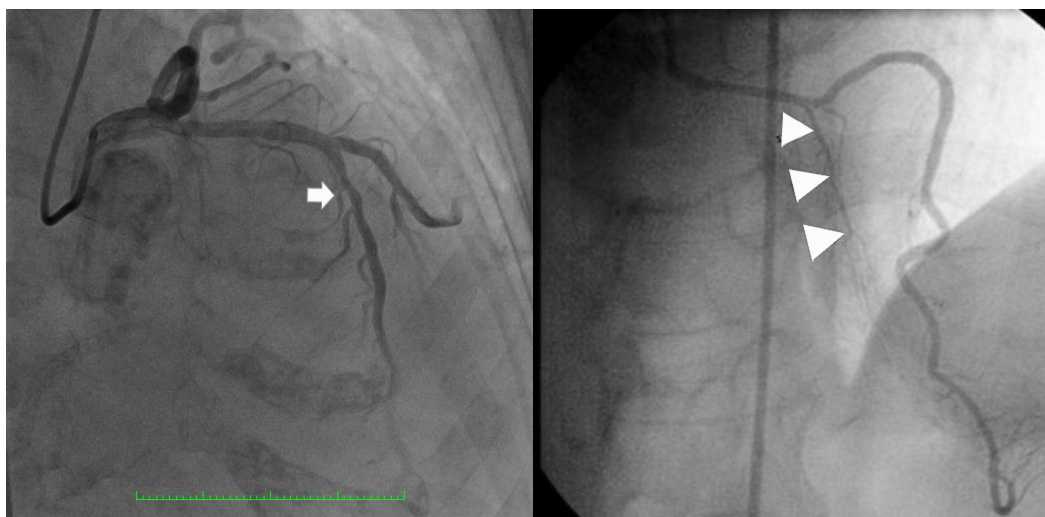


Figure 3. (A) Coronary angiography of the patient showing the left anterior descending artery (arrow) which was a good-sized vessel, with no significant stenosis but with absent first (major) septal perforator branch. (B) Normal major septal perforator (white arrowheads) originating from the long LAD from a 52 year-old female.¹¹

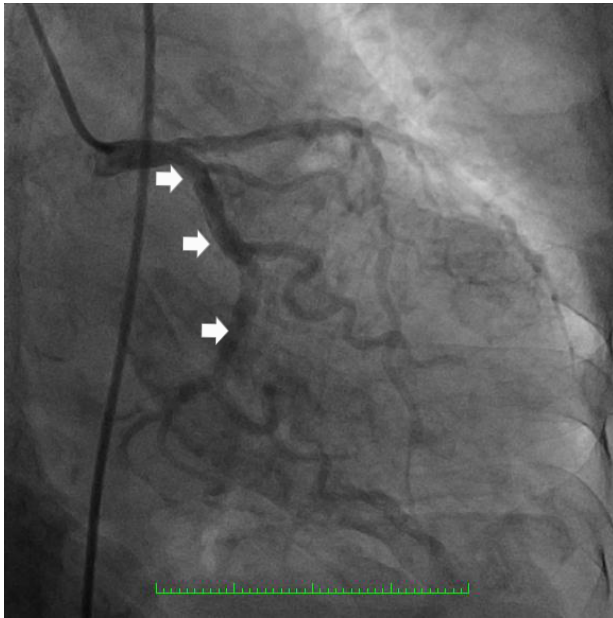


Figure 4. Coronary angiography showing the left circumflex coronary artery which was a good-sized vessel with no significant stenosis (arrows).

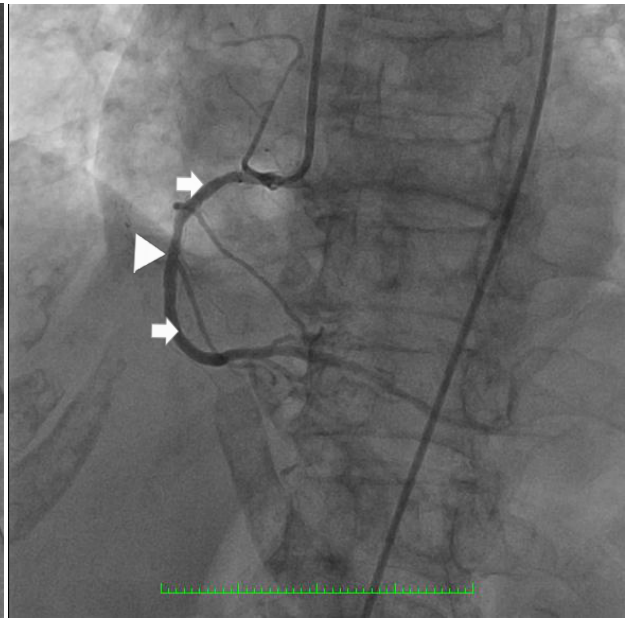


Figure 5. Coronary angiography showing the right coronary artery (RCA) (red arrows) which was a good-sized vessel with patent stent at the proximal to mid segment (arrow-head) with good flow and with no significant stenosis

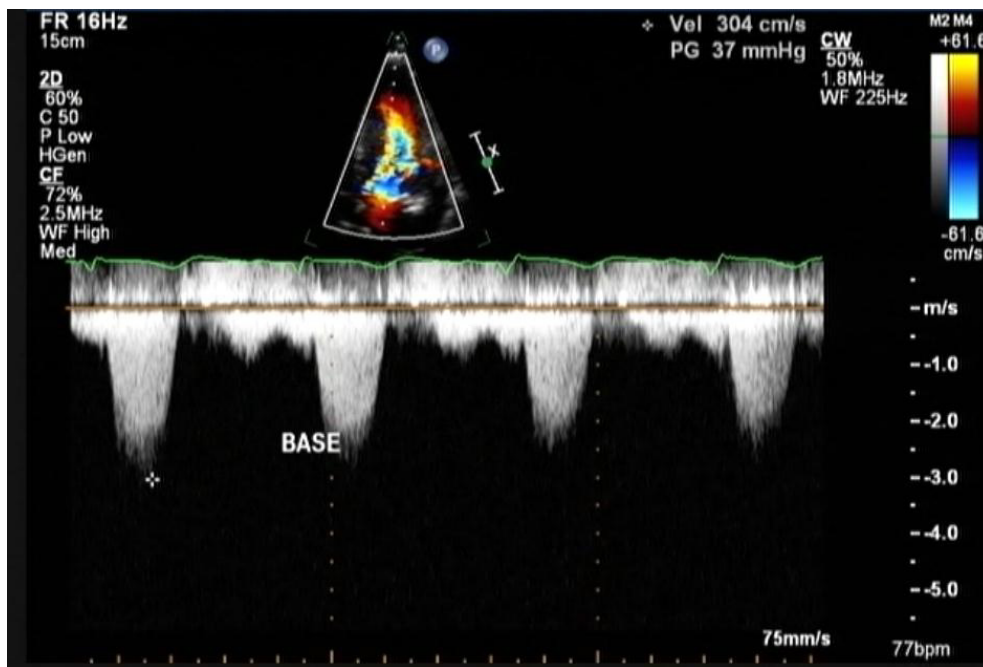


Figure 6. Color flow Doppler study of the patient showing a peak instantaneous gradient of 37 mmHg at post-implantation of dual chamber pacemaker. (This was previously described as 194 mmHg before implantation of pacemaker).

DISCUSSION

The American College of Cardiology/European Society of Cardiology, and American Heart Association has recommended surgical septal myectomy as the preferred primary management option for patients with HCM with severe drug-refractory NYHA class III/IV symptoms and those with obstruction to LV outflow under basal conditions with physiologic exercise (≥ 50 mmHg).^{2,3,10} The objective of surgery is the reduction in heart failure symptoms and improved quality of life, by virtue of relieving the SAM and outflow obstruction, and normalizing LV pressures. In patients who underwent surgery, 95% of patients experienced permanent eradication of the basal outflow gradient and 85% experienced symptom relief during periods of up to 25 years.^{2,3,10} Surgery is not recommended in patients who are asymptomatic or mildly symptomatic because of the lack of conclusive evidence that prophylactic relief of obstruction is advantageous. Its operative mortality has decreased steadily and is now less than 1% at selected myectomy centers.¹²

Alcohol septal ablation is an alternative to myectomy and involves injection of 1 to 3 mL of 95% alcohol into a major septal perforator coronary artery to create necrosis and a permanent transmural myocardial infarction localized to the proximal ventricular septum which leads to progressive thinning and restricted basal septal excursion, and reduction in LV outflow tract gradient. ASA is considered an alternative treatment modality to septal myectomy in the following settings: (1) patients whose symptoms limit daily activities (functional class III or more, or exercise-induced syncope) despite medical therapy or if medical therapy cannot be tolerated; (2) patients with a significant level of outflow obstruction (i.e. pressure drop >50 – 60 mmHg with provocation by a valsalva maneuver, bicycle stress, or postextrasystolic augmentation); (3) patients with a suitable left ventricular and coronary morphology, that is, those with a “classical,” subaortic obstruction produced by the protruding septum and the “SAM” of the mitral valve and one or more septal perforator arteries that serve the septal area. Several published studies on alcohol septal

ablation demonstrated immediate reductions in the mean resting LVOT gradient from 65 to 17 mmHg and the mean post-extrasystolic gradient from 125 to 53 mmHg, with persistence of reduction even after 12 months of treatment (16 and 32 mmHg, respectively).¹³ Meta-analyses have indicated no difference between septal ablation and myectomy in the medium-term incidence of SCD or all-cause mortality.¹³

Dual-chamber pacemaker implantation was proposed as an alternative treatment for patients with severe symptomatic obstructive HCM. Although the exact mechanism of improvement with pacing remains unknown, the decrease in gradient may be caused by timing of septal contraction but may also reflect long-term remodeling. Although there was an initial enthusiasm for dual-chamber pacing as a primary treatment for patients with obstructive HCM, subsequent RCTs demonstrated long-lasting beneficial results in only a small minority of patients.^{14,15} The overall success rate in symptom relief and gradient reduction is significantly lower compared to those patients who undergo septal myectomy.^{14,15} The mean residual gradient after septal myectomy is 10 mmHg compared with a 40 to 50 mmHg gradient after dual-chamber pacing.^{14,15} Patients >65 years of age may be a subgroup who achieve the greatest benefit.¹⁴

Individualizing Treatment Options. In our case, the patient was appraised for surgical myectomy. However, she refused surgery and opted for an alternative, less invasive option – alcohol septal ablation. Unfortunately, on coronary angiography, there was absence of major septal perforator coronary anatomy rendering her unsuitable for ASA. Consequently, an alternate option (dual chamber pacing) was offered with the goal of reducing the LV outflow tract gradient and improvement of symptoms. The absence of septal perforator branches of the left anterior descending artery was described by Angelini et al. in 1999 and classified under “other anomalies” with an incidence of 0.27% using 1950 coronary angiograms.¹⁶ While the first septal perforator branch of the left anterior descending artery (LAD) is the typical channel for ASA, HCM patients with severe septal hypertrophy may rarely present

with unusual septal perforator anatomy.¹⁷ The absence of septal perforator coronary arteries in these patients render them unsuitable for ASA.³

Outcome and Follow-up. She underwent dual chamber pacemaker implantation as alternate to ASA and documented immediate significant reduction in the peak instantaneous gradient across the basal segment and obliteration of the systolic anterior motion of the mitral valve. There was also noted improvement in overall systolic function. These hemodynamic changes were coupled with symptomatic improvement as the patient remained stable and asymptomatic after implantation. Five months post-implantation of dual chamber pacemaker, the patient had an outpatient follow-up and was reported to have absence of symptom recurrence since she was discharged.

CONCLUSION

We presented a case of hypertrophic cardiomyopathy with angiographically-absent major septal perforator branch of the left anterior descending coronary artery (LAD) treated with dual chamber pacemaker implantation to reduce the LV outflow gradient. To our knowledge, our case is not only the first reported angiographically-absent first septal perforator coronary anatomy in the setting of hypertrophic cardiomyopathy, but also the first description of dual chamber pacemaker implantation to relieve the LVOT obstruction.

Although the role of dual-chamber pacing has become limited in HCM because surgical myectomy has set the standard for therapy and alcohol septal ablation has been accepted as suitable alternative, this modality remains essential and may still be considered as the treatment strategy of choice in patients who refuse surgery and who are not suitable for alcohol septal ablation.

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Intralobar and Extralobar Pulmonary Sequestration with Scimitar Syndrome: a complex variant

Annalee de Leon-Manalo, MD; Dulce Requiron-Sy, MD; Ernesto Salvador, Jr., MD

Background --- Pulmonary sequestration is a rare developmental anomaly of the lower respiratory tract which can be intralobar or extralobar. The occurrence of both in a patient is an exceedingly rare phenomenon much more when associated with scimitar syndrome. Such condition has been described as a variant of pulmonary sequestration spectrum.

Case --- A 16-year old female adolescent, previously managed as a case of pneumonia, tuberculosis and bronchiectasis, was referred in our institution due to recurrent massive hemoptysis. Diagnostic tests showed right lower lobe pulmonary sequestration, both extralobar and intralobar, and scimitar syndrome. The patient underwent lobectomy of the right lower lobe with uneventful postoperative course.

Conclusion --- It is indeed warranted that children presenting with recurrent hemoptysis should be investigated for any congenital abnormality of the lung. The recurrence of massive hemoptysis on such cases may justify surgical intervention. *Phil Heart Center J 2016;21(1):79-84.*

Pulmonary sequestration is a very rare congenital malformation which constitutes 0.15 - 6.4% of all congenital pulmonary malformations. It refers to a dysplastic lung tissue which lacks normal communication with the tracheobronchial tree and receives blood supply from the systemic arteries. There are two types of pulmonary sequestration, intralobar and extralobar.¹ Coexistence of both type is extremely rare.^{2,3}

It is widely agreed that there are many variants to the pulmonary sequestration spectrum that arise from a common embryologic pathogenesis. This includes scimitar syndrome, horse-shoe lung, cystic adenomatoid malformation, and pulmonary arteriovenous fistula/malformation.

Case

This is a case of a 16-year old female adolescent who presented with recurrent massive hemoptysis. Prenatal history was unremarkable. The patient was born term via normal spontaneous delivery at home assisted by a midwife

with no complications noted. Review of past medical history showed that the patient had episodes of cough and colds being managed on an outpatient basis and was treated as Primary Tuberculosis for 6 months at the age of 5.

At the age of 12, the patient had occasional cough and sudden onset of massive hemoptysis approximately 100-200 ml per bout. The patient was managed as a case of pneumonia and tuberculosis. Since then, the patient had no recurrence of hemoptysis however, the patient had episodes of cough and colds resolving with medications.

At about a year prior to admission in our institution, there were more frequent episodes of massive hemoptysis of about 200 ml per bout. She was admitted several times in other institutions and was managed as bronchiectasis. On follow-up, a chest CT-scan was done showing right lower lobe pneumonia to consider pulmonary vascular malformation. Hence, they were advised to seek consult in a bigger center for further management

One month prior to admission in our institution, she was admitted at a nearby medical center for evaluation and management. Chest CT scan and angiography were done of which according to the informant revealed scimitar syndrome. She was then referred in our institution for further management. On physical examination, patient had stable vital signs, however was noted to be pale. Chest findings showed symmetrical chest wall expansion, no lagging, no retraction, increased vocal and tactile fremitus, dullness of percussion and decreased breath sound on the right lower lobe. The rest of the examination findings were unremarkable. On chest radiograph, there was noted confluent tubular and hazy density in the right lower lung which may represent an anomalous vessel rule out pneumonia, the right lung is smaller than the left with paucity of vascularity in the right upper lobe and the heart shadow is shifted to the right (*Figure 1*). A review of the chest CT-scan and angiography done outside showed that right lung was bilobed (absent middle lobe) and was relatively smaller than the left. The right pulmonary artery, right inferior and superior pulmonary veins were small in size (*Figure 2*). There was an anomalous artery

arising from the abdominal aorta which trifurcates, a branch supplying the right lower lateral segment separated from the rest of the lung parenchyma, having its own pleura and drained by a scimitar vein into the inferior vena cava, and the other 2 branches supplies the right lower lobe. An anomalous vein (scimitar vein) eventually draining into the inferior vena cava was seen draining the right lower lobe (*Figure 3*). Pulmonary function test was normal. Two dimensional echocardiography showed partial anomalous pulmonary venous return (right pulmonary veins to the inferior vena cava) with normal pulmonary artery pressure. She was also referred to a gastroenterologist to rule out other possible sources of bleeding. Endoscopic findings showed no gross bleeding, no erosions noted with smooth mucosa (*Figure 4*). The patient underwent lobectomy of the right lower lobe. The patient's clinical course was unremarkable and was eventually discharged improved (*Figure 5*). The histopathologic appearance of the airways and alveoli together with the hemorrhage are seen in intralobar pulmonary sequestration. The small node of atelectatic lung tissue is probably extralobar, however, its blood supply is not discernible.

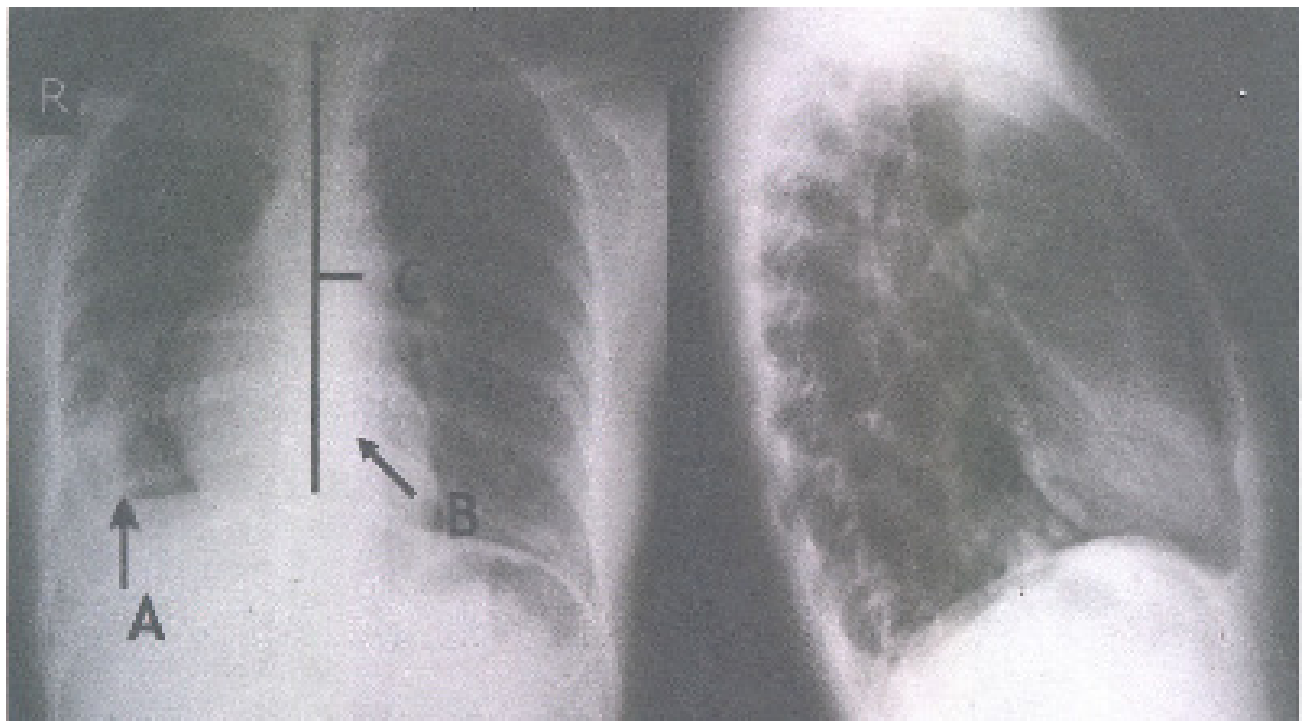


Figure 1. Chest radiograph showing A.) confluent tubular and hazy density in the right lower lung (arrow), B.) smaller right lung compared to left (arrow) and C.) the heart shadow is shifted to the right (arrow).

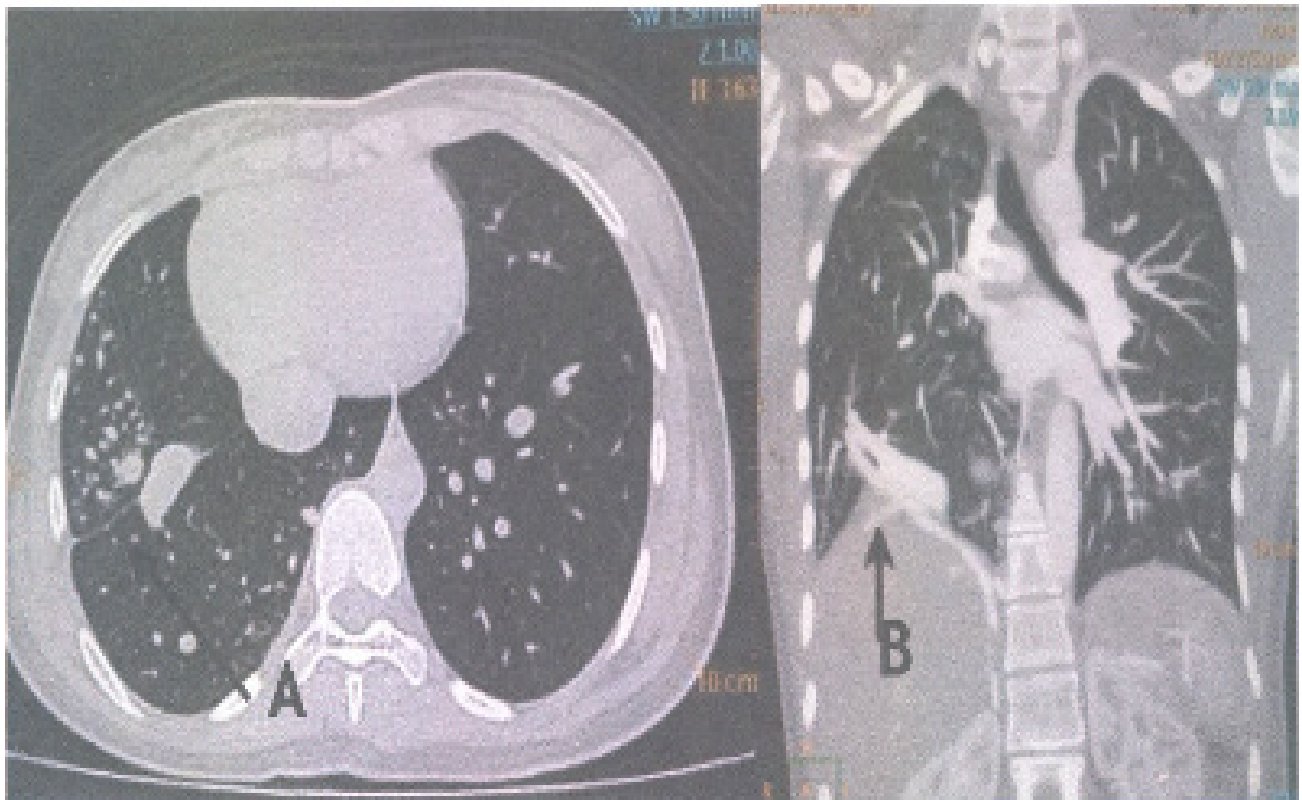


Figure 2. A: Axial view of chest CT-scan showing sequestered lung with its own pleura (arrow). B: Coronal view of chest CT-scan with the scimitar vein (arrow).

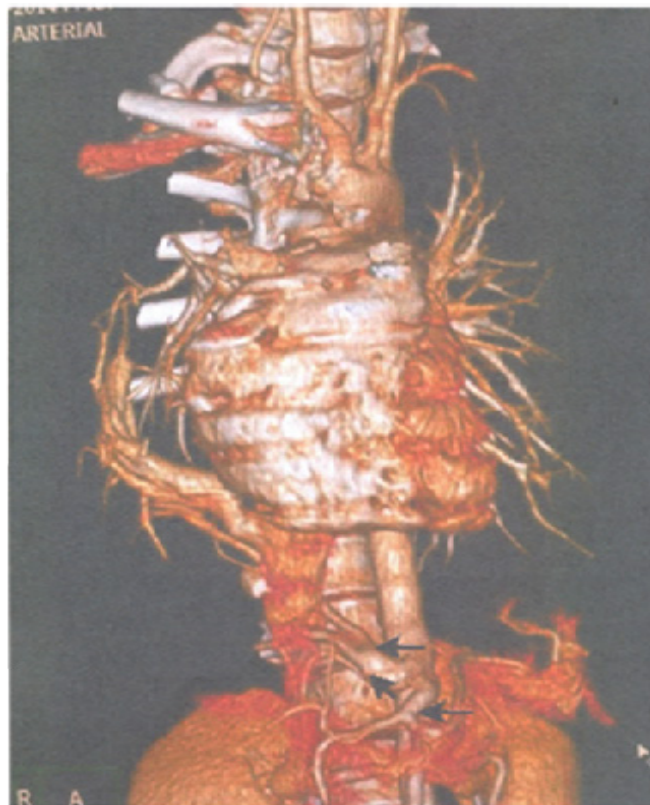


Figure 3. The 3 dimensional angiographic chest CT-scan demonstrating the anomalous artery arising from the abdominal aorta which trifurcates (arrows).

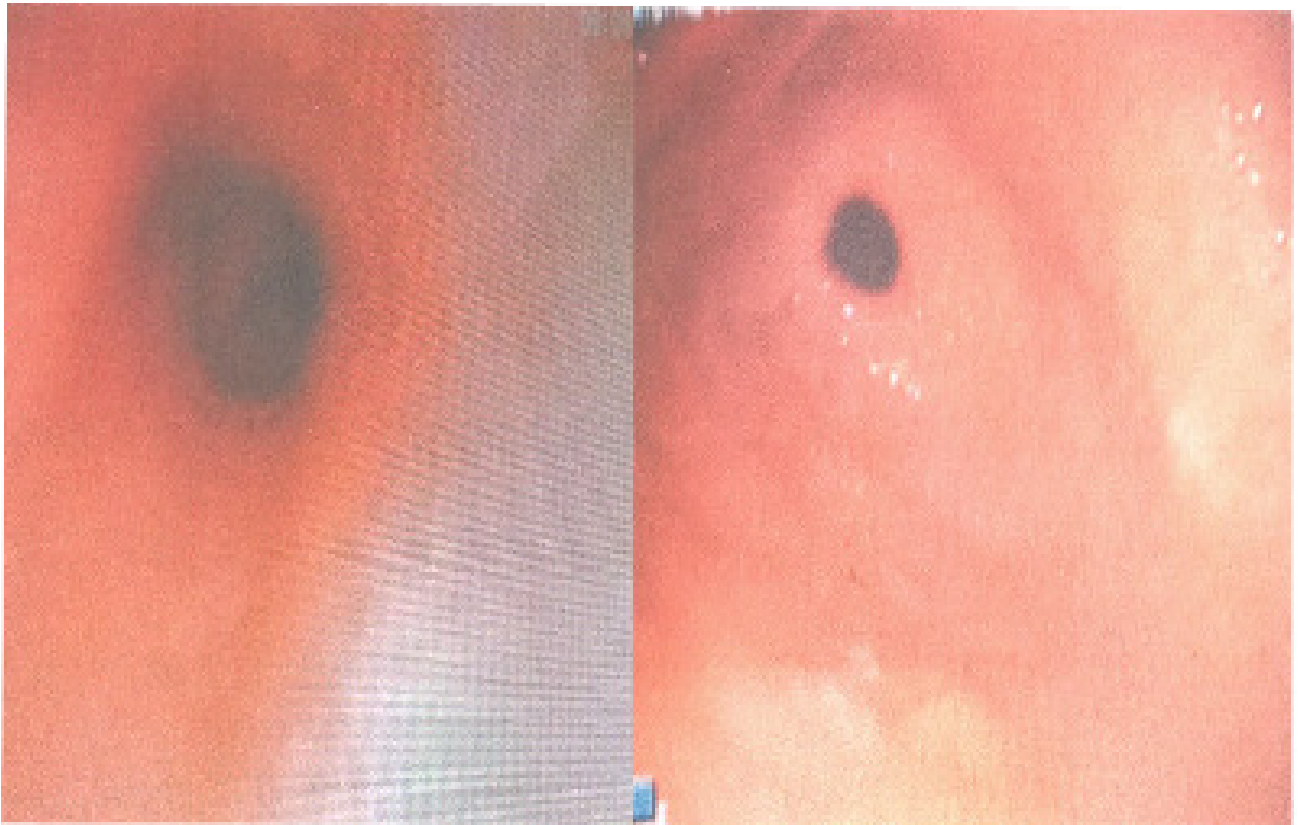


Figure 4. Endoscopic findings showing smooth mucosa of the upper gastrointestinal tract with no evidence of bleeding.

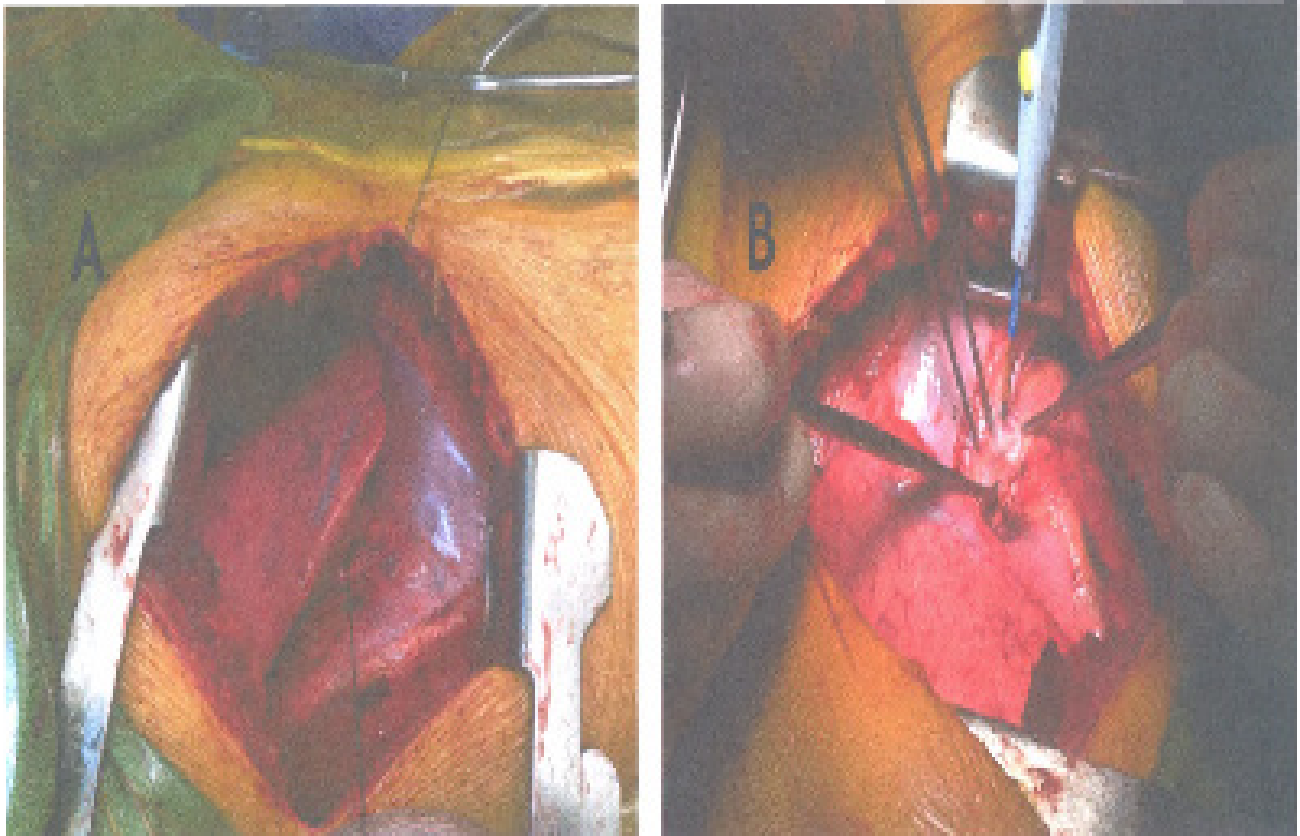


Figure 5. Intraoperative pictures showing (A) ligation of the anomalous vessels and (B) lobectomy of the right lower lobe.

DISCUSSION

Pulmonary sequestration is divided morphologically into intralobar and extralobar. Intralobar sequestration comprises majority of sequestrations. It shares the visceral pleura with the normal lung tissue, receiving its blood supply from the aorta and draining into the pulmonary venous system. Extralobar sequestration, on the other hand, has its own visceral pleura, and may even occur outside the thorax. Its blood supply is usually systemic, from branches of the aorta and the venous drainage is mainly via the azygos-hemiazygos system.²

Most patients with pulmonary sequestration are asymptomatic and were diagnosed incidentally. Some may present with recurrent pneumonia, chest pain, respiratory distress, hemoptysis, feeding difficulties, mass effect or congestive heart failure. Radiologic imaging particularly angiography, helps in the diagnosis of pulmonary sequestration. It is the gold standard for identifying sequestration.⁴ It confirms the anatomy, identifies the systemic supply, and shows the venous drainage.

Our patient manifested with recurrent massive hemoptysis. Although the etiology of the hemoptysis is uncertain, it is thought to be due to high-pressure blood flow in the sequestered lung from the anomalous systemic arteries.⁵ Our patient was diagnosed to have both intralobar and extralobar pulmonary sequestration as shown in the chest CT-scan and angiography results described as right-sided bronchopulmonary malformations, partial anomalous pulmonary venous drainage and systemic arterial supply to the right lung. This finding was supported by the histopathology result. Intralobar and extralobar pulmonary sequestration may be present simultaneously as reported in literatures. However, its occurrence is extremely rare. Most of the reported cases involves the ipsilateral lung as seen in our patient.^{2,3}

Sequestration spectrum is the collection of abnormalities of the lung parenchyma and of its blood supply, with other associated anomalies. Literatures stated that there are many “variants” to the pulmonary sequestration spectrum and that

include scimitar syndrome, horseshoe lung, cystic adenomatoid malformation, and pulmonary arteriovenous fistula/malformation.⁶

In scimitar syndrome, the anomalous vein drains into the inferior vena cava or at its junction at the right atrium. This vein has the appearance of a scimitar. This may or may not be accompanied by hypoplasia of the right lung and dextrocardia, anomalies of the lobes of the right lung, hypoplasia of the right pulmonary artery, and an anomalous systemic vascular supply to the lung.⁷ Our patient was also diagnosed to have a concomitant scimitar syndrome. On imaging studies, scimitar sign and dextrocardia were noted on chest x-ray, and on chest CT-scan, the right lung was smaller than the left because it was bilobed and the right pulmonary artery was small in size. On echocardiography, partial anomalous pulmonary venous return was seen.

The treatment approach is somewhat controversial and depends on the time of diagnosis, the patient’s respiratory status, evidence of recurrent infections, or if the patient is asymptomatic. There is a general consensus that sequestrations causing symptoms should be resected.⁸ Our patient had underwent lobectomy of the right lower lobe due to recurrent massive hemoptysis. The patient had an uneventful post-operative course.

CONCLUSION

Our patient had presented a unique co-existence of intralobar and extralobar sequestration associated with scimitar syndrome. This is a rare developmental anomaly of the lung, described as a variant of pulmonary sequestration spectrum. When presented with a case of recurrent hemoptysis in a seemingly well patient, it is invaluable to suspect an underlying lung malformation. Imaging studies are of great help for early diagnosis and proper management.

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Case Report - Cardiovascular Anesthesia

Anesthesia for a Patient With Large Left Anterior Mediastinal Tumor: a case report

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Background --- Anterior mediastinal tumors are not common lesions seen in the clinical practice in anesthesia. Patients known to have mediastinal tumors are at risk for cardiopulmonary complications in the perioperative period as a result of mass effect to the surrounding mediastinal structures. The objective of this case study is to discuss the anesthetic management of a patient who underwent excision of large left anterior mediastinal tumor.

Case --- Patient is a 41-year-old female with 5 years history of recurrent non-productive cough. Work-ups done revealed a diagnosis of Mediastinal Teratoma. Her symptoms progressed to difficulty of breathing and orthopnea. Patient underwent excision of large left anterior mediastinal mass under General Anesthesia. Anesthetic management was planned considering the size and the location of the mass causing symptoms of airway obstruction and cardiovascular compromise. Airway was secured by fiber-optic guided intubation and induction of anesthesia followed with careful titration of midazolam, fentanyl, and sevoflurane without muscle relaxant. Crystalloids, blood, blood components, and norepinephrine drip were given for the hypotension. Postoperative pain control was achieved with epidural morphine. A huge solid mass was excised from the patient. She tolerated the surgery and was sent to the SICU post-operatively with retained endotracheal tube for post-operative lung recruitment maneuvers.

Conclusion --- Large anterior mediastinal tumors can cause compression of surrounding mediastinal structures causing significant airway obstruction and cardiovascular compromise that may be exacerbated by general anesthesia. Detailed preoperative assessment and perioperative planning is a requisite for safe conduct of anesthesia. *Phil Heart Center J 2016;21(1):85-90.*

Key Words: Anterior Mediastinal Tumors ■ Anesthesia

Anterior mediastinal tumors are not common lesions seen in the clinical practice in anesthesia.¹ Mediastinal teratomas account for 15% of the adult anterior mediastinal mass.² Patients known to have mediastinal tumors are at risk for cardiopulmonary complications in the perioperative period as a result of mass effect to the surrounding mediastinal structures.³

Patients presenting with anterior mediastinal mass for surgery brings about unique dilemma to the anesthesiologists during general anesthesia as a consequence of the compression and other changes in the anatomy of the airway and obstruction of the venous return and cardiac output.⁴

This case is presented to discuss the anesthe-

tic considerations and management of an elective excision of large mediastinal teratoma in a 41-year old female patient who complained of unresolved recurrent cough, difficulty in breathing, and orthopnea.

Case

The patient is a 41-year old female who came in as a referral from another hospital for surgical management of a left anterior mediastinal tumor. Five years prior to admission, patient developed unresolving nonproductive cough associated with weight loss. Fever and difficulty of breathing were not noted during this time. Chest x-ray revealed anterior mediastinal mass. Bronchoscopy was done with normal results. She was advised to have biopsy of the mass but the patient refused.

Patient tolerated the symptoms. Two years prior to admission, patient noted increasing easy fatigability, difficulty of breathing, and persistence of non-productive cough. She sought consult with another physician. Biopsies done 4 times revealed inconclusive findings. She was referred to this institution for further work-ups and management.

On admission, she had exertional dyspnea, 3-pillow orthopnea, and was speaking in phrases. Her point of maximal cardiac impulse was deviated at the right parasternal area of the chest. She also had lagging of the left hemithorax during inspiration, breath sounds were not appreciated in the left lung field.

Chest x-ray revealed complete opacification of the left hemithorax with contralateral deviation of the mediastinal structure, wherein the true cardiac size cannot be ascertained but the cardiac shadow is deviated to the right (*Figure 1*). Marked tracheal deviation to the right is also noted. Two-dimensional echocardiogram revealed normal cardiac function and volumes with ejection fraction of 75% and absence of pericardial effusion. ECG studies showed normal sinus rhythm. Spirometry revealed severe restrictive ventilatory defect with no significant response to bronchodilator. Chest CT scan imaging showed large, markedly heterogeneous mass in the left hemithorax with calcification, areas of cystic degeneration/necrosis measuring 17.5x 15.6 x 29.4 cm (APWCC) and significant mass effect. Further, it also showed mass compression of the left bronchial structures resulting in collapse of the left lung. The heart and other mediastinal structures are displaced to the right with compression of the left pulmonary artery and vein branches. Branches of the left pulmonary artery appear to supply the mass. (*Fig 2A and 2B*). Hematologic and blood chemistry laboratory results were within normal limits. Baseline ABG at room air is within normal limits.

Patient was seen an evening prior to the day of surgery. Patient's condition, surgical plan, and anesthetic plan as well as the risk of anesthesia were explained to the patient. After which consent was secured. Considering that the patient already had respiratory distress, she was not given sedative or anxiolytic medications as premedications.

Patient was brought in to the operating room awake, calm, on high backrest position per stretcher. Monitors were attached (pulse oximeter, blood pressure, ECG), invasive arterial blood pressure monitoring was inserted at the right femoral artery using gauge 18 abbocath. Central venous pressure monitoring was inserted at the right femoral vein using Cavafix 370 inserted through a 6F introducer sheath with local anesthesia ensuring that the tip of the CVP line is at the right atrium. Oropharynx was sprayed with Lidocaine 2%. Fentanyl and midazolam was given on titration. Oxygen was administered via nasal cannula at 2lpm. Awake oral fiberoptic intubation with endotracheal tube 7.5 mm ID was performed with ease. Induction of anesthesia carried on with additional midazolam, fentanyl, and sevoflurane carefully titrated to maintain normal hemodynamics. Boluses of phenylephrine were given for episodes of hypotension.

Muscle relaxant was avoided. Additional arterial femoral access was secured for possible CPB cannulation as the need may arise in the course of the operation. Median sternotomy, which extended to anterior thoracotomy was done. Isolation of pleural mass with ligation of feeding vessels and excision of large pleural mass followed.

Estimated blood loss was 3,000cc. Crystalloids, PRBC, platelet concentrate, and FFP were given to a volume of 2,500cc. Hemodynamics was labile with persistence of hypotension prompting the use of vasoconstrictor Norepinephrine.

Hemostasis and insertion of JP drain at the pericardium and CTT was done and the chest was closed. Epidural catheter was inserted at the level of T8 leaving 2.5 cm mark for administration of epidural morphine for post-operative pain control. Patient was brought to the SICU with retained endotracheal tube for post-operative left lung recruitment strategies. Patient was extubated on the 3rd post-operative day, tolerating oxygen inhalation via nasal canula. On the 5th post-operative day, patient was transferred to the ward with CTT in place.



Figure 1. Chest x-ray showing markedly deviated trachea to the right

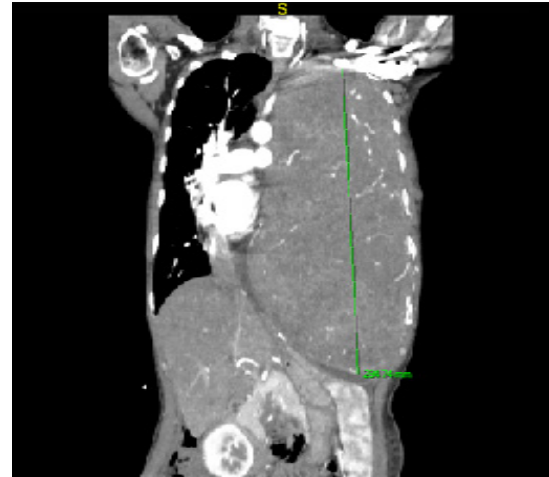


Figure 2A. CT scan - markedly heterogenous mass in the left hemithorax measuring 17.5 x 15.6 x 29.4 cm (APWCC) and significant mass effect

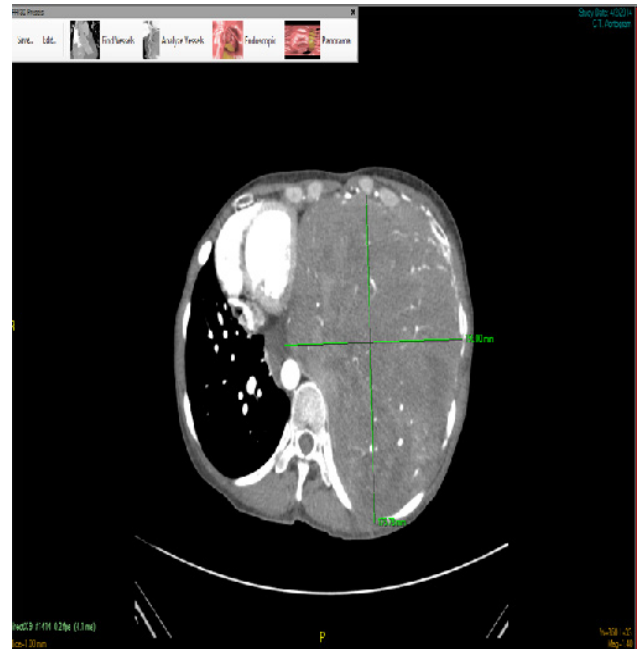


Figure 2B. CT scan image showing mass compression of the left bronchial structures resulting in collapse of the left lung. The heart and other mediastinal structures are displaced to the right with compression of the left pulmonary artery and vein branches

DISCUSSION

Often times, patients with anterior mediastinal tumors are asymptomatic but usually become symptomatic as the tumor enlarges. It is recommended to surgically excise the mediastinal tumor, whether benign or malignant. The rationale of removing benign tumors is to avoid compression of the vital intrathoracic organs before the tumors enlarge in size.⁴ Anesthesia management for these patients is challenging as the patient may have compromised airway and hemodynamics.

Preoperatively, patients should be evaluated for extension of the tumor to determine whether the tumor affects the other mediastinal structures that can lead to respiratory and hemodynamic stability.⁵

The anesthesiologist should have a high index of suspicion for increased dyspnea or orthopnea, which may signify increased risk of airway complications and syncopal symptoms or pericardial effusion, which suggests increased risk of cardiovascular complications.⁶ It can be noted that our patient had dyspnea and orthopnea, which relates with the spirometry result of severe restrictive airway defect. The CXR and CT image of severe tracheal deviation and compression show the risk of the patient for airway compromise especially with general anesthesia. The study of Slingers showed that now-loop did not offer benefit in the management with these patients. However, It also showed that patient's history and imaging has the best predictive value for airway compromise.⁵ Pre-medication of sedative and anxiolysis was withheld for this reason. However, a case study by Subanna et al, presented a patient with mediastinal mass and was premedicated with alprazolam the night prior to surgery.⁷ Tracheal deviation as seen in the imaging technique mandates the use of fiber-optic for intubation.

Previous case reports showed that 20% of the patients with anterior mediastinal tumors are associated with severe respiratory and cardiovascular compromise. But these studies and case series described the pediatric population. Studies of adult population with anterior mediastinal tumor are still lacking. A large case series exhibited that intraoperative cardiovascular and respiratory complications were associated only with the presence of a pericardial effusion,⁸ which our patient did not have and would explain the stable hemodynamics on induction.

Postoperative complications were predicted among patients with severe symptoms such as orthopnea and tracheal compression of >50%, thus the decision to retain the endotracheal tube post-operatively.

General anesthesia was induced in slow titration of midazolam, fentanyl, and sevoflurane because the loss of spontaneous ventilation, may it be due to deep anesthesia or neuromuscular blocking agents, may predispose to airway collapse due to loss of tone of the chest wall and tracheobronchial tree. General anesthesia per se reduces the functional residual capacity and alters the respiratory mechanics, favoring obstructive respiratory defect. Extrinsic support of the airway secondary to muscle relaxation may lead to airway obstruction despite having intubated the patient because most obstruction of the tracheobronchial tree occur at the level of the carina, mostly at the tip of the endotracheal tube.⁹

Many authors have advocated avoidance of muscle relaxants during the induction and maintenance of anesthesia. Although few case reports describes giving muscle relaxant to patients with anterior mediastinal mass, other case reports showed airway collapse after giving muscle relaxants.^{7,10}

Large bore intravenous cannula was placed in the lower half of the body to replace the blood loss, SVC obstruction is a common presenting sign in large anterior mediastinal tumors either by tumor invasion or compression.¹¹

Some authors have advocated the use of cardiopulmonary bypass to address the concerns on intraoperative gas exchange and cardiovascular collapse in patients with severe airway narrowing and involvement of the pulmonary artery. Case reports describe the use of femoro-femoral bypass instituted with local anesthesia before induction of anesthesia.¹¹ CPB was not utilized with this patient.

Intraoperatively, the patient had hemodynamic instability probably because the heart and the major vessels are surrounded by the tumor on top of the massive blood loss of 3L. The SVC is susceptible to compression. Compression of either the SVC and the heart, manifested as an increased CVP opening pressure of 27 mmHg, decreases the RV filling and thus the cardiac output. This was managed accordingly by increasing the venous return with crystalloids, blood, blood component, and vasoconstrictor.¹²

Epidural analgesia with morphine sulfate provided adequate pain control to the patient. This has been considered by many as the gold standard of post-operative pain control especially if the epidural mixture of local anesthesia and morphine are used.¹³ This combination is the only way to minimize motor and sympathetic blockade, maintain level of consciousness and cough reflex and increase respiratory function after thoracotomy.

CONCLUSION

Anterior mediastinal tumor is an uncommon disease and surgical procedures for patients with this tumor pose great challenge for an anesthesiologist. Large anterior mediastinal tumors can cause compression of surrounding mediastinal structures and cause significant airway obstruction and cardiovascular compromise, which may be exacerbated by general anesthesia. Detailed preoperative assessment and perioperative planning is a requisite for a safe conduct of anesthesia.

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