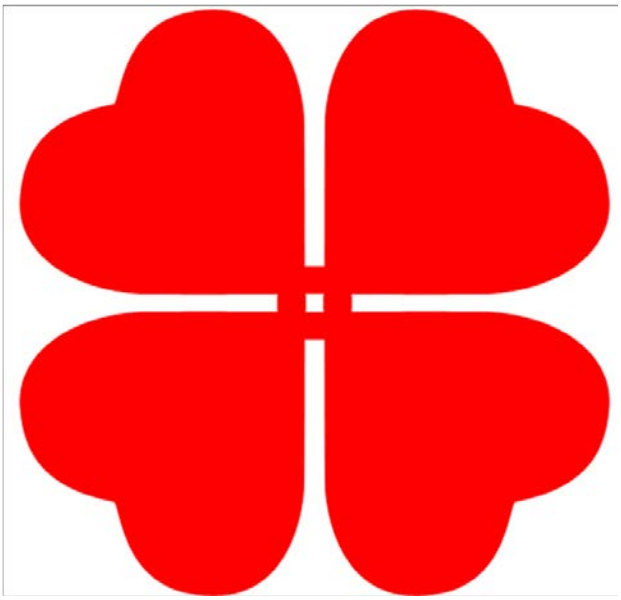
ISSN 0118-9034

Philippine Heart Center Journal



Vol 18 January - December 2014

Editorial

Call to Create Research Study Groups
Leahdette O. Padua, MD

Consultant 's Corner

Immunocell Therapy on Pulmonary Artery Sarcoma
Avenilo P. Aventura, MD; Samuel D. Bernal, MD; Ludgerio Torres, MD; Jose-Santos Abad, MD; Romeo Divinagracia, MD; Avenilo L. Aventura Jr., MD; Teresita de Guia, MD; Ruth C. Ong, MD

Original Articles

Accuracy of Tissue Doppler Strain in Predicting Significant Coronary Artery Stenosis
Ana Beatriz R. Medrano, MD; Warren S. Rondilla, MD

Prevalence of Clopidogrel Resistance Among Filipinos with Coronary Artery Disease: a Philippine Heart Center experience
Frederick S. Gabriel, MD; Ana Beatriz Medrano, MD; Ariel S. Miranda, MD; Jose Navarro, MD

Association of Electrocardiographic Ischemia Grades with Clinical and Angiographic Outcomes of Patients with ST-Elevation Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention
Jeffrey Chua, MD

Conventional Coronary Stenting Versus Direct Coronary Stenting in Coronary Artery Disease Patients Undergoing Elective Percutaneous Transluminal Coronary Angioplasty: a Philippine Heart Center experience
Dodee Niño V. Rigor, MD; Ronaldo H. Estacio, MD; Melquides Pua, MD

Association of Severity of Sleep Apnea Syndrome with Driving Accidents
Irenee Faustina J. Casino, MD; Encarnita B. Limpin, MD; Aileen G. Banzon, MD; Joseph Hope Cal, MD; Teresita Celestina S. Fuentes, MD

Predictors of Postoperative Pulmonary Complications in Children Undergoing Cardiothoracic Surgery at the Philippine Heart Center (PREdICt Phase I)
Maria Niña F. Banque, MD; Teresita S. De Guia, MD; Fernando G. Ayuyao, MD; Milagros S. Bautista, MD; Ma. Dulce Requiron-Sy, MD; Maria Nerissa Atienza-De Leon, MD

The Accuracy of Hounsfield Unit CT Attentuation in Differentiating Transudative From Exudative Pleural Effusion Based on Light 's Criteria
Allan P. Celi, MD; Harold L. Tan, MD

A Comparison of Patient-Controlled Analgesia (PCA) with Nurse-Administered Analgesia (NAA) in Post-Operative Pain Control Among Open Heart Surgery Patients at the Philippine Heart
Juffey Tabingan, MD; Carina Dipasupil, MD; Veronica Durante, MD

Case Report

Familial Interstitial Lung Disease in a Family with Familial Juvenile Idiopathic Arthritis
Charo N. Francisco, MD

Official Publication of the Philippine Heart Center

PHILIPPINE HEART CENTER JOURNAL TABLE OF CONTENTS

Volume 18 January - December 2014

Editorial

Call to Create Research Study Groups ---------- iii
Leahdette O. Padua, MD

Original Articles

Immunocell Therapy on Pulmonary Artery Sarcoma ---------- 1
Avenilo P. Aventura, MD; Samuel D. Bernal, MD; Ludgerio Torres, MD; Jose-Santos Abad, MD; Romeo Divinagracia, MD; Avenilo L. Aventura Jr., MD; Teresita de Guia, MD; Ruth C. Ong, MD

Accuracy of Tissue Doppler Strain in Predicting Significant Coronary Artery Stenosis ---------- 8
Ana Beatriz R. Medrano, MD; Warren S. Rondilla, MD

Prevalence of Clopidogrel Resistance Among Filipinos with Coronary Artery Disease: a Philippine Heart Center experience ---------- 20
Frederick S. Gabriel, MD; Ana Beatriz Medrano, MD; Ariel S. Miranda, MD; Jose Navarro, MD

Association of Electrocardiographic Ischemia Grades with Clinical andAngiographic Outcomes of Patients with ST-Elevation Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention ---------- 29
Jeffrey Chua, MD

Conventional Coronary Stenting Versus Direct Coronary Stenting in Coronary Artery Disease Patients Undergoing Elective Percutaneous Transluminal Coronary Angioplasty:a Philippine Heart Center experience ---------- 39
Dodee Niño V. Rigor, MD; Ronaldo H. Estacio, MD; Melquides Pua, MD

Association of Severity of Sleep Apnea Syndrome with Driving Accidents ---------- 45
Irenee Faustina J. Casino, MD; Encarnita B. Limpin, MD; Aileen G. Banzon, MD; Joseph Hope Cal, MD; Teresita Celestina S. Fuentes, MD

Predictors of Postoperative Pulmonary Complications in Children Undergoing Cardiothoracic Surgery at the Philippine Heart Center (PREdICt Phase I) ---- 52
Maria Niña F. Banque, MD; Teresita S. De Guia, MD; Fernando G. Ayuyao, MD; Milagros S. Bautista, MD; Ma. Dulce Requiron-Sy, MD; Maria Nerissa Atienza-De Leon, MD

The Accuracy of Hounsfield Unit CT Attentuation in Differentiating Transudative From Exudative Pleural Effusion Based on Light's Criteria ---- 68
Allan P. Celi, MD; Harold L.Tan, MD

A Comparison of Patient-Controlled Analgesia (PCA) with Nurse-Administered Analgesia (NAA) in Post-Operative Pain Control Among Open Heart Surgery Patients at the Philippine Heart ---- 75
Juffey Tabingan, MD; Carina Dipasupil, MD; Veronica Durante, MD

Case Report

Familial Interstitial Lung Disease in a Family with Familial Juvenile Idiopathic Arthritis ---- 80
Charo N. Francisco, MD

Information for subscribers ---- iv

Information for authors ---- v

Editorial

Call to Create Research Study Groups

Leahdette O. Padua, MD

The research milieu that is existing in our institution is mostly geared towards researches done by individuals, mostly by the trainees and by a few consultants. We have been proud that some of these individual researches had been recognized locally and internationally.

However, there are a lot of limitations for researches carried out by an individual effort. Compared with researches done by a group, individual researches may have some limitations in recruiting subjects. Although they may reach the target sample size, this may not necessarily be the optimal sample size, since the computation is adjusted to the constraints imposed by the feasibility of recruiting the ideal number of subjects. Moreover, there is limitation in the time frame to conduct researches by individuals. Individual investigators should work within the time frame imposed by their training programme; otherwise, they will not graduate on time. This will not be a problem for studies to be conducted by group (e.g. a certain section study group). They can create a study that can have a five to ten years follow up, which is enough to observe long-term outcomes in certain diseases and interventions. Also, for longitudinal studies, studies done by individuals may just opt to collect historical data; as opposed to studies done by a group, data can be collected retrospectively or prospectively.

The “group” in researches conducted by a set of individuals should not just be limited to the division, section or department they belong to. Although this set up is ideal since the group already have set goals, meeting dates and familiarity with each other, working with other departments/sections/ divisions can provide a different perspective in the research. These collaborative researches can be done by multiple disciplines involved in the management of patients. (e.g. creation of PHC-VTE study group may involve specialists in pulmonary and vascular medicine, as well as radiologists).

It is high time to instigate interests in researches to be done by groups. Efforts are already being done to equip these individuals with tools on the how to’s of doing research. Technical support is also available. Incentives may be given to recognize the efforts of creating group researches, from the protocol to the final paper.

We dare not say that we should abandon doing individual papers; however, there should be a thrust to create research study groups if we want to contribute more to the advancement in cardiovascular care.

Immunocell Therapy on Pulmonary Artery Sarcoma

Avenilo P. Aventura, MD; Samuel D. Bernal, MD; Ludgerio Torres, MD; Jose-Santos Abad, MD; Romeo Divinagracia, MD; Avenilo L. Aventura Jr., MD; Teresita de Guia, MD; Ruth C. Ong, MD

***Background* ---** Pulmonary artery sarcoma is a rare tumor that is often confused with chronic thromboembolic disease and have poor prognosis.

***Case Presentation* ---** We report two (2) cases of pulmonary artery sarcoma presenting with signs and symptoms of venous thromboembolism, which after thorough diagnostic work-up showed the presence of mass lesion at the pulmonary artery. We aim to strategize a multimodality management utilizing surgery, immunocell therapy and MTT (Molecular Targeted Therapy) to improve survival.

Conclusion* ---** Pulmonary artery sarcoma is often mistaken for acute pulmonary embolism. Early diagnosis and proper imaging technique may prompt aggressive intervention. Multimodality treatment with immunocell therapy as an adjunct may improve survival. ***Phil Heart Center J 2014;18(1):1-7.

Key Words: Pulmonary Artery Sarcoma ■ Immunocell Therapy ■ Pulmonary Embolism

Immune system modulation to treat cancer had been extensively studied since the 1970’s. Melanoma, renal cell carcinoma, colorectal cancer and non small cell lung cancer had shown sensitivity to such therapy. Immunotherapy for therapeutic cancer management is designed to target cancer-associated antigen and regulatory signaling molecules. As understanding of the complex signaling pathways in immune system regulation and genetic analysis of normal and tumor cells is markedly accelerated, many preclinical trials have shown various therapeutic strategies. The requirement for successful interventions is to target specific tumor antigens with regulators of antitumor immune response. Approaches of immunotherapy involved interleukin (IL)-2, interferon (IFN)-alpha-2b, antibody therapy with muromonab -CD3, lymphokine-activated killer cell infusions, tumor-infiltrating lymphocyte infusions, dendritic cell infusions, peptide-stimulated vaccine infusions, and various combinations of the above treatment modality.[1]

Pulmonary artery sarcoma is a rare type of tumor with malignant propensity.[2] We presented two cases of main pulmonary artery neoplasm that underwent pulmonary thrombarterectomy in conjunction with immunocell therapy following surgery.

Case I: The first case involved a 29/F (50 kg, 157.4 cm) who was admitted due to recurrent syncopal attacks. Symptoms of vertigo and body weakness had been present for nine months. She eventually presented with easy fatigability three months prior to admission. She had murmur on physical examination, cardiomegaly on chest x-ray and a shunt anomaly causing volume and pressure overload on right heart on 2D echocardiography. She was started on digoxin and diuretics. She had a syncopal attack prompting admission. Pertinent findings included a grade 2/6 murmur at the 4th LICS parasternal border, normal neurologic examination, and clubbing of digits. She had leukocytosis with elevated hematocrit and hypomagnesaemia. There was a suspicious pulmonary nodule at the left upper lobe on chest x-ray with an impression of main pulmonary artery mass.

Transesophageal echocardiography showed the presence of a main pulmonary artery mass, measuring 4.2cm x 1.5cm, causing significant obstructive hemodynamic effect; a patent foramen ovale, with right to left shunt, causing dilation of both right atrium and right ventricle; severe tricuspid regurgitation; moderate pericardial effusion; and the left ventricle had adequate contractility and systolic function.

Lung perfusion scintigraphy showed a diminished perfusion in left upper lung segment and totally absent perfusion in left lower lung lobe and lingular segment with normal ventilation, consistent with obstruction of left main pulmonary artery. DVT screening showed no evidence of acute proximal deep vein thrombosis on both upper extremities and lower extremities.

On the 13th hospital day, she underwent excision of the said mass. An hour after incision, she had sinus bradycardia and an epicardial pacemaker was inserted. Excision of pulmonary artery mass was successfully done under profound hypothermia and total circulatory arrest. Frozen section and left lung biopsy showed pleomorphic sarcoma, Grade III. Another piece of the tumor was sent for antigen extraction. Three days after, she developed acute respiratory distress syndrome and an emergency extracorporeal membrane oxygenator was instituted using veno-venous approach via the right femoral vein as the inflow and left femoral vein as the outflow for two days. A month after ECMO, she was gradually weaned off from the oxygen therapy. A repeat 2D echocardiography showed that the main pulmonary artery mass was not noted.

Immunocell Therapy was initiated using 40cc of blood sample collected intravenously. White blood cells were separated and cultured in Roswell Park Memorial Institute (RPMI) medium, which was expanded and induced to become dendritic cells. The cells were prepared using specific antigen from tumor cells. The cell processing took around two to three weeks and she was prepared for injection. Granulocyte Colony Stimulating Factor (G-CSF) 30 Mio U/E was given subcutaneously followed by intradermal injection of the immunocell preparation at the deltoid area. She remained stable before, during and after injection. The wheal that was produced during injection subsided after an hour. Injection site were cleared with no erythematous nor hypersensitivity reactions noted. She received a total of two injections and was subsequently discharged.

On the fourth month, she had low grade fever, vomiting and occasional left scapular pain. Repeat 2D echocardiography detected a huge RV mass that was partially obstructing the right ventricular outflow tract. The previous echocardiography a month prior was devoid of any mass. Because of severe dyspnea, she was intubated. However, she had persistent oxygen desaturation and was subsequently hypotensive. Her unresponsiveness to supportive therapy led to her demise.

Case 2: The second case involved a 38 year old female (57kg, 170cm) who was admitted due to progressive dyspnea and pleuritic chest pain since a year prior to admission. Work-ups showed an elevated D-dimer and 2D echocardiography showed a right coronary sinus of valsalva aneurysm with pulmonic regurgitation; mitral regurgitation; and an elevated pulmonary artery pressure (95mmHg). She was treated as a case of pulmonary embolism. However, there was persistence of dyspnea and pleuritic chest pain, which was now accompanied by occasional occurrence of central cyanosis, leg edema and appreciable weight loss. A repeat transthoracic echocardiography confirmed the same elevated pulmonary artery pressure (89 mmHg). On consultation at our institution, a pulmonary artery and right ventricular wall masses were discovered. She underwent pulmonary thromboendarterectomy with patch reconstruction of pulmonary artery using autologous pericardium under cardiopulmonary bypass utilizing profound hypothermia and total circulatory arrest. Tumor resection was extensive from the ventricular septum of right ventricular outflow tract (RVOT) as well as the pulmonic valve. RVOT was reconstructed using Gortex composite graft from the main pulmonary artery. Pulmonic valve was replaced using a tissue valve. Frozen section and histopathologic examination showed pulmonary artery sarcoma that was pleomorphic and with vessel wall involvement. (*Figure 1*) Another piece was sent for antigen extraction and molecular profiling and chemotherapy resistance. The rest of the hospital stay was unremarkable and she was discharged home after 49 days.

On follow-up one month post-op, she had occasional left scapular pain responsive to pain reliever. A repeat 2D echocardiography showed normal functioning bioprosthetic pulmonic valve with good opening and closing motion

and a maximum gradient of 13mmHg. The main and branch pulmonary arteries showed normal dimension. After thorough evaluation, the patient consented for the adjunct treatment plan of immunocell therapy in combination with chemotherapy.

The procedure of immunotherapy required granulocyte-colony stimulating factor (G-CSF) injection, leukapheresis cell expansion, culture and processing prior to final injection of the processed cells. Two months after surgery, she was readmitted for the immunotherapy. Granulocyte Colony Stimulating Factor 30 Mio U/E was injected subcutaneously 24 hours prior to leukapheresis. She had a port placed at the right internal jugular vein. Leukapheresis, a procedure that involved leukocytes separation, started with adequate solution priming on the apheresis machine. Data on patient height, weight, sex and hematocrit were entered into the machine and it automatically computed for the predicted time or target time (319 minutes) and the amount to be collected (286 ml). The initial extraction was yellow colored plasma fluid until layering occurs where red blood cell (RBC) occupied the lower most portion of the blood bag followed by white blood cell (WBC). Lymphocytes stayed on the third layer with monocytes on top and the plasma was on the uppermost layer. Monocytes harvest was done collecting 301 milliliters. She tolerated the procedure well except for an episode of vomiting and hypotension at 184 minutes. The vomiting resolved spontaneously while hypotension was relieved by position changes and volume challenge. She had generalized fatigue, peri-oral numbness, and leg muscle cramps, which were the clinical manifestation of hypocalcemia. Serum calcium level showed hypocalcemia 1.97 (2.1-2.55) and this was corrected.

Blood work-ups on the collected cells showed an adequate yield of leukocyte (58 microliter) and monocytes (25.2 microliter) The adequacy of collected cells showed it has ample amounts of plasma and dendritic cells 80-90% confluent, thereby incubation and cell processing was started.

Immunocell injection was done a week after. This involved an initial subcutaneous injection of a dose of G-CSF followed by dendritic cell injected intradermally at bilateral deltoid area. The procedure was well tolerated except for a sudden hot flush that occurred 30 minutes after injection. Vital signs as well as temperature were stable. She was discharged home well the following day.

She underwent monthly immunocell injection that was initiated on the third month of the postoperative period. Monthly injection along with monthly surveillance utilizing blood chemistry and echocardiography showed relatively controlled activity. Oncologic consult was likewise done and planned chemotherapy utilizing nanocell and calyx regimen were contemplated.

Two weeks prior to her last dose of immunocell injection, she had hemoptysis. Warfarin was withheld and prothrombin determination revealed normal results. There was two weeks delay in the administration of immunocell therapy secondary to funding difficulties. A week after, she experienced severe non productive cough accompanied by dyspnea, peripheral cyanosis and sleeping difficulty. This resulted to subsequent admission.

On admission, her initial O2 saturation was 96% and her heart rate was at 110-120. Chest radiography noted a significant interval increase in the size of right mid lung nodular density and a prominent pulmonary artery segment. 2D echocardiography showed a 1.7 cm x 2.0 cm echogenic density at the RVOT bifurcation of left and right pulmonary artery. This mass was partially obstructing the RVOT. Chest CT showed that the previously 0.9cm x 1.0cm mass in the superior segment of right lower lobe had increased to 4.0cm x 3.7cm x 3.6cm. There was an interval appearance of another ovoid mass in the aortopulmonary window, which measured 2.0cm x 4.2cm x 2.3cm, causing extrinsic compression to the left pulmonary artery, resulting in severe stenosis. *(Figure 2)*

The last dose of immunocell therapy was given to boost her immune system. She was started with a molecular targeted therapy (MTT) agent, Trabectedin, an antineoplastic agent from a naturally occurring compound derived from marine organism (*Ecteinascidia turbinate*). She

had vomiting despite ranisetron and metoclopramide administration that lasted for around 3-4 days. The plan was to have simultaneous MTT and Intensity–Modulated Radiation Therapy (IMRT).She was seen by Radio-oncologist; however, the cell type was not responsive to radiation therapy. She survived for two years since diagnosis and finally succumbed secondary to recurrence.

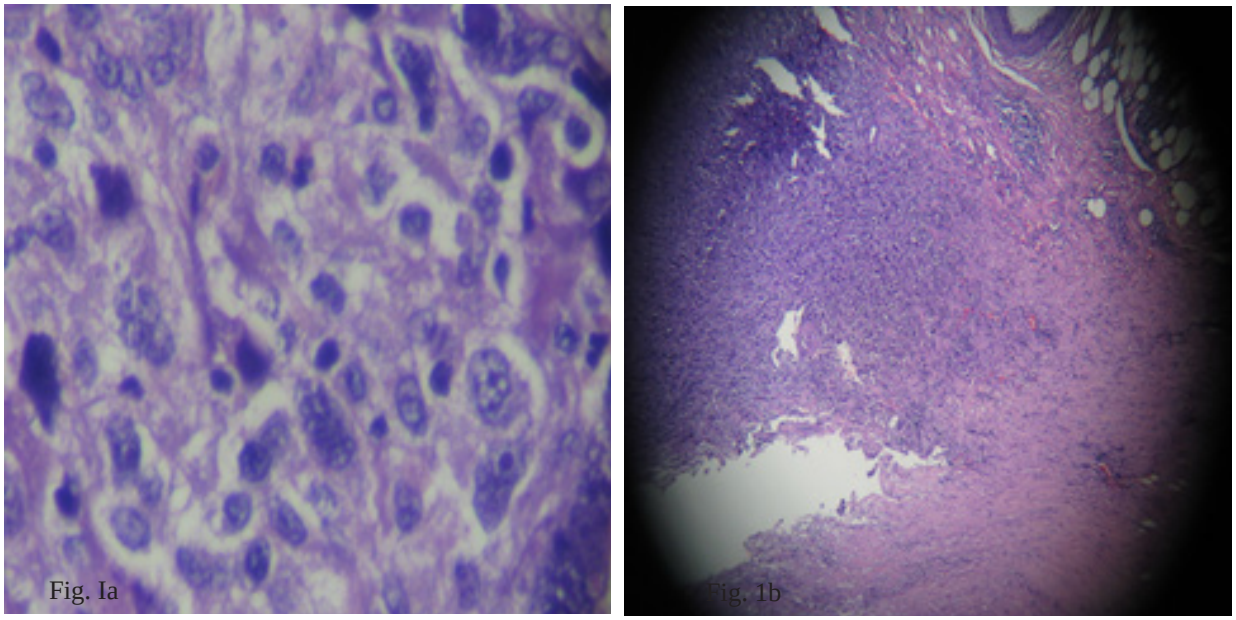


Figure 1. Microscopic examination of the pulmonary artery mass from a 38 year old female who presented with progressive dyspnea and pleuritic chest pain. High power field of pulmonary artery sarcoma (a) with vessel wall involvement (b)

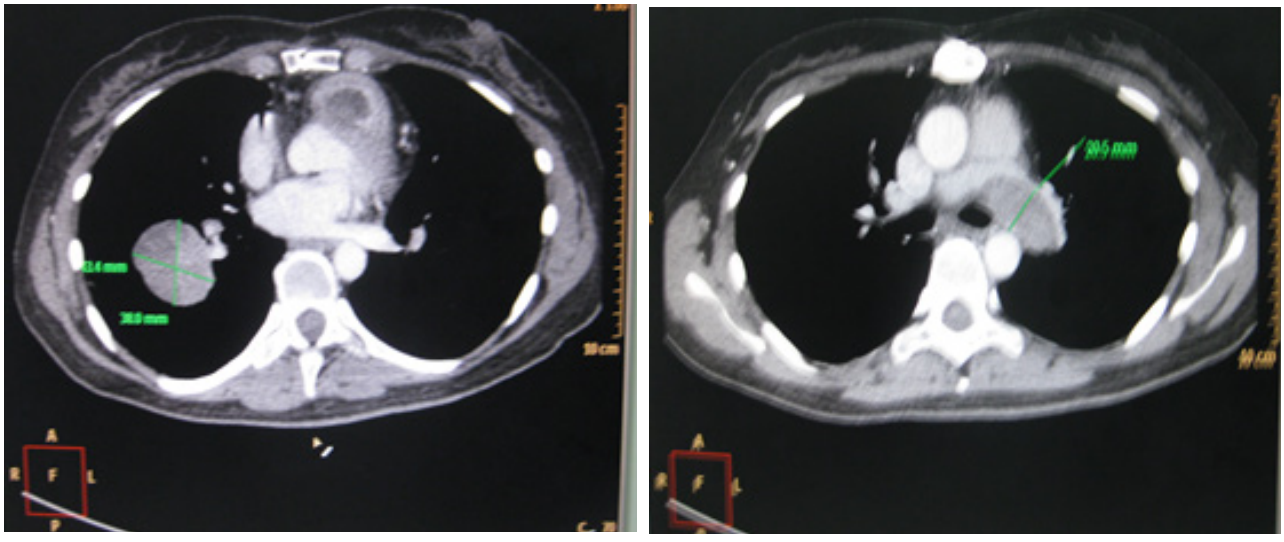


Figure 2. Chest CT Scan of a 38 year old female taken 8 months after excision of pulmonary artery mass and immune cell therapy. There was an interval increase in the mass at the superior segment of right lower lobe and an interval appearance of another ovoid mass in the aortopulmonary window causing extrinsic compression to the left pulmonary artery.

DISCUSSION

Pulmonary Artery Sarcoma is a rare malignant mesenchymal type sarcoma that was first described by Mandelstamm in 1923.[2-5] Its true incidence is unknown due to its similar presentation with thromboembolism and majority of cases were under diagnosed.[5] The prevalence of chronic thromboembolic pulmonary hypertension in the general population cannot be accurately determined and may have been significantly underestimated.[4] Recent prospective epidemiologic data showed an incidence of approximately 4% after acute symptomatic pulmonary thromboembolism.[4] The etiology is unknown; however, it has been suggested to arise in large vessels such as aorta and pulmonary artery. The tumor is characterized by luminal growth leading to intimal obstruction or emboli seeding.[6,7] The prognosis is poor. Reported life expectancy from symptom onset is from 12 to 18 months;[7] whereas, one-and two-year survival rates are 22% and 7% respectively.[8] Surgical excision is the mainstay of treatment; adjuvant radiotherapy and/or chemotherapy may be necessary for complementation.[5,9,10] In one study, they reported the survival according to the completeness of resection: 36.5 ± 20.2 months for complete resection and 11 ± 3 months for incomplete resection.[11] With regards to the modality of treatment, survival was increased to 24.7 ± 8.5 months in multimodality treatment versus 8 ± 1.7 months using single modality.[11]

Pulmonary artery sarcomas are rare and are usually diagnosed during surgery or autopsy. There is a wide range of age presentation (22 to 81 years), with majority presenting in the fifth decade and some report female sex predominance.[8]

Signs and symptoms include progressive dyspnea and cyanosis, which are similar to chronic thromboembolic disease conditions, precluding early diagnosis.[5,6,8] Imaging utilizing echocardiography, computed tomography, scintigraphy are needed for confirmation delineation and evaluation of extent of involvement.[5-7,12]

Histopathologic examination of tumor cells yield spindle cell, myxoid and pleomorphic type is leiomyosarcoma or undifferentiated spindle cell sarcoma.[13] In this case series, both our patients presented with pleomorphic type with spindle characteristics. Immunohistochemistry showed submembranous staining with SMA; focal strong staining with desmin; diffused strong staining with neuron-specific enolase (NSE); and negative staining through cytokeratin. Proliferation markers (p53, MIB-1) showed positive staining in 75% of tumor cells. Molecular profile on our second patient showed that PTEN (phosphatase and tensin homologue) was present and EGFR (epidermal growth factor receptor) was negative.

Chemotherapy using anthracycline and alkylating agent was reported to have a 20% response rate. [14-16] There was a report of successful treatment using Ifosfamide and Epirubicin by Uchida et al.[14]

Cell based immunotherapies, which may consist of immune cells such as lymphocytes, macrophages, dendritic cells, NK (Natural killer) cells, and CTL (Cytotoxic T- lymphocytes), work together to improve the body's defense.[1] The goal of immunotherapy is education of body's immune system to recognize malignant cells. This process intensifies cellular interaction as it provides a focus for immune attack.[1] Tumor tissues harvested during surgical excision were modified in laboratory so that it will no longer multiply; however, it still displays the surface antigens to stimulate the immune system when replaced in the body.

With the advent of molecular profiling, identifying mutations leads to personalized treatment, with a better chance of it working since it targets specific mutations found in that tumor. This also prevents patients from being exposed to drugs that have a limited chance of success, eliminating toxicity and improving quality of life. The treatment modality will be greatly enhance as it focus on target receptors.[18-20]

Our first patient received immunocell therapy a month after operation and was symptom-free and negative for recurrence on diagnostic surveillance. She presented with fever and left shoulder pain and on repeat 2D echocardiography showed retrograde recurrence to right ventricle partially obstructing the right ventricular outflow tract. Recurrence occurred on the

third month post surgery.

Our second patient was a rare case of intimal sarcoma affecting the right ventricular outflow tract as well. There were also seeding in the lungs. Her tissue showed negative for increased gene copy number of epidermal growth factor receptor (EGFR) but there was the presence of gene amplification. The tissue revealed the presence of an average of 2.20 copies /cell of the EGFR gene located at 7 p12. She received immunocell therapy on the third month after operation. She went on to her usual activities of daily living with good quality of life. She nearly completed the six (6) sessions of treatment; however, recurrence occurred on the 8th months post surgery. With the observed pattern, tumor replication was rapid and simultaneous multimodality treatment was the only hope to halt tumor aggressiveness, thus the current plan is simultaneous MTT (Molecular Targeted Therapy) and Intensity Modulated Radiation Therapy (IMRT).

Molecular Targeted Therapy, such as using Trabectedin, works by targeting the DNA of tumor cells resulting to bending of the DNA at the minor groove and binding of the other molecule to a protein prevent activation of cellular repair mechanism to take place. This induces cell death and apoptosis on tumor cells. MTT also stops the molecular signals sent by cancer cell to build blood vessels resulting to tumor deprivation. One important feature of MTT, in comparison to chemotherapy, is that it minimizes the effects on healthy cells; whereas, chemotherapy affects both tumor cells and healthy cells.[19,20]

On the other hand, IMRT is a type of highly precise, advance type of 3D radiation therapy that utilized Computed Tomography as guide.[21,22] Computer controlled x-ray accelerators modulate and distribute radiation doses to the tumor bulk while protecting the surrounding tissues.[22]

CONCLUSION

Pulmonary Artery Sarcoma, intimal type is a rare malignancy. Early diagnosis is essential as it provides greater chance of survival. Secondary to its pleomorphic features, multimodality intervention is suggested. Surgery is still the main therapeutic option; chemotherapy and radiotherapy may prolong survival; and immunotherapy as part of the adjuncts in management, enable better survival as well as quality of life.

CONSENT

Written informed consent was obtained from the patient for the procedure and its publication as well as the diagnostic images.

COMPETING INTERESTS

The authors declare no competing interest.

AUTHOR'S CONTRIBUTIONS

Dr. Ruth Ong collected the data and drafted the manuscript. Dr. Avenilo P. Aventura, Dr. Samuel Bernal, Dr. Ludgerio Torres, Dr. Jose Santos-Abad, Dr. Romeo Divinagracia, Dr. Teresita de Guia , and Dr. Avenilo L. Aventura revised and approved the manuscript. All authors have read and approved the final manuscript.

ACKNOWLEDGEMENTS

The authors would like to extend their utmost gratitude to all physicians, nurses, molecular technologist, and biochemist from Philippine Heart Center, Globe Tek Science Foundation, National Kidney and Transplant Institute, Lung Center of the Philippines, who participated in medical care of the two patients described in this report.

REFERENCES

1. Nemunaitis, J, Khun JA. Immune modulation as cancer treatment using gene therapy. BUMC Proceedings. 1999;12:231-237.
2. Mandelstamm M. U¨ber primäre Neubildungen des Herzens. Virchows Arch Pathol Anat 1923;245:43–45.
3. Widera E, Sulica R. Pulmonary artery sarcoma misdiagnosed as chronic thromboembolic pulmonary hypertension. Mt Sinai J Med. 2005;72(6):360-4
4. Kerr KM. Pulmonary artery sarcoma masquerading as chronic thromboembolic pulmonary hypertension. Nat Clin Pract Cardiovasc Med. 2005;2(2):108-12
5. Scheffel H, Stolzmann P, Plass A, Weber A, Prêtre R, Marincek B, et al. Primary intimal pulmonary artery sarcoma: a diagnostic challenge. J Thorac Cardiovasc Surg. 2008;135(4):949-50.

6. Furest I, Marin M, Escribano P, Gomez MA, Cortina J, Blanquer R. Intimal sarcoma of the pulmonary artery: a rare cause of pulmonary hypertension. Arch Bronco-pneumol. 2006;42:148-150.
7. Ozbek C, Emrecan B, Calli AO, Gurbuz A. Intimal sarcoma of the pulmonary artery with retrograde extension into the pulmonic valve and right ventricle. Tex Heart Inst J. 2007;34(1):119-21.
8. Hsing JM, Thakkar SG, Borden EC, Budd GT. Intimal Pulmonary Artery Sarcoma presenting as Dyspnea: Case Report. Intl Sem Surgl Oncol. 2007;4:14
9. Nakajima J, Morota T, Matsumoto J, Takazawa Y, Murakawa T, Fukami T, et al. Pulmonary intimal sarcoma treated by a left pneumonectomy with pulmonary arterioplasty under cardiopulmonary bypass: report of a case. Surg Today. 2007;37(6):496-9.
10. Parish JM, Rosenow EC, Swensen SJ, Crotty TB. Pulmonary artery sarcoma. Clinical features. Chest. 1996;110(6):1480-8
11. Blackmon SH, Rice DC, Correa AM, Mehran R, Putnam JB, Smythe WR, et al. Management of primary pulmonary artery sarcomas. Ann Thorac Surg. 2009;87(3):977-84.
12. Djordjevic I, Pejcic T, Rancic M, Radovic M, Golubovic S, Dacic D et al. Difficulties in establishing a timely diagnosis of pulmonary artery sarcoma misdiagnosed as chronic thrombo-embolic pulmonary disease: a case report. J Med Case Reports. 2009;3:64
13. Sebenik M, Ricci A Jr, DiPasquale B, Mody K, Pytel P, Jee KJ, et al. Undifferentiated intimal sarcoma of large systemic blood vessels: report of 14 cases with immunohistochemical profile and review of the literature. Am J Surg Pathol. 2005;29(9):1184-93.
14. Uchida A, Tabata M, Kiura K, Tanimoto Y, Kanehiro A, Aoe M. Successful treatment of pulmonary artery sarcoma by a two-drug combination chemotherapy consisting of ifosfamide and epirubicin. Jpn J Clin Oncol. 2005, 35:417-419.
15. Nakahira A, Ogino H, Sasaki H, Katakami N. Long-term survival of a pulmonary artery sarcoma produced by aggressive surgical resection and adjuvant chemo-radiotherapy. Eur J Cardiothorac Surg. 2007;32(2):388-90.
16. Hirose T, Ishikawa N, Hamada K, Inagaki T, Kusumoto S, Shirai T, et al. A case of intimal sarcoma of the pulmonary artery treated with chemoradiotherapy. Intern Med 2009:48(4):245-9.
17. Long HQ, Qin Q, Xie CH. Response of pulmonary artery intimal sarcoma to surgery, radiotherapy and Chemotherapy: A Case Report. Med Case Reports. 2008 Jun 25:2:217
18. Laheru, DA, Pardoll DM, Jaffee EM. Genes to Vaccines for immunotherapy: How the molecular biology revolution has influenced cancer immunology. Mol Cancer Ther. 2005; 4:1645-1652
19. Tsuruo T, Naito M, Tomida A, Fujita N, Mashima T, Sakamoto H, Haga N. Molecular targeting therapy of cancer: drug resistance, apoptosis and survival signal. Cancer Sci. 2003;94(1):15-21
20. AACR 2009: Molecular Profiling of Tumors Improves Cancer Treatment. Medscape. Apr 21, 2009.
21. Teh BS, Woo SY, Butler EB. Intensity modulated radiation therapy (IMRT): a new promising technology in radiation oncology. Oncologist. 1999;4(6):433-42.
22. Staffurth J. A review of the clinical evidence for intensity-modulated radiotherapy. Clin Oncol (R Coll Radiol). 2010 Oct;22(8):643-57.

Accuracy of Tissue Doppler Strain in Predicting Significant Coronary Artery Stenosis

Ana Beatriz R. Medrano, MD; Warren S. Rondilla, MD

Background --- Strain and strain rate are new techniques in echocardiography that measures the time course of tissue deformation. They are highly sensitive to regional ischemia. The aim of this study is to determine the accuracy of tissue doppler strain in predicting significant coronary artery stenosis.

Methods --- This is a cross-sectional study involving 79 consecutive adults with a diagnosis of coronary artery disease who underwent coronary angiography during the same hospital admission. Strain and strain rate analysis along the areas supplied by the respective coronary artery were done. These were correlated with the results of the coronary angiogram.

Results --- Among the four myocardial segments supplied by the left circumflex artery, ≥2 abnormal segments by strain had a sensitivity of 100%, specificity of 92.9%, positive predictive value of 92.5% and negative predictive value of 100% and ≥2 abnormal segments by strain rate had a sensitivity of 100%, specificity of 83.3%, positive predictive value of 84.1% and negative predictive value of 100% in predicting at least 70% coronary artery stenosis.

Among the three myocardial segments supplied by the right coronary artery, ≥2 abnormal segments by strain had a sensitivity of 96.9%, specificity of 97.9%, positive predictive value of 96.9% and negative predictive value of 97.9% and >2 abnormal segments by strain rate had a sensitivity of 100%, specificity of 93.6%, positive predictive value of 91.4% and negative predictive value of 100% in predicting at least 70% coronary artery stenosis.

Conclusion --- Determination of the number of abnormal myocardial segments by strain and strain rate analysis of areas supplied by a particular coronary artery had high sensitivity and specificity and good positive and negative predictive value in predicting significant coronary artery stenosis. ***Phil Heart Center J 2014;18(1):8-19.***

Key Words: Strain ■ Strain Rate ■ Coronary Artery Disease

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in the world. Thus, the approach is towards prevention of the development of CAD and any cardiovascular events that may arise from it. The presence of CAD can be elicited through history and physical examinations. Several diagnostic procedures have also been of great help in the diagnosis of CAD. The gold standard used for its diagnosis is coronary angiography. The severity of the coronary artery stenosis should be established as well as the anatomy of the coronaries and the lesions before any intervention is planned.

The American College of Cardiology/ American Heart Association published guidelines for coronary angiography.[1] Like any other procedure, coronary angiography has complications. Aside from the complications, the cost of the procedure should also be considered before requesting for coronary angiography. There are occasions where the use of coronary angiography cannot be questioned like in ST segment elevation myocardial infarction (STEMI). Current guidelines mandate immediate reperfusion of totally occluded arteries either through thrombolysis or percutaneous intervention. In non-ST segment elevation myocardial infarction (NSTEMI), however, the culprit vessel is usually patent hence the strategy is aggressive anti-thrombotic therapy with intervention reserved for high-risk patients. However, the larger subset of CAD patients belongs

2nd Place, Oral Presentation 20th PHC Annual Research Paper Competition held on February 23, 2012_at Philippine Heart Center, *Correspondence to* ***Dr. Ana Beatriz Medrano,*** Department of Adult Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication** ISSN 0018-9034

to those who have chronic stable angina and those who have silent ischemia. The appropriateness of coronary angiography among these patients should be established first though non-invasive diagnostic tests aside from the history and physical examination.

One of the most helpful diagnostic modality in establishing the presence of CAD is through echocardiography. Myocardial perfusion at rest begins to diminish with coronary artery diameter stenosis ≥70%. Myocardial reserve is usually exhausted when the percent diameter stenosis reaches 90%. However, despite significant coronary artery stenosis, patients can still exhibit normal resting wall motion and ejection fractions on 2D-echocardiographic study. A possible explanation is visual analysis of wall motion is often subjective and prone to variability.[2] Quantitative techniques using tissue doppler velocities and derived values including strain and strain rate offer increased sensitivity and reproducibility in detecting wall motion abnormalities secondary to ischemia.[2]

Echocardiography has been used as one of the first-line diagnostic modalities in assessing cardiovascular diseases due to its low cost, absence of radiation, fast results and availability. It is also regarded as "one-stop-shop" because within minutes and in one study, it can already evaluate right and left ventricular function and structure, valvular problems, pericardial abnormalities, aortic diseases and other structural problems. One primary use of echocardiography is in the assessment of patients with coronary artery disease (CAD). CAD is usually diagnosed by regional wall motion abnormality.

The severity of coronary artery stenosis can be detected through echocardiography. More than 50% coronary artery stenosis can be detected by stress echocardiography with 80% to 90% sensitivity.[3] When compared with nuclear perfusion imaging, it's sensitivity was slightly lower but specificity was slightly higher.[4] Another technique used to diagnose CAD is contrast echocardiography. In a study that compared contrast echocardiography and dobutamine stress echocardiography, contrast echocardiography was more sensitive and accurate in predicting more that 75% coronary artery stenosis than dobutamine stress echocardiography.[5]

There are newer echocardiographic modalities that determine wall motion and deformity of the left ventricle by using doppler or speckle tracking. This offers a quantitative tool providing a more objective assessment of traditional wall motion. These new modalities measures regional myocardial strain and strain rate. Strain and strain rate are highly sensitive to regional ischemia as shown in a study of Voight, et al. In this study, nuclear perfusion imaging was compared with strain and showed that strain imaging is able to detect stress induced ischemia. This is especially helpful in cases where visual interpretation is inconclusive.[2]

Detection of ischemia may be aided by detecting stress-induced reduction and delay in systolic regional deformation. Very typical of ischemia is a shift in the maximum deformation in the late systole even after aortic valve closure, called the post-systolic deformation or thickening. This is caused by the retardation of systolic deformation.[6]

Strain and strain rate are new techniques in echocardiography using two-dimensional techniques or doppler which measures the time course of tissue deformation. Every time the ventricle contracts, there is longitudinal and circumferential muscle shortening. This is called negative strain. Also, during contraction, there is thickening and lengthening in the radial direction, this is called positive strain. These are basic descriptors of the function and nature of cardiac tissue. Since this is new, its analysis include technical complexities and poses great challenges to the echocardiographers.[7]

Strain rate can be correlated with rate of change in pressure (dp/dt). Rate of change in pressure is a parameter used to reflect contractility, while ejection fraction is correlated with strain.[8] Thus, like in ejection fraction, when preload is increased, the strain will increase at all levels of wall stress. Whereas, when afterload is increased, there is a reduction in stain. Strain rate, on the other hand, is less related to preload and afterload. A left ventricular (LV) cavity size that is normal or close to the normal range has

limited impact on strain. Even if this is the case, small ventricles have an increased in radial strain and a decrease in longitudinal strain.

Detection of stress-induced reduction and delay in systolic regional deformation may help in the detection of inducible ischemia. Shift in the maximum of deformation to late systole or even after aortic valve closure called post-systolic deformation or thickening can be attributed to the retardation of systolic deformation. This is typical of ischemia but is not specific.[9,10] In acute myocardial infarction, the extent of tissue necrosis is inversely related to the amount of residual deformation or strain. In a study by Vartdal et al, he found out that within 2 hours after acute ST segment elevation myocardial infarction, longitudinal strain correlated inversely and well with infarct size measured using late enhancement magnetic resonance imaging (MRI) nine months later.[10]

In line with CAD, determination of strain is not just important in the diagnosis it is also important in determination of the contractile reserve of dysfunctional and viable myocardium. This will indicate a possible benefit of revascularization as well as detection of remaining inducible ischemia. Thus, it guides the clinician in the management and decision making.[9] Clinicians use stress echocardiography and nuclear perfusion methods to know these. A more objective way than the traditional methods are through determination of residual strain, particularly radial strain.[11] The amount of residual strain will predict the likelihood of recovery. Another parameter of likelihood of recovery is an increase in strain rate under low-dose dobutamine.[12]

Strain has a role in demonstrating acute myocardial infarction, both subendocardial and transmural infarctions. Normally, the systolic strain is characterized by shortening. In transmural infarctions, strain is characterized by systolic lengthening and post-systolic shortening. Subendocardial contraction is represented by longitudinal deformation and midmyocardial and subepicardial contraction is represented by circumferential deformation. Longitudinal contraction is more sensitive to subendocardial necrosis and ischemia than circumferential contraction.[13, 14]

A study by Chan et al, aimed to differentiate the transmural and subendocardial extent of myocardial infarction with the use of two-dimensional strain rate imaging to assess short and long axes myocardial function. In this study, the echocardiographic strain was compared with contrast-enhanced MRI. The results showed that there was a lower circumferential strain in transmural infarction than subendocardial infarcts and normal myocardium. There were similar radial strain and strain rate in transmural and subendocardial infarcts. There was significant reduction in longitudinal strain in subendocardial infarcts compared with normal myocardium.[13,14]

There are two methods for measurement of strain: strain by doppler and by speckle tracking. Sjoli et al, determined the diagnostic capability and reproducibility of the two among patients with acute myocardial infarction. Results showed that circumferential strain was better in separating transmural from subendocardial necrosis than longitudinal strain in the acute phase of patients with STEMI. Overall, the results showed that the two methods have good and excellent reproducibility.[15] In the same study, the authors found out that viable and necrotic myocardium in acute and chronic myocardial infarctions were not detected by post-systolic shortening, contrary to the report of Skultad.[6] Also, the authors of the study were able to determine that peak negative segmental longitudinal strain, peak systolic and end systolic were able to differentiate normal from infarcted myocardium. They were also able to differentiate subendocardial from transmural infarction on a group level, regardless, whether doppler or speckle strain imaging was used.[15]

Strain echocardiography has already been validated as a prognostic indicator.[6,15] It can accurately measure regional left ventricular regional systolic function [16,17] and it can demonstrate different levels of infarct sizes.[18] In STEMI patients, infarct sizes of both acute and chronic phases correlate well with left ventricular systolic function.[6,18] This is important because infarct size is a strong predictor of major adverse cardiovascular events and mortality.[19] Electrocardiogram is only modestly correlated with infarct size.[20] There are also a number

of patients with NSTEMI that have substantial infarction. However, most of these patients do not have the criteria for immediate reperfusion.[21,22] There is a study by Eek et al, which used strain echocardiography and wall motion score index to predict final infarct size in patients with NSTEMI. In this study, ejection fraction, wall motion score index and circumferential, longitudinal and radial strain using a 16-segment left ventricular model were used to assess left ventricular function. Patients underwent late enhancement MRI after 6 to 12 months. After comparing the results, the authors found good correlation with LV function parameters and infarct size. Global longitudinal strain and wall motion index were found out to be excellent modalities to identify patients with NSTEMI who have substantial myocardial infarction. These can guide the clinician in identifying patients who will benefit from urgent reperfusion therapy.[21]

Another study by Grenne et al, showed that strain can identify acute coronary occlusions in patients with NSTEMI. In this study, the infarct size and left ventricular ejection fraction of patients with NSTEMI with and without acute coronary occlusion were compared. Patients presenting with NSTEMI underwent strain echocardiography, using territorial and circumferential strain, within 1 hour of symptom onset and underwent coronary angiography within 15 to 57 hours. The authors found out that territorial circumferential strain was the best parameter to predict acute coronary occlusion. A value of 10% had a sensitivity of 90% and specificity of 88% and an area under the curve of 0.93 for determining acute occlusion. This study also showed that territorial circumferential strain is capable of very early identification of acute coronary occlusion in patents presenting with NSTEMI. This can be used in identification of patients who needs urgent revascularization.[22]

There is another study by Eek et al[23, 24] that demonstrated the ability of strain echocardiography in predicting acute occlusion. Patients who presented with NSTEMI for the first time underwent longitudinal strain echocardiography and wall motion scoring by visual assessment prior to coronary angiography. These were assessed by using the 16-segment model. The results showed that an area of more than or equal to 4 adjacent dysfunctional segments, that is strain greater than or equal to -14%, has an 85% sensitivity and 70% specificity in identifying patient with acute coronary occlusion. In this study also, strain was more accurate than wall motion score.

Echocardiographic strain and strain rate served several other purposes aside from diagnosing and assessing patients with CAD. Some of these are in the assessment of myocardial viability with the use of low-dose dobutamine infusion, assessment of resting ventricular function and stress testing for ischemia.[25] These were also used for the assessment of right and left ventricular resting functions, identification of myocardial diseases and assessment of treatment response.[26]

The aim of this study therefore is to determine the accuracy of tissue doppler strain in predicting significant coronary artery stenosis among patients suspected with coronary artery disease undergoing coronary angiography.

METHODOLOGY

This is a cross-sectional, analytical study done at the Philippine Heart Center involving adult subjects suspected with coronary artery disease undergoing coronary angiography. Excluded were those patients with poor image quality on baseline echocardiogram; those with left and right bundle branch block; those with moderate to severe valvular heart disease; those with congenital heart disease; those with atrial fibrillation; those with pacemaker; and those previously diagnosed with cardiomyopathy. The informed consent and the written research protocol were reviewed and approved by the Technical Review Board and the Institutional Ethics Review Board of the Philippine Heart Center (PHC).

Patients who were about to undergo coronary angiography were screened for possible inclusion in the study. Objectives and methodology of this research were explained and permission of the attending doctors were obtained to all those who fulfilled the eligibility criteria. The patients were asked to fill up

and sign a written informed consent. A patient database was filled-up primarily by the historian. Pertinent personal, medical and social histories as well as present medications, laboratory and ancillary examinations of the patients were included in the database.

Tissue doppler strain and strain rate determination were performed for all 16 segments of the left ventricle. The results of strain and strain rate were compared to the normal values adjusted for age and sex of the patients. This was done by one technician who is well-trained in tissue doppler strain and strain rate imaging.

The coronary angiogram was evaluated by a physician blinded to the result of the tissue doppler strain of the patient. The following information were recorded: percent diameter coronary stenosis, presence of totally occluded coronary artery disease, the coronary artery involved, the segment in each coronary artery involved (proximal or mid) and presence of collaterals. The coronary lesion was graded as severe if it measured ≥70% diameter stenosis in relation to the reference segment for the left anterior descending, left circumflex, and right coronary arteries. For left main stenosis, percent diameter stenosis of ≥50% was graded as severe.

Echocardiographic procedure: Conventional transthoracic echocardiogram and longitudinal two-dimensional strain and strain rate measurements were performed using a cardiac ultrasound scanner and a 2.5 MHz transducer (Philips IE-33). Patients included were evaluated in the left lateral decubitus position by one observer trained in strain and strain rate analysis.

An image with a good tissue doppler that contained at least two completed beat cycles and three R waves were used for the analysis. The walls of the image to be accessed were centered on the screen. A high frame rate was used in obtaining the image. Patients were also asked to suspend breathing while the image is being acquired. The image loop was trimmed down by removing excess frames.

The left ventricular four-chamber, three-chamber and two-chamber views were utilized to obtain longitudinal two-dimensional study images. Using the four-chamber view, the posterior interventricular septum and the lateral wall were divided into basal, middle and apical segments. Six segments of the left ventricle were analyzed using the four-chamber view. Using the three-chamber view, the posterior wall and anterior interventricular septum were divided into basal and middle segments. Four segments were analyzed using the three-chamber view. Using the two-chamber view, the inferior and anterior walls were divided into basal, middle and apex segments. Six segments were analyzed using the two-chamber view. A total of 16 left ventricular segments were analyzed for calculation of longitudinal peak systolic strain and peak systolic strain rates. All measurements were obtained by one experienced investigator who is unaware of the patient characteristics. Measurements were calculated at least two times and the average of two measurements were determined. Segments with insufficient image quality were excluded from the analysis.

Cineloop formats were recorded on the hard disk of the echocardiography machine for off-line analysis.

Statistical analysis: Quantitative data were presented as mean standard deviation and qualitative variables in frequency and patient distribution. Qualitative data were analyzed by t-test statistic. To determine the rate of significant coronary artery stenosis among patients who underwent coronary angiography, frequency was taken. To determine the number of abnormal segments by tissue doppler strain and strain rate predictive of severe coronary stenosis, sensitivity, specificity, positive predictive value and negative predictive value were computed and ROC analysis was performed.

Sample size: The computed minimum sample size is 57. The sample size was based on an estimated 82% prevalence of significant coronary artery stenosis among patients who underwent coronary angiography with a relative error of 20% and confidence level of 95.[27]

RESULTS

There were a total of 79 patients enrolled in this study. Among the 79 patients, 66 (83.5%) had significant coronary artery stenosis defined as 70% or more stenosis while 13 (16.5%) patients had less than 70% coronary artery stenosis. Among those who had significant CAD, 28 (43%) had three-vessel involve ment, 18 (27%) with two-vessel involvement and 20 (30%) had one-vessel disease. The mean age of patients with significant CAD was 59±10 years old while those with insignificant CAD were 50±11 years old. The mean left ventricular ejection fraction of patients with significant CAD was 59±15% while those with insignificant CAD were 71±4%. Only the mean ejection fraction was statistically significant (p-value = 0.013.)

Majority of patients for both groups were less than 65 years of age comprising 51 (77%) patients for those with significant CAD and 13 (100%) patients for those with insignificant CAD. Majority of patients for both groups were male comprising 45 patients (68%) for those who had significant CAD and 8 patients (62%) for those with insignificant CAD. In both groups, majority were overweight with a body surface area (BMI) of 25-29. In terms of cardiac history, among patients with significant CAD, 3 (5%) had unstable angina, 14 (21%) had NSTEMI and 9 (14%) had STEMI. None among the patients with insignificant CAD had an acute coronary syndrome. For both groups, majority belonged to NYHA Class 2. There were 35 patients (53%) for those with significant CAD and 9 patients (70%) for those with insignificant CAD. In terms of medical history, hypertension, diabetes and dyslipidemia were present in 49 (74%), 27 (41%) and 13 (20%) patients respectively; while among those with insignificant CAD, hypertension and diabetes comprised 5 (38%) and 2 (15%) patients respectively. Hypothyroidism, dyslipidemia, COPD and stroke had equal occurrence (8%). Majority of the patients in both groups were smoker comprising 34 (52%) and 2 (15%) for those with significant and insignificant CAD, respectively. In terms of medications, statins (47%), clopidogrel (45%), beta-blocker (44%), aspirin (42%) and nitrates (41%) were the most commonly used medications among patients with significant CAD while aspirin (100%), calcium channel blocker (92%), statins (92%), nitrates (85%) and trimetazidine (85%) were the most commonly used medications among patients with insignificant CAD. Chest pain was the most common symptom the patients experienced for both groups comprising of 59 (89%) and 9 (70%) for those with significant and insignificant CAD respectively. Majority of patientsfor both groups had good systolic function with an ejection fraction of more than 55%.

There was no significant difference between the groups in terms of age, gender, cardiac history, symptoms and ejection fraction. There was also no significant difference between the two groups in terms of diabetes, hypothyroidism, dyslipidemia, COPD, stroke, history of alcohol intake and drug abuse. However, there were more hypertensive patients and more smokers among patients with significant CAD with p-value of 0.039 and 0.020, respectively. In terms of medications, more patients with significant CAD were on clopidogrel compared with patients with insignificant CAD (p-value of 0.001.)

Table 2 shows that four or more abnormal segments by strain out of nine segments supplied by the left anterior descending coronary artery was predictive of >70% coronary artery stenosis. It had a sensitivity of 100%, specificity of 91.7%, positive predictive value of 93.5%, negative predictive value of 100% with a kappa of 0.923±0.112 and p-value of 0.000.

Figure 1 is the receiver operator curve of strain in predicting significant coronary artery stenosis based on the number of abnormal segments for left anterior descending coronary artery. It shows a high sensitivity (100%) and specificity (91.7%).

Table 1. Clinical Profile of Patients who Underwent Coronary Angiography at the Philippine Heart Center (PHC, 2012)

Characteristics	≥ 70% Coronary Artery Stenosis		≤ 70% Coronary Artery Stenosis		p value
	No. (n=66)	%	No. (n=13)	%	
Age, mean ± SD	59 ± 10	-	50 ± 11	-	0.11
≥65	15	23	0	0	
≤65	51	77	13	100	0.064
Gender, Male	45	68	8	62	0.749
BMI					
18-22.9	8	12	3	23	
23-24.9	16	24	1	8	
25-29	29	44	4	31	0.505
30-34	12	18	5	38	
>34	1	2	0	0	
Cardiac history					
UA	3	5	0	0	1.00
NSTEMI	14	21	0	0	0.180
STEMI	9	14	0	0	0.110
NYHA					
Class I	3	4	2	15	
Class II	35	53	9	70	**0.039**
Class III	27	41	2	15	
Class IV	1	2	0	0	
Medical history §					
Hypertension	49	74	5	38	**0.020**
Diabetes	27	41	2	15	0.117
Hyperthyroidism	3	4	1	8	0.520
Dyslipidemia	13	20	1	8	0.444
COPD	1	2	1	8	0.304
Stroke	1	2	1	8	0.304
Personal history §					
Alcoholic	19	29	1	8	0.166
Smoker	34	52	2	15	**0.030**
Drug Abuse	1	2	0	0	1.00
Medications §					
Aspirin	28	42	13	100	0.266
Clopidogrel	30	45	10	77	**0.001**
ACE Inhibitor	7	11	6	46	1.00
ARB	17	26	7	54	1.00
Beta-blocker	29	44	10	77	0.182
CCB	10	15	12	92	0.316
Statins	31	47	12	92	0.359
Nitrates	27	41	11	85	0.119
Digoxin	3	5	1	8	1.00
Trimetazidine	10	15	11	85	0.447
Fish oils	3	5	0	0	0.252
Nicorandil	1	2	0	0	1.00
Spirinolactone	3	5	1	8	0.627
Furosemide	1	2	1	8	1.00
Metformin	14	21	5	38	0.114
Gliclazide	5	8	4	31	1.00
Glimeperide	3	5	0	0	0.252
Insulin	2	3	1	8	1.00
Symptoms §					
Chest pain	59	89	9	70	0.076
Dyspnea	17	26	4	31	0.737
Asymptomatic	4	6	1	8	1.00
EF					
Mean	59 ± 15	-	71 ± 4	-	0.013
>55	43	65	9	70	
40-55	25	38	0	0	
30-40	1	2	0	0	0.309
<30	1	2	0	0	

BMI-body mass index; BSA-body surface area; EF-ejection fraction; ACS-Acute Coronary Syndrome; UA-Unstable Angina; NSTEMI-Non-ST segment elevation myocardial infarction; STEMI-ST segment myocardial infarction; NYHA-New York Heart Association; COPD-Chronic Obstructive Pulmonary Disease; ACE-angiotensin converting enzyme;ARB-angiotension receptor blocker; CCB-calcium channel blocker

p-value <0.05 considered to be significant
§ occur in multiples

Table 2. Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value of Doppler Tissue Longitudinal Strain in Predicting Significant Coronary Artery Stenosis Based on Number of Abnormal Segments for Left Circumflex (LCX) Coronary Artery (PHC, 2012)

No. of Abnormal Segments by Strain Rate	No. of patients		Sn	Sp	PPV	NPV	Kappa	P-value*
	≥ 70% LAD Stenosis	≤70% LAD Stenosis						
9	4	2						
<9	39	34	9.3	99.4	66.7	46.6	0.035 ± 0.055	0.266
TOTAL	43	36						
≥8	6	2						
<8	37	34	14.0	94.4	75	47.9	0.078 ± 0.063	0.109
TOTAL	43	36						
≥7	11	3						
<7	32	33	25.6	91.7	78.6	50.8	0.162 ± 0.081	0.023
TOTAL	43	36						
≥6	19	3						
<	24	33	44.2	91.7	86.4	57.9	0.342 ± 0.010	0.000
TOTAL	43	36						
≥5	37	3						
<5	6	33	86	91.7	92.5	84.6	0.772 ± 0.112	0.000
TOTAL	43	36						
≥4	**43**	**3**						
<4	**0**	**33**	**100**	**91.7**	**93.5**	**100**	**0.923 ± 0.112**	**0.000**
TOTAL	**43**	**36**						
≥2	43	10						
<2	.	26	100	72.2	81.1	100	0.789 ± 0.109	0.000
TOTAL	43	36						
≥1	43	15						
1	0	21	100	58.3	74.1	100	0.604 ± 0.103	0.000
TOTAL	43	36						

LAD-left anterior descending; Sn- Sensitivity; Sp- Specificity; NPV-negative predictive value; PPV-positive predictive value
p-value <0.05 considered to be significant

Table 3. Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value of Doppler Tissue Longitudinal Strain in Predicting Significant Coronary Artery Stenosis Based on Number of Abnormal Segments for Left Circumflex (LCX) Coronary Artery (PHC, 2012)

No. of Abnormal Segments by Strain Rate	No. of Patients		Sn	Sp	PPV	NPV	Kappa	P-value*
	≥ 70% LCx Stenosis	≤70% LCx Stenosis						
4	21	0						
<4	16	42	56.8	100	100	72.4	0.583 ± 0.102	0.050
TOTAL	37	42						
≥2	**37**	**3**						
<2	**0**	**39**	**100**	**92.9**	**92.5**	**100**	**0.924 ± 0.112**	**0.000**
TOTAL	**37**	**42**						

LCX-left circumflex; Sn- Sensitivity; Sp- Specificity; NPV-negative predictive value; PPV-positive predictive value
p-value <0.05 considered to be significant

Table 4. Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value of Doppler Tissue Longitudinal Strain in Predicting Significant Coronary Artery Stenosis Based on Number of Abnormal Segments for Right Coronary Artery (RCA) (PHC, 2012)

No. of Abnormal Segments by Strain Rate	No. of Patients		Sn	Sp	PPV	NPV	Kappa	P-value*
	≥ 70% RCA Stenosis	≤70% RCA Stenosis						
3	16	1						
<3	16	46	50.0	97.9	94.1	72.4	0.517 ± 0.102	0.000
TOTAL	32	47						
≥2	**31**	**1**						
<2	**1**	**46**	**96.9**	**97.9**	**96.9**	**97.9**	**0.947 ± 0.113**	**0.000**
TOTAL	**32**	**47**						
≥1	32	11						
1	0	36	100	76.6	74.4	100	0.726 ± 0.108	0.000
TOTAL	32	47						

RCA-right coronary artery; Sn- Sensitivity; Sp- Specificity; NPV-negative predictive value; PPV-positive predictive value
p-value <0.05 considered to be significant

Table 5. Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value of Doppler Tissue Longitudinal Strain Rate in Predicting Significant Coronary Artery Stenosis Based on Number of Abnormal Segments for Left Anterior Descending (LAD) Coronary Artery (PHC, 2012)

No. of Abnormal Segments by Strain Rate	No. of patients		Sn	Sp	PPV	NPV	Kappa	P-value*
	≥ 70% LAD Stenosis	≤70% LAD Stenosis						
9	12	0						
<9	31	36	27.9	100	100	53.7	0.261 ± 0.076	0.002
TOTAL	43	36						
≥8	15	0						
<8	28	36	34.9	100	100	56.3	0.378 ± 0.083	0.109
TOTAL	43	36						
≥7	16	3						
<7	27	33	37.2	100	100	57.1	0.351 ± 0.086	0.000
TOTAL	43	36						
≥6	27	0						
<	16	33	62.8	100	100	69.2	0.606 ± 0.103	0.000
TOTAL	43	36						
≥5	37	1						
<5	6	35	86	97.2	97.4	85.4	0.823 ± 0.112	0.000
TOTAL	43	36						
≥4	**43**	**1**						
<4	**0**	**35**	**100**	**97.2**	**97.7**	**100**	**0.974 ± 0.112**	**0.000**
TOTAL	**43**	**36**						
≥2	43	3						
<2	0	33	100	91.7	93.5	100	0.923 ± 0.112	0.000
TOTAL	43	36						
≥1	43	5						
1	0	31	100	86.1	89.6	100	0.871 ± 0.112	0.000
TOTAL	43	36						

LAD-left anterior descending; Sn- Sensitivity; Sp- Specificity; NPV-negative predictive value; PPV-positive predictive value
p-value <0.05 considered to be significant

Table 6. Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value of Doppler Tissue Longitudinal Strain Rate in Predicting Significant Coronary Artery Stenosis Based on Number of Abnormal Segments for Left Circumflex (LCX) Coronary Artery (PHC, 2012)

No. of Abnormal Segments by Strain Rate	No. of Patients		Sn	Sp	PPV	NPV	Kappa	P-value*
	≥ 70% LCx Stenosis	≤70% LCx Stenosis						
4	20	1						
<4	17	41	54.1	97.6	95.2	70.7	0.530 ± 0.102	0.050
TOTAL	37	42						
≥2	**37**	**7**						
<2	**0**	**35**	**100**	**83.3**	**84.1**	**100**	**0.824 ± 0.112**	**0.000**
TOTAL	**37**	**42**						

LCX-left circumflex; Sn- Sensitivity; Sp- Specificity; NPV-negative predictive value; PPV-positive predictive value
p-value <0.05 considered to be significant

In the left circumflex artery territory (*Table 3*), two or more abnormal segments by strain out of four segments was predictive of ≥70% coronary artery stenosis with a sensitivity of 100%, specificity of 92.9%, positive predictive value of 92.5%, negative predictive value of 100%, kappa of 0.924 ± 0.112 and p-value of 0.000.

In the right coronary artery territory (*Table 4*), two or more abnormal segments by strain out of three segments was predictive of ≥70% coronary artery stenosis with a sensitivity of 96.9%, specificity of 97.9%, positive predictive value of 96.9%, negative predictive value of 97.9% with a kappa of 0.947 ± 0.113 and p-value of 0.000.

Table 5 shows that ≥4 abnormal segments by strain rate out of nine segments supplied by the left descending coronary artery was predictive of ≥70% coronary artery stenosis. It had a sensitivity of 100%, specificity of 97.2%, positive predictive value of 97.7%,

negative predictive value of 100% with a kappa of 0.974 ± 0.112 and p-value of 0.000.

Table 6 shows that ≥2 abnormal segments by strain rate out of four segments supplied by the eft circumflex coronary artery was predictive of ≥70% coronary artery stenosis with a sensitivity of 100%, specificity of 83.3%, positive predictive value of 84.1%, negative predictive value of 100% with a kappa of 0.824 ± 0.111 and p-value of 0.000.

Table 7 shows that ≥2 abnormal segments by strain rate out of three segments supplied by the right coronary artery was predictive of ≥70% coronary artery stenosis with a sensitivity of 100%, specificity of 93.6%, positive predictive value of 91.4%, negative predictive value of 100% with a kappa of 0.922 ± 0.112 and p-value of 0.000.

DISCUSSION

Coronary artery stenosis causes impairment and reduction myocardial blood flow resulting in ischemia and hypocontractility.[8] However, despite significant coronary artery stenosis patients can still have normal resting qualitative wall motion and ejection fractions on 2D-echocardiographic study. In our study, ejection fraction was unable to identify patients with significant coronary artery stenosis. In the group with severe coronary stenosis, 65% of patients had normal ejection fractions. In these patients, exercise and dobutamine stress can be used to illicit ischemia and induce hypokinesia.[6] The subjective measurement of wall motion is the major limitation in evaluating contractility. Recent developments in measuring regional wall motion using the doppler method provide a quantitative tool to evaluate contractility more precisely.

Table 7. Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value of Doppler Tissue Longitudinal Strain Rate in Predicting Significant Coronary Artery Stenosis Based on Number of Abnormal Segments for Right Coronary Artery (RCA) (PHC, 2012)

No. of Abnormal Segments by Strain Rate	No. of Patients		Sn	Sp	PPV	NPV	Kappa	P-value*
	≥ 70% RCA Stenosis	≤70% RCA Stenosis						
3	24	0						
<3	8	47	75	100	94.1	85.5	0.781 ± 0.110	0.000
TOTAL	32	47						
≥2	**32**	**3**						
<2	**0**	**44**	**100**	**93.6**	**94.1**	**100**	**0.922 ± 0.112**	**0.000**
TOTAL	**32**	**47**						
≥1	32	27						
1	0	20	100	42.6	54.2	100	0.375 ± 0.088	0.000
TOTAL	32	47						

RCA-right coronary artery; Sn- Sensitivity; Sp- Specificity; NPV-negative predictive value; PPV-positive predictive value
p-value <0.05 considered to be significant

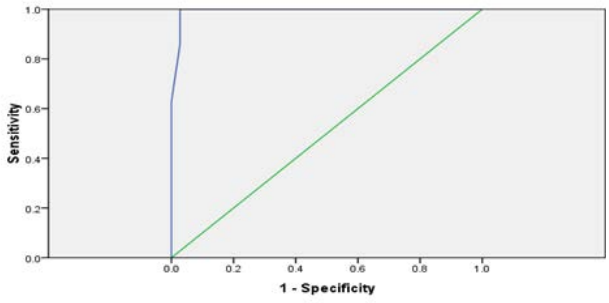


Figure -1. Receiver Operator Curve of Strain in Predicting Significant Coronary Artery Stenosis Based on Number of Abnormal Segments for Left Anterior Descending (LAD) Coronary Artery (PHC, 2012)

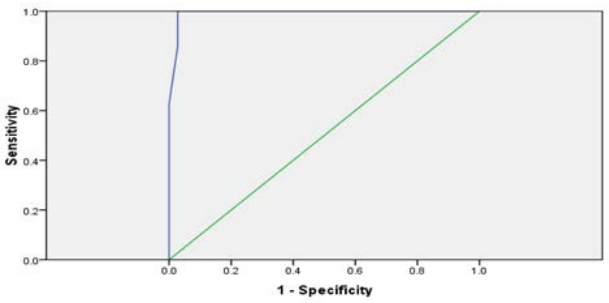


Figure -2. Receiver Operator Curve of Strain Rate in Predicting Significant Coronary Artery Stenosis Based on Number of Abnormal Segments for Left Anterior Descending (LAD) Coronary Artery (PHC, 2012)

Strain and strain rate analysis quantifies the elongation and the shortening of the myocardium during contraction. The more negative the value, the better is myocardial shortening and elongation. Strain and strain rate analysis is therefore a more precise and reproducible measure of wall motion abnormalities.

The ability to predict significant coronary stenosis based on resting doppler strain and strain rate has significant clinical utility because it can stratify patients at high risk for ischemic events.[21] Furthermore, not all patients can undergo exercise or pharmacologic stress testing. In these patients the results of our study show that the use of doppler strain and strain rate has significant accuracy to predict significant coronary artery stenosis. In the emergency room, doppler strain and strain rate analysis can identify patients with coronary artery disease who present with chest pain with normal wall motion on echocardiogram.

In our study, the presence of ≥4 abnormal segments served by the LAD territory using strain and strain rate analysis predicted the presence of ≥70% coronary artery stenosis with a positive predictive value of 93.5%. In smaller vascular territories like the left circumflex and right coronary artery territory, ≥2 abnormal segments on strain and strain rate analysis gave the best trade off between sensitivity and specificity.

This study is the first local published report on the use of doppler strain and strain rate in identifying patients with stable coronary artery disease and severe coronary artery disease. Most of the available literature has used doppler strain and strain rate in identifying patients with inducible ischemia during stress/pharmacologic testing or in identifying patients with NSTEMI with occluded culprit coronary arteries.[8,22-23] This study shows that the presence of ischemia produces quantitative changes measured by doppler strain/strain rate analysis even at rest.

Since this study used tissue doppler imaging, only the longitudinal strain was taken. The radial and circumferential strains, as well as the global systolic function, were not part of this study. The authors of this study recommend a prospective validation study to determine the utility of the wall motion score by strain and strain rate in predicting severe coronary artery stenosis.

The same study can also be done by using speckle strain and strain rate analysis from the longitudinal strain and strain rate. This includes radial and circumferential strain. The global systolic strain can also be determined and analyzed.

REFERENCES

1. Scanlon PJ, Faxon DP, Audet AM, Carabello B, Dehmer GJ, Eagle KA et al. Recommendations: A Report of the American College of Cardiology/ American ACC/AHA Guidelines for Coronary Angiography: Executive Summary and Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography) Developed in collaboration with the Society for Cardiac Angiography and Interventions. Circulation 1999; 99; 2345-2357.2.
2. Voigt JU, Exner B, Schmiedehausen K, Huchzermeyer C, Reulbach U, Nixdorff U., et al. Strain rate imaging during dobutamine stress echocardiography provides objective evidence of inducible ischemia. Circulation 2003; 107: 2120-2126.
3. Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D et al. European Association of Echocardiography. Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur J Echocardiogr 2008; 9: 415-437.
4. Geleijnse ML, Elhendy A, van Domburg RT, Cornel JH, Rambaldi R, Salustri A et al. Cardiac imaging for risk stratification with dobutamine-atropine stress testing in patients with chest pain, echocardiography, perfusion scintigraphy, or both? Circulation 1997; 96: 137-147.
5. Elhendy A, O'Leary EL, Xie F, McGrain AC, Anderson JR, Porter TR. Comparative accuracy of real-time myocardial contrast perfusion imaging and wall motion analysis during dobutamine stress echocardiography for the diagnosis of coronary artery disease. J Am Coll Cardiol. 2004 Dec 7;44(11):2185-91.
6. Skulstad H, Edvardsen T, Urheim S, Rabben SI, Stugaard M, et al. Postsystolic shortening in ischemic myocardium: active contraction or passive recoil? Circulation. 2002 Aug 6;106(6):718-24.
7. Kowalski M, Kukulski T, Jamal F, D'hooge J, Weidemann F, Rademakers F. et al. Can natural strain and strain rate quantify regional myocardial deformation? A study in healthy subjects. Ultrasound Med Biol. 2001 Aug;27(8):1087-97.

8. Weidemann F, Jamal F, Sutherland GR, Claus P, Kowalski M, Hatle L, et al. Myocardial function defined by strain rate and strain during alterations in inotropic states and heart rate. Am J Physiol Heart Circ Physiol. 2002 Aug;283(2):H792-9.
9. Flachskampf FA, Daniel WG. Cardiac imaging in the patient with chest pain: echocardiography. Heart. 2010 Jul;96(13):1063-72.
10. Vartdal T, Brunvand H, Pettersen E, Smith HJ, Lyseggen E, Helle-Valle T, et al. Early prediction of infarct size by strain doppler echocardiography after coronary reperfusion. J Am Coll Cardiol. 2007 Apr 24;49(16):1715-21.
11. Becker M, Lenzen A, Ocklenburg C, Stempel K, Kühl H, Neizel M, et al. Myocardial deformation imaging based on ultrasonic pixel tracking to identify reversible myocardial dysfunction. J Am Coll Cardiol. 2008 Apr 15;51(15):1473-81.
12. Hanekom L, Jenkins C, Jeffries L, Case C, Mundy J, Hawley C, et al. Incremental value of strain rate analysis as an adjunct to wall-motion scoring for assessment of myocardial viability by dobutamine echocardiography: a follow-up study after revascularization. Circulation. 2005 Dec 20;112(25):3892-900.
13. Chan J, Hanekom L, Wong C, Leano R, Cho GY, Marwick TH. Differentiation of subendocardial and transmural infarction using two-dimensional strain rate imaging to assess short-axis and long-axis myocardial function. J Am Coll Cardiol. 2006 Nov 21;48(10):2026-33.
14. Brunvand H, Rynning SE, Hexeberg E, Westby J, Grong K. Non-uniform recovery of segment shortening during reperfusion following regional myocardial ischaemia despite uniform recovery of ATP. Cardiovasc Res. 1995 Jul;30(1):138-46.
15. Sjøli B, Ørn S, Grenne B, Ihlen H, Edvardsen T, Brunvand H. Diagnostic capability and reproducibility of strain by Doppler and by speckle tracking in patients with acute myocardial infarction. JACC Cardiovasc Imaging. 2009 Jan;2(1):24-33.
16. Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, Lyseggen E, et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol. 2006 Feb 21;47(4):789-93.
17. Urheim S, Edvardsen T, Torp H, Angelsen B, Smiseth OA. Myocardial strain by doppler echocardiography. Validation of a new method to quantify regional myocardial function. Circulation. 2000 Sep 5;102(10):1158-64.
18. Gjesdal O, Helle-Valle T, Hopp E, Lunde K, Vartdal T, Aakhus S, et al. Noninvasive separation of large, medium, and small myocardial infarcts in survivors of reperfused ST-elevation myocardial infarction: a comprehensive tissue doppler and speckle-tracking echocardiography study. Circ Cardiovasc Imaging. 2008 Nov;1(3):189-96.
19. Burns RJ, Gibbons RJ, Yi Q, Roberts RS, Miller TD, Schaer GL, et al. The relationships of left ventricular ejection fraction, end-systolic volume index and infarct size to six-month mortality after hospital discharge following myocardial infarction treated by thrombolysis. J Am Coll Cardiol. 2002 Jan 2;39(1):30-6.
20. Stanton T, Leano R, Marwick TH. Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. Circ Cardiovasc Imaging. 2009 Sep;2(5):356-64.
21. Kontos MC, Kurdziel KA, Ornato JP, Schmidt KL, Jesse RL, Tatum JL. A nonischemic electrocardiogram does not always predict a small myocardial infarction: results with acute myocardial perfusion imaging. Am Heart J. 2001 Mar;141(3):360-6.
22. Martin TN, Groenning BA, Murray HM, Steedman T, Foster JE, Elliot AT, et al. ST-segment deviation analysis of the admission 12-lead electrocardiogram as an aid to early diagnosis of acute myocardial infarction with a cardiac magnetic resonance imaging gold standard. J Am Coll Cardiol. 2007 Sep 11;50(11):1021-8.
23. Eek C, Grenne B, Brunvand H, Aakhus S, Endresen K, Hol PK, et al. Strain echocardiography and wall motion score index predicts final infarct size in patients with non-ST-segment-elevation myocardial infarction. Circ Cardiovasc Imaging. 2010 Mar;3(2):187-94.
24. Eek C, Grenne B, Brunvand H, Aakhus S, Endresen K, Smiseth OA, et al. Strain echocardiography predicts acute coronary occlusion in patients with non-ST-segment elevation acute coronary syndrome. Eur J Echocardiogr. 2010 Jul;11(6):501-8.
25. Grenne B, Eek C, Sjøli B, Dahlslett T, Uchto M, Hol PK, et al. Acute coronary occlusion in non-ST-elevation acute coronary syndrome: outcome and early identification by strain echocardiography. Heart. 2010 Oct;96(19):1550-6.
26. Marwick TH. Measurement of strain and strain rate by echocardiography: ready for prime time? J Am Coll Cardiol. 2006 Apr 4;47(7):1313-27.
27. Chassin MR, Kosecoff J, Solomon DH, Brook RH. How coronary angiography is used. Clinical determinants of appropriateness. JAMA. 1987 Nov 13;258(18):2543-7.
28. Marwick TH, Yu CM, Sun JP. Myocardial Imaging: Tissue Doppler and Speckle Tracking. Blackwell Publishing, 2007. pp. 36-54.

Prevalence of Clopidogrel Resistance Among Filipinos with Coronary Artery Disease: a Philippine Heart Center Experience

Frederick S. Gabriel, MD; Anna Beatriz Medrano, MD; Ariel Miranda, MD; Jose Navarro, MD

***Background* ---** Clopidogrel is an antiplatelet medication used in patients with coronary artery disease. A considerable number of patients still experience recurrent ischemic events secondary to thrombosis despite its use. A myriad of factors might contribute to individual responsiveness to clopidogrel. We evaluated the prevalence of clopidogrel resistance among Filipinos and its associated risk factors.

***Methods* ---** One hundred eleven (111) patients with documented stable coronary artery disease and who had acute coronary syndrome for more that 6 weeks on a maintenance dose of 75mg clopidogrel for at least two weeks were enrolled. Baseline clinical characteristics were gathered. Whole blood sampling was done to measure platelet function by impedance aggregometry using a point-of-care testing (Multiplate® analyzer; Dynabyte Medical, Munich, Germany).

***Results* ---** Seventeen (15%) out of 111 patients recruited in the study were classified as low responders to clopidogrel. The mean age of patients recruited was 60 years old and majority of those recruited were males (n=83, 75%). On multivariate analysis, the use of proton pump inhibitors (PPIs) was associated with statistically significant greater odds of clopidogrel resistance (OR 6.5, 95% CI: 1.96-22.09 p=0.010). On further analysis of patients taking proton pump inhibitors, we found that only those exposed to omeprazole had a significant association with clopidogrel resistance (OR 9.83, 95% CI: 2.54 to 39.35). No significant correlation was demonstrated in the other clinical parameters observed.

Conclusion* ---** The prevalence of clopidogrel resistance using the multiplate assay in Filipinos with stable CAD was 15%. Concomitant use of the proton pump inhibitors, specifically omeprazole, significantly increase the odds of clopidogrel resistance by 9.83. ***Phil Heart Center J 2014;18(1):20-28.

Key Words: Clopidogrel Resistance ■ Coronary Artery Disease ■ Proton-pump Inhibitors

Activation and aggregation of platelets play a major role in the reproduction of intracoronary thrombi after spontaneous atherosclerotic plaque disruption that results in myocardial ischemia or infarction in the acute coronary syndromes (ACS),[1] or the mechanical disruption that results from percutaneous coronary intervention (PCI).[2] Platelets initially stick to collagen and von Willebrand factor at the site of the dislocated plaque, resulting in an initial platelet monolayer. After activation, platelets release secondary agonists such as thromboxane A2 and adenosine diphosphate (ADP),[1] which together with "thrombin generated by the coagulation cascade result in stimulation and recruitment of additional platelets."[1,2] This is the underlying reason why antiplatelet therapy is a cornerstone in the management of ACS patients, especially those undergoing PCI.[3-5]

Aspirin plays a key role in the treatment and prevention of ischemic cardiovascular events. In the Antithrombotic Trialists' Collaboration meta-analysis of patients with previous thrombotic events or other predisposing conditions, aspirin use reduced the risk for vascular mortality by 15%, nonfatal myocardial infarction (MI) by 34%, nonfatal stroke by 25%, and their composite by 22%.[6] Benefits were seen in men and women. However, when stratified by dose, trials that used doses of aspirin of more than 75 mg/day were seen to provide significant reduction in cardiovascular events, whereas the 3 trials using doses less than 75 mg/day did not.[7] Similarly,

Finalist, Oral Presentation 20th PHC Annual Research Paper Competition held on February 23, 2012 at Philippine Heart Center,
Correspondence to ***Dr. Frederick Gabriel,*** Department of Adult Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100
Available at **http://www.phc.gov.ph/journal/publication** ISSN 0018-9034

the most recent large trial of aspirin in primary prevention in women failed to demonstrate a benefit of very-low-dose aspirin (100mg every other day).[8] Conversely, an analysis from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial found a 2-fold greater risk for bleeding with doses ranging from 200-325mg compared with doses of 75–100 mg.[3] These new data raise questions about the optimal dosage of aspirin.

Clopidogrel is an important part of therapy for patients with acute coronary syndromes (ACS) and patients who undergo percutaneous coronary intervention (PCI) with stent placement. Thienopyridines (ticlopidine or clopidogrel) have been shown to reduce the risk for subacute stent thrombosis[9] and are beneficial when used before PCI, with pre-treatment ranging from 10 days to 2 hours before PCI.[10,11] Similarly, in patients with unstable angina or non–ST-elevation MI, clopidogrel significantly decreased the incidence of cardiovascular death, nonfatal MI, or stroke over a 1-year period.[12] Benefit has also now been seen in patients with ST-elevation MI.[13,14]

There is evidence, however, that not all people respond comparably to antiplatelet drugs; hence, the concept of aspirin and clopidogrel "resistance" has emerged. Although antiplatelet agents reduce ischemic events, "resistance" to their effects continues to occur. The term "resistance" in this setting is challenging because "it has been variably used to indicate failure of an agent to prevent the clinical condition for which it is intended or failure of the agent to achieve the biochemical effect."[15]

Clopidogrel resistance is a rising clinical scenario, as antiplatelet therapy has become a standard of modern cardiovascular treatment. This phenomenon leads to increased cardiovascular morbidity and mortality.[16] Clopidogrel resistance has been defined as situations in which there is incomplete blockade of the platelet P2Y12 receptor in a patient taking clopidogrel. A myriad of causes are implicated including variations in absorption, metabolism or in the interaction of the drug to its specific platelet receptor.[17] Several studies have suggested that this variation in response to clopidogrel may be related to the individual variation in response to ADP.[18,19] Michelson et al showed that 20micromol ADP prior to administration of clopidogrel predicted the post clopidogrel ADP response.[18] Hepatic enzymes involved in the metabolism of clopidogrel such as CYP 1A2, CYP3A4, and CYP2C19 or in the platelet P2Y12 receptor may affect platelet reaction.[20,21]

A new and important piece to the emerging clopidogrel resistance picture was reported in a study by Matetzky and colleagues.[22] They have demonstrated the correlation of a laboratory measure of clopidogrel nonresponse with clinical outcomes. They have concluded that up to 25% of STEMI patients undergoing primary PCI with stenting are resistant to clopidogrel and therefore may be at increased risk for cardiovascular events. Although the study population was small, the data strongly suggest that there is "individual variability in response to clopidogrel in the setting of PCI after STEMI and more broadly that clopidogrel resistance may be a marker for increased risk of recurrent cardiovascular events."[22]

There have been numerous studies regarding aspirin and clopidogrel resistance and its correlation with morbidity among patients with coronary artery disease. Among Filipinos, no data has yet been published regarding this. This study focuses on the prevalence of clopidogrel resistance. The need for an additional antiplatelet medication or an increase in the dosage of aspirin or clopidogrel might be necessary if this is proven. This study aims to determine prevalence of clopidogrel resistance using a point-of-care multiplate platelet function analyzer among Filipino patients with coronary artery disease. Moreover, this study aims to identify associated factors, particularly drug interactions, that can contribute to clopidogrel response variability.

METHODOLOGY

This is a cross-sectional study conducted at the Philippine Heart Center involving subjects with documented coronary artery disease (using any of these methods: ECG, coronary angiography or history of acute coronary syndrome of more than six weeks, but are currently stable).

Clopidogrel 75mg should be a part of their medical management. Excluded were the following: patients who have estimated creatinine clearance of less than 59 ml/min using the Cockcroft-Gault formula, liver and hematologic disorder, those who received unfractionated or low molecular weight heparin or glycoprotein IIb IIIa, warfarin, cilostazol and NSAIDs. Informed consent was taken from the study subjects. This study was approved by the institutional ethics review board and all subjects signed an informed consent prior to participation.

We interviewed each subject to determine their age, co-morbidities, risk factors and current medications. After getting their baseline characteristics, clopidogrel assay was done using the Multiplate analyzer.

Clopidogrel Assay: 3mL of blood was sampled from each of the subjects and placed in the anticoagulated test tubes that contain 25ug/mL of hirudin, a direct thrombin inhibitor. Whole blood samples were analyzed 30-180 minutes after their collection for in-vitro platelet function via impedance aggregometry using the Multiplate analyzer. The analysis was done using single-use test cell with two independent impedance sensors. 300uL of patient blood with hirudin and 300uL of saline were transferred into the test cell using an electronic pipette. The solution was allowed to incubate at 37^0C for 3 minutes. The agonist, 6.4umol/L of ADP, was added into the solution and real time recording started. In six minutes, the capacity of platelets to adhere to the 2 metal electrodes was continuously recorded by noting the change in electrical resistance or impedance between them. The resistance change was transformed to arbitrary aggregation units (AUs) and plotted against time. The area under the aggregation curve (AUC) was used to measure the aggregation response. Double determination was performed during each measurement for quality assurance. Results were reported as a platelet aggregation with an area under the curve of greater than or equal to 55 AUC. The analysis was performed inside the clinical laboratory.

Statistical Analysis. Statistical data were analyzed using STATA 11. Categorical data were displayed as frequencies and percentages. The chi-square test was used for dichotomous analysis of categorical data. Continuous data were presented as mean values and standard deviation (SD) and were compared. Multiple logistic regressions to determine the association of independent factors with occurrence of clopidogrel resistance was done. A p value of less than 0.05 were considered significant.

RESULTS

The subjects' baseline characteristics are shown in Table 1. The mean age of patients recruited was sixty years old where majority of those recruited were males (n=83, 75%).

The subjects' clinical laboratory results are shown in Table 2. The laboratory parameters recorded such as creatinine, hemoglobin, platelet, lipid profile, ALT, AST, 12 lead ECG, 2D echocardiogram derived systolic function, and coronary angiogram data shows no significant difference between the two groups. The presence of diastolic dysfunction documented by 2D echocardiogram showed an almost significant (53% versus 26%, p=0.051) correlation with the presence of a poor response to clopidogrel. Table 2 likewise contains the mean values for platelet aggregation for clopidogrel responders (71AU*min) and non-responders (27AU*min).

Individual results of platelet aggregation are plotted in Figure 1 where results of 55AU*min was selected as the cutoff for clopidogrel resistance. Patients demonstrating equal or higher platelet aggregation than the arbitrary cutoff value of 55AU*min were thus classified as clopidogrel resistant. The gathered data shows that seventeen (15%) out of 111 patients recruited in the study had an aggregation value of $\geq$ 55U. This group of patients was classified as low responders to clopidogrel and was compared to the remaining subjects with a good response to clopidogrel. On multivariate analysis, the use of proton pump inhibitors was associated with statistically significant greater odds of clopidogrel resistance (OR 6.5, 95% CI: 1.96-22.09 p=0.010). Among the patients taking proton pump inhibitors, we found that only those exposed to omeprazole had a significant association with clopidogrel resistance (OR 9.83,

95% CI: 2.54 to 39.35). No significant correlation was noted among those taking the other types of proton pump inhibitors, namely; esomeprazole, lansoprazole and pantoprazole. The other clinical parameters observed such as age, sex, BMI, past medical history, use of cigarette, alcohol or illicit drugs did not show any correlation with a patients' response to clopidogrel.

Table 1. Demographic data, medical history, concomitant medication, and platelet aggregation of stable CAD subjects, Philippine Heart Center 2011

	Resistant (n=17)	Non-resistant (n=94)	p value
Age, mean ± SD,y	60 ± 8	60 ± 11	0.942
Male, n (%)	12 (71)	71 (75)	0.387
Female, n (%)	5 (29)	23 (24)	
BMI, mean ± SD, Kg/m^2	24 ± 3.3	24 ± 4.1	0.747
Past medical history			
Hypertension, n (%)	14 (82)	76 (81)	0.744
Diabetes, n (%)	10 (59)	36 (39)	0.202
Dyslipidemia, n (%)	9 (53)	44 (47)	1.000
COPD, n (%)	0 (0)	6 (6)	0.587
Hyperthyroidism, n (%)	0 (0)	3 (3)	1.000
Hypothyroidism, n (%)	1 (6)	3 (3)	0.512
Gout, n (%)	0 (0)	5 (5)	0.590
ACS, n (%)	15 (88)	71 (75)	0.759
CABG, n (%)	3 (18)	6 (6)	0.160
Stroke, n (%)	5 (29)	12 (13)	0.418
Cigarette smoker, n (%)	7 (41)	56 (59)	0.121
Illicit drug abuse, n (%)	1 (6)	3 (3)	0.512
Family history			
Hypertension, n (%))	14 (82)	60 (64)	0.413
Diabetes, n (%)	10 (59)	41 (44)	0.443
Dyslipidemia, n (%)	4 (23)	20 (21)	1.000
ACS, n (%)	6 (35)	44 (47)	1
Stroke, n (%)	1 (6)	24 (25)	0.069
Concomitant drug intake)			
ACE inhibitors, n (%)	2 (11)	32 (34)	0.055
ARB, n (%)	12 (71)	39 (41)	0.071
Beta blockers, n (%)	10 (59)	40 (43)	0.439
CCB, n (%)	3 (18)	17 (18)	1.000
Diuretics, n (%)	5 (29)	12 (13)	1.000
Nitrates, n (%)	8 (47)	45 (48)	0.802
Digoxin, n (%)	3 (18)	22 (23)	0.759
Statin, n (%)	17 (100)	73 (78)	0.187
Aspirin, n (%)	8 (47)	43 (46)	1.000
Antithyroid, n (%)	0 (0)	1 (1)	1.000
Antibiotics, n (%)	2 (12)	12 (13)	0.775
Proton pump inhibitors, n (%)	10 (59)	15 (16)	0.001
Esomeprazole, n (%)	3 (18)	4 (4)	0.083
Lansoprazole, n (%)	0 (0)	1 (1)	1.000
Omeprazole, n (%)	8 (47)	7 (7)	0.000
Pantoprazole, n (%)	0 (0)	3 (3)	1.000

Table 2. Baseline laboratory results of stable CAD subjects, Philippine Heart Center 2011

	Resistant (n=17)	Non-resistant (n=94)	p value
Creatinine, mean ± SD, mmol/L	0.10 ± 0.06	0.13 ± 0.15	0.356
Hemoglobin, mean ± SD, mmol/L	132 ± 10	134 ± 15	0.540
Platelet, mean ± SD, mmol/L	221 ± 67	252 ± 90	0.164
Lipid Profile			
Total cholesterol, mean ± SD, mmol/L	179 ± 71	181 ± 104	0.938
Triglycerides, mean ± SD, mmol/L	158 ±153	145 ± 84	0.591
LDL, mean ± SD, mmol/L	93 ± 38	101 ± 49	0.500
HDL, mean ± SD, mmol/L	43 ± 12	42 ± 18	0.884
ALT, mean ± SD, mmol/L	37 ± 25	31 ± 14	
AST, mean ± SD, mmol/L	28 ± 23	23 ± 10	0.162
FBS, mean ± SD, mmol/L	136 ± 61	119 ± 41	
HBA1c, mean ± SD, mmol/L	6.8 ± 1.7	6.3 ± 1.7	0.238
12 Lead ECG			
Sinus, n (%)	0 (0)	1 (1)	0.669
Ischemia, n (%)	4 (24)	20 (21)	1.000
Infarction, n (%)	8 (47)	36 (38)	0.793
Ischemia + infarction n (%)	6 (35)	27 (29)	0.950
2D echocardiogram			
EF, mean ± SD, %	60 ± 14	57 ± 12	
Systolic dysfunction, n (%)	5 (29)	24 (26)	1.000
Diastolic dysfunction, n (%)	9 (53)	24 (26)	0.051
Coronary angiogram			
Insignificant	4 (24)	17 (18)	0.744
Significant	14 (82)	76 (81)	0.744
Platelet aggregation, mean ± SD, AU*min	71	27	

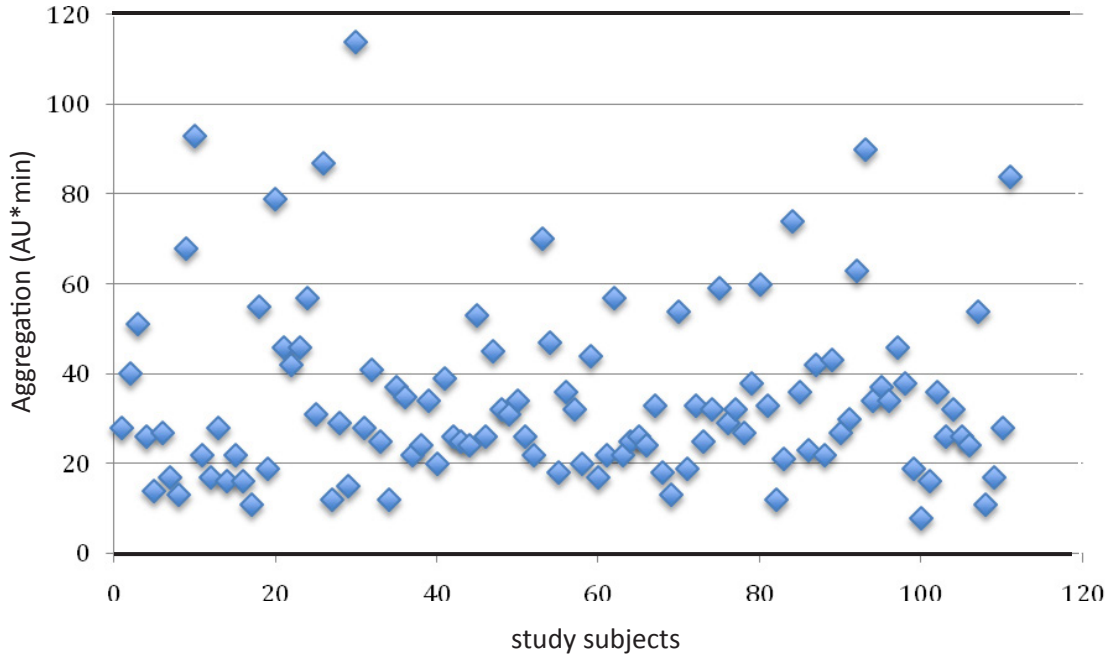


Figure 1. Platelet aggregation of 111 stable CAD patients using impedance aggregometry (Multiplate® Analyser, Dynabyte Medical, Munich)

DISCUSSION

To date, the prevalence and risk factors that impact clopidogrel resistance among Filipinos with stable coronary artery disease has not been investigated before. The availability of clopidogrel testing method is required to address this issue. Platelet aggregation to ADP is frequently used as an assay to check an individual's response to clopidogrel. Platelet response to ADP as well as inhibition by clopidogrel depends on the concentration of the agonist. At low concentrations, the response to ADP is high ly dependent on the production of thromboxane and is inhibited by aspirin.[24] Higher concentrations of ADP leads to full and irreversible platelet aggregation that is insensitive to aspirin but is inhibited by up to 90% in the presence of a P2Y12 antagonist. Hence, the assay is an effective means of assessing the response to clopidogrel. Other point-of-care assays are sensitive to P2Y12 antagonism. Born's aggregation is the current "gold standard" that detects platelet function in platelet-rich plasma is laborious and is not appropriate for on-site testing.[25] For this reason, tests suited for point-of-care analysis such as the Multiplate Analyzer, which was used in this study, have been developed. Multiplate Analyzer is a whole-blood aggregation analyzer that uses single-use test cells and electronic interactive pipetting. With this method, we are able to identify patients with low response to clopidogrel through the amount of residual platelet activity. Inhibition of platelet aggregation to ADP by clopidogrel is variable and shows a normal distribution; ranging from 40% to 50% inhibition.[26] This wide variation in response implies several issues including several extrinsic and intrinsic mechanisms. Extrinsic mechanisms of clopidogrel resistance include clopidogrel under dosing, variable absorption of the prodrug or clearance of the metabolite, drug-to-drug interactions, and the amount of CYP3A4 activity.[27] Intrinsic mechanisms could include variability of P2Y12 receptor, release of ADP, or up regulation of other platelet activation pathways.

Like other drugs that are metabolized by members of the enzyme cytochrome p450, clopidogrel has drug-to-drug interactions. A class of drug relevant to this matter is the "statins" or HMG-CoA reductase inhibitors which has been demonstrated in vitro to suppress clopidogrel 's activation by 90%.[28] Similarly, co-administration of atorvastatin suppresses the antiplatelet effect of clopidogrel. Evidence of a clinically significant interaction, however, has not been demonstrated in two studies of lower-risk patient cohorts.[29,30] The absence of a clinical correlation on of the effect "statins" to clopidogrel is in concordance with our results (p=0.187). Both clopidogrel and the PPIs, in varying degrees, are both metabolized by the same cytochrome p450 enzyme – CYP2C19. This interaction brings about the potential to inhibit the metabolism of clopidogrel to its active metabolite.[31,32]

The earliest evidence of a pharmacological interaction involving clopidogrel and PPIs is from platelet aggregation studies. A study of 105 patients found PPI users (omeprazole, n = 24) had higher VASP phosphorylation levels than none PPI users and suggested an interaction.[33] In the OCLA study,[34] measurements of VASP expressed as platelet reactivity index (PRI) were measured in 124 patients undergoing coronary stent insertion. Patients on clopidogrel and aspirin were treated with omeprazole 20 mg or placebo for 7 days. At the end of the study, 60.9% of omeprazole-treated patients and 26.7% of placebo-treated patients were classified as poor responders to clopidogrel (PRI > 50%) indicating a significantly decreased effect of clopidogrel with exposure to a PPI.

In the background that all PPIs are metabolized by CYP2C19 to varying degrees and share the ability to inhibit CYP2C19, the issue whether all PPIs have negative effects on clopidogrel is raised. A number of studies have attempted to answer this question. A small study showed that lansoprazole 30mg when given to clopidogrel 300 mg diminished the inhibition of platelet aggregation when compared with clopidogrel alone.[35] A different study found all PPIs to be comparable in terms of their inhibitory profiles, although with some heterogeneity; lansoprazole is the most potent in vitro inhibitor of CYP2C19 with pantoprazole exhibiting more of an effect on CYP2C9. Even though lansoprazole has been shown to be the strongest inhibitor of CYP2C19,[36] other evidence reports that concurrent treatment with lansoprazole does not alter the pharmacokinetics

of clopidogrel.[35] Results from patients on clopidogrel undergoing angiography (n=1000) examined the effect the various PPIs had on platelet aggregation.[37] Platelet aggregation was higher in patients prescribed omeprazole than in those without PPI therapy. It was observed that platelet aggregation was similar in patients taking clopidogrel and pantoprazole, esomeprazole or no PPI. In another study, they found that omeprazole use (n=3132) was associated with adverse cardiovascular outcomes.[38] Similar results were found with rabeprazole. In patients with coronary artery disease undergoing PCI, there was no difference between esomeprazole (n=74) and pantoprazole (n=152), in 300 patients looking at clopidogrel responsiveness by VASP phosphorylation and platelet aggregometry. This showed no suggestion that either was associated with impaired response to clopidogrel.[39] Evidence suggests that pantoprazole has less of a deleterious effect on clopidogrel than omeprazole.[40] PRI VASP was measured in patients (n=104) undergoing PCI who were randomized to either pantoprazole (n=52) or omeprazole (n=52) in addition to both aspirin and clopidogrel. Results show pantoprazole had significantly better platelet response to clopidogrel (36% vs. 48%). These observations have led authors to recommend pantoprazole as the preferred PPI in the context of concomitant clopidogrel use.[41-43] Some data suggest that pantoprazole is less likely to inhibit the enzyme CYP2C19 than omeprazole and does not attenuate the pharmacodynamic response to clopidogrel.[36,39,40,43] However, recent guidelines showed no preferentiality of using one PPI over another since there are no head-to-head trials comparing PPIs and studies comparing PPIs were conducted in different populations. [44] Even though drug–drug interactions of omeprazole for CYP2C19 are thought to be one of competitive inhibition, the issue of its short plasma half-life (<1h) has been brought up to refute this argument.[41] Then again, omeprazole has a high affinity for CYP2C19 and its binding is extensive and it is unknown how long this inhibition persists. Omeprazole has a short half-life; however, separating the dose of omeprazole and clopidogrel is not a way of overcoming the interaction as some CYP2C19 may still be bound by omeprazole metabolism.[41] Furthermore, no obvious dose–response relationship was found between PPI dose and adverse outcomes, which one would expect from competitive inhibition.[38,41] At present, there is not enough evidence to recommend a particular PPI (e.g. pantoprazole) in preference to another to avoid a drug-to-drug interaction. In November 2009, the FDA announced that clopidogrel should not be taken with proton pump inhibitors such as omeprazole and esomeprazole.[45] The ongoing SPICE trial directly compares the effect of all PPIs on platelet aggregation and VASP and should help answer the question of which PPI is preferable. In addition, the trial will examine clopidogrel resistance, CYP2C19 polymorphism and its effect on PPI on the antiplatelet activity of clopidogrel, mortality and the need to stop medication due to peptic ulcer disease or GI bleeding.[46]

CONCLUSION

The overall prevalence of clopidogrel resistance of patients with CAD using the multiplate assay in this study with stable CAD was 15%. Concomitant use of the proton pump inhibitors, specifically omeprazole significantly increase the odds of clopidogrel resistance by 9.83 (CI 95%, 2.54 to 39.35, p=0.000).

REFERENCES

1. McNicol A, Israels S. Platelets and anti-platelet therapy. J Pharmacol Sci. 2003;93:381–396.
2. Patrono C, Bachmann F, Baigent C, Bode C, De Caterina R, Charbonnier B, et al. Expert consensus document on the use of antiplatelet agents. The Task Force on the Use of Antiplatelet Agents in Patients with Atherosclerotic Cardiovascular Disease of the European Society of Cardiology. Eur Heart J. 2004;25:166–181.
3. Antman E, Anbe D, Armstrong P, Bates E, Green L, Hand M, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: executive summary: a report of the ACC/AHA Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines on the Management of Patients With Acute Myocardial Infarction). Circulation. 2004 Aug 3;110(5):588-636.

4. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, et al. ACC/AHA guideline update for the management of patients with unstable angina and non–ST segment elevation myocardial infarction 2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). Circulation. 2002;106:1893–1900.
5. Smith SC Jr, Dove JT, Jacobs AK, Kennedy JW, Kereiakes D, Kern MJ, et al. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines). Circulation. 2001;103:3019-3041
6. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324: 71–86.
7. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med. 2005;352:1293-1304.
8. Peters RJ, Mehta SR, Fox KA, Zhao F, Lewis BS, Kopecky SL, et al, for the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Trial Investigators. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. Circulation. 2003;108:1682–1687.
9. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, et al., for the Stent Anticoagulation Restenosis Study Investigators. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. N Engl J Med 1998;339:1665– 1671.
10. Steinhubl SR, Berger PB, Mann JT III, Fry ET, DeLago A, Wilmer C, Topol EJ, for the CREDO Clopidogrel for the Reduction of Events During Observation Investigators. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411-2420.
11. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, et al., for the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-Thrombolysis in Myocardial Infarction (TIMI) 28 Investigators. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. JAMA 2005; 294: 1224 –1232.
12. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, for the Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494 –502.
13. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, et al, for the CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005;352:1179 –1189.
14. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, et al., for the COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1607–1621.
15 Wiviott SD, Antman EM.Clopidogrel resistance: a new chapter in a Fast-Moving Story. Circulation. 2004; 109:3064-67.
16. Sugunaraj JP, Palaniswamy C, Selvaraj DR, Chaitanya Arudra SK, Sukhija R. Clopidogrel Resistance. Am J Ther. 2010;17:210-5.
17. Cairns, JA, Eikelboom, J. Clopidogrel resistance: more grist for the mill. J Am Coll Cardiol 2008; 51:1935.
18. Michelson, AD, Linden, MD, Furman, MI, Li Y, Barnard MR, Fox ML, et al. Evidence that pre-existent variability in platelet response to ADP accounts for 'clopidogrel resistance'. J Thromb Haemost 2007; 5:75.
19. Gurbel, P, Bliden, KP, Tantry, U. Evidence that pre-existent variability in platelet response to ADP accounts for 'clopidogrel resistance': a rebuttal. J Thromb Haemost 2007; 5:1087.
20. Nguyen, TA, Diodati, JG, Pharand, C. Resistance to clopidogrel: a review of the evidence. J Am Coll Cardiol 2005; 45:1157.
21. Umemura, K, Furuta, T, Kondo, K. The common gene variants of CYP2C19 affect pharmacokinetics and pharmacodynamics in an active metabolite of clopidogrel in healthy subjects. J Thromb Haemost 2008; 6:1439.
22. Matetzky, S, Shenkman, B, Guetta, V, Shechter M, Beinart R, Goldenberg I, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. Circulation 2004; 109:3171.
23. Wiviott SD, Antman EM. Clopidogrel resistance: a new chapter in a fast-moving story. Circulation 2004; 109: 3064-3067.
24. Maree AO, Fitzgerald DJ. Variable platelet response to aspirin and clopidogrel in atherothrombotic disease. Circulation. 2007;115:2196–2207.
25. Eikelboom J, Hankey G. Aspirin resistance: a new independent predictor of vascular events? J Am Coll Cardiol 2003;41:966-68.
26. Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Bhatt DL, Topol EJ. Variability in platelet responsiveness to clopidogrel among 544 individuals. J Am Coll Cardiol. 2005;45:246.
27. Lau WC, Gurbel PA, Watkins PB, Neer CJ, Hopp AS, Carville DGM, et al. Contribution of hepatic cytochrome P450 3A4 metabolic activity to the phenomenon of clopidogrel resistance. Circulation. 2004; 109: 166.

28. Clarke TA, Waskell LA. The metabolism of clopidogrel is catalyzed by human cytochrome P450 3A and is inhibited by atorvastatin. Drug Metab Dispos. 2003;31:53–59.
29. Serebruany VL, Midei MG, Malinin AI, Oshrine BR, Lowry DR, Sane DC, et al. Absence of interaction between atorvastatin or other statins and clopidogrel: results from the interaction study. Arch Intern Med. 2004;164:2051–2057.
30. Saw J, Brennan DM, Steinhubl SR, Kereiakes DJ, Serbruary VL, Brennan D, et al. Lack of evidence of a clopidogrel-statin interaction in the CHARISMA trial. J Am Coll Cardiol. 2007;50:291–295.
31. Hulot JS, Bura A, Villard E, Azizi M, Remones V, Govenvalle C, et al. Cytochrome P450 2C19 loss-of function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. Blood 2006; 108: 2244–7.
32. Ishizaki T, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors-emphasis on rabeprazole. Ailment Pharmacol Ther 1999; 13(Suppl. 3): 27–36.
33. Gilard M, Arnaud B, Le Gal G, Abgrall JF, Boschat J. Influence of omeprazole on the antiplatelet action of clopidogrel associated to aspirin. J Thrombo Haemost 2006; 4: 2508–9.
34. Gilard M, Arnaud B, Comily JC, Le Gal G, Lacut K, Le Calvez G, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. J Am Coll Cardiol 2008; 51: 256–60.
35. Small DS, Farid NA, Payne CD, Weerakkody DJ, Li YG, Brandt JT, et al. Effects of the proton pump inhibitor lansoprazole on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel. J Clin Pharmacol 2008; 48: 475–84.
36. Li XQ, Andersson TB, Ahlstrom M, Weidolf L. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. Drug Metab Dispos 2004; 32: 821–7.
37. Sibbing D, Morath T, Stegherr J, Braun S, Voqt W, Hadamitzky M, et al. Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. Thromb Haemost 2009; 101:714–9.
38. Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, et al. Risk of adverse outcomes with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA 2009; 301: 937–44.
39. Siller-Matula JM, Spiel AO, Lang IM, Kreiner G, Christ G, Jilma B. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. Am Heart J 2009; 157: 145–8.
40. Cuisset T, Frere C, Quilici J, Poyet R, Gavorit B, Bali L et al. Comparison of omeprazole and pantoprazole influence on a high 150-mg clopidogrel maintenance dose: the PACA (Proton Pump Inhibitors and Clopidogrel Association) prospective randomized study. J Am Coll Cardiol 2009; 54:1149–53.
41. Norgard NB, Mathews KD, Wall GC. Drug-drug interaction between clopidogrel and the proton pump inhibitors. Ann Pharmacother 2009; 43: 1266–74.
42. Juhasz M, Herszenyi L, Tulassay Z. Current standings of the proton pump inhibitor and clopidogrel cotherapy: review on an evolving field with the eyes of the Gastroenterologist. Digestion 2010; 81:10-5.
43. Juurlink DN. Proton pump inhibitors and clopidogrel: putting the interaction in perspective. Circulation 2009; 120: 2310–2.
44. Abraham NS, Hlatky MA, Antman EM, Bhatt DL, Bjorkman DJ, Clark CB, et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. J Am Coll Cardiol 2010; 56: 2051–66.
45. DeNoon, DJ. FDA Warns Plavix Patients of Drug Interactions. WebMD. [cited on 2009 Nov 23] Available from: URL: http://www.webmd.com/heart-disease/news/20091117/fda-warns-plavix-patients-drug-interactions
46 Evaluation of the Influence of Statins and Proton Pump Inhibitors on Clopidogrel Antiplatelet Effects (SPICE). Available at: http://clinicaltrials.gov/ct2/show/NCT00930670. Accessed November 30, 2010.

Association of Electrocardiographic Ischemia Grades with Clinical and Angiographic Outcomes of Patients with ST-Elevation Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention

Jeffrey Chua, MD

Background **---** A sizeable proportion of ST Elevation in Myocardial Infarction (STEMI) patients treated with Primary Percutaneous Coronary Intervention (PPCI) demonstrate inadequate perfusion of the infarcted myocardium after successful restoration of epicardial coronary blood flow resulting to adverse angiographic and clinical outcomes. We sought to determine the association of ischemia grade on admission electrocardiogram (ECG) with the clinical and angiographic outcomes of patients with STEMI who will undergo PPCI.

Methods **---** This is a single-centre, prospective cohort study, conducted on April to December 2011 among patients presenting with acute STEMI and underwent PCI in the Philippine Heart Center. They were classified into two groups based on the absence [34 patients without Grade 3 ischemia (non-GI3)] or presence [34 patients with Grade 3 ischemia (GI3)] of distortion of the terminal portion of the QRS complex on the admission ECG (ECG Ischemia Grade). In-hospital outcomes were determined during the course of the study. It included death and a composite secondary endpoint comprising of heart failure, malignant arrhythmia, hemodynamic instability, and stroke.

Results **---** There were no significant differences in the baseline characteristics in terms of age, gender, and coronary artery risk factors between patients with GI3 and non-GI3. Myocardial infarction presenting as Killip Class 3 and 4 occurred more frequently in patients with GI3 (p=0.001) as they have significantly lower mean systolic and diastolic blood pressures (p=0.001 and p=0.000, respectively) and unexpectedly lower use of ACE inhibitors (p=0.003). Incidence of cardiogenic shock was also higher among these patients (11 out of 12 cases) which subsequently necessitated use of IABP (p = 0.006). Baseline angiography showed that patients with GI3 had longer lesion lengths (p=0.053) and insignificantly more likely to have multivessel coronary disease and poor collateral flow to the infarct-related artery (p=0.084 and p=0.061, respectively). The incidence of pre-revascularization TIMI ≤ 1 in the infarct related artery (IRA) and high-burden thrombus formation was comparable between the two patient groups. Failure to gain re-flow in the IRA after PPCI occurred in 58.8% (40 patients), including a combined 39.7% with TIMI ≤ 2 flow and 19.1% with TIMI 3 flow but myocardial blush grade (MBG) ≤ 1. Grade 3 ischemia is associated with a higher incidence of angiographic no re-flow post-PPCI (p = 0.000). This translated to a higher in-hospital mortality among these patients compared with non-GI3 (26.5% vs. 2.9%, p=0.013). More cardiac complications were also observed in patients with GI3 than did those with non-GI3, particularly heart failure (p = 0.000), malignant arrhythmia (p=0.000), hemodynamic instability (p = 0.000), and stroke (p=0.001).

Conclusion **---** ECG ischemia grade on admission can be a predictive tool of adverse clinical and angiographic outcomes associated with abnormalities of myocardial reperfusion. It is possible that patients with GI3 who will undergo PPCI will benefit further if angiographic no re-flow can be prevented and treated. ***Phil Heart Center J 2014;18(1):29-38.***

Key Words: Primary Percutaneous Coronary Intervention ■ Electrocardiogram, ST Elevation Myocardial Infarction

Primary Percutaneous Coronary Intervention (PPCI) is the preferred treatment for reperfusion in high risk patients with ST elevation myocardial infarction (STEMI).[1] A sizeable

Finalist, Oral Presentation 20th PHC Annual Research Paper Competition held on February 23, 2012 at Philippine Heart Center,
Correspondence to ***Dr. Jeffrey Chua,*** Department of Adult Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100
Available at **http://www.phc.gov.ph/journal/publication** ISSN 0018-9034

proportion of patients treated with PCI demonstrate inadequate perfusion of the infarcted myocardium after successful restoration of epicardial coronary blood flow[2] which ultimately results in a larger infarct size, worse left ventricular ejection fraction, and increased mortality and cardiovascular events.[3-6] This phenomenon termed as "no-reflow" was angiographically defined as a substantial coronary antegrade flow reduction less than Thrombolysis in Myocardial Infarction (TIMI) flow Grade 3 without mechanical obstruction.[7]

An electrocardiogram (ECG) is considered to be an appropriate method for risk stratification in patients with reperfusion abnormalities.[8] ST segment resolution (STR) was shown to be a very powerful predictive factor for outcomes after thrombolytic therapy and PPCI.[9,10] In retrospect, the initial admission ECG itself has been proven to be able to predict STR even before they undergo reperfusion therapy. One of the variables available is the ischemia grading system.[11] The ischemia grade system consists of three grades. Grade 1 (GI1): tall upright T waves without ST segment elevation; Grade 2 (GI2): ST segment elevation in > 2 adjacent leads without terminal QRS distortion; and Grade 3 (GI3): ST segment elevation with terminal QRS distortion in >2 adjacent leads characterized by the absence of S wave in leads with Rs pattern, and/or a take-off of the ST segment at >50% of the R wave in leads with qR pattern (*Figure 1*).[12] Patients with GI3 on their admission ECG are demonstrated to have higher mortality, larger infarcts, less myocardial salvage, and less benefit with thrombolytic therapy with higher rates of reinfarction than those with GI2.[13-16]

This is the first local study conducted to investigate whether Grade III ischemia detected on admission ECG is associated with worse angiographic and clinical outcomes in patients with STEMI who will undergo PPCI.

METHODOLOGY

This is a single-center, prospective cohort study, conducted on April to December 2011 among patients with acute STEMI and candidates for primary PCI presenting in the Philippine Heart Center. The study was conducted after the Institutional Ethics Review Board (IERB) has approved this research protocol. Informed consent was obtained from all subjects prior to participation.

Included were adult patients who presented at the emergency room with symptoms of ischemia and an ECG showing either tall upright T-waves without ST segment elevation or ST-elevation of > 0.1 mV in ≥ 2 leads and underwent PPCI. Excluded were the following: those with history of previous myocardial infarction; those who had previous PCI or coronary artery bypass surgery; those with concomitant significant valvular or myopathic heart disease; those who had rescue or facilitated PCI after thrombolytic therapy; those who have a life-threatening disease with prognosis of < 6 months; those with negative T waves in ≥ 2 adjacent leads with maximal ST elevation; those with other ECG abnormalities such as left-bundle branch block, WPW syndrome, pacemaker rhythm; and those with uninterpretable ECG data.

Information on demographic and clinical characteristics was gathered from existing data available from the patient's chart record made on the time of admission at the Emergency Room. All patients were treated with aspirin (300 mg followed by 80 mg/day), heparin (5000 IU) followed by infusion of 80 units/hour, clopidogrel (300-600 mg followed by 75 mg/day), and statin (80 mg) directly following the electrocardiographic confirmation of STEMI.

Electrocardiographic analysis: The ECGs were analyzed according to the ischemia grading system by two other interventional cardiologists blinded to the patient's clinical and angiographic outcome. We obtained ECGs for each patient on ER admission. The study population was divided into groups according to the electrocardiographic ischemia grades (*Figure 1*). GI3 is defined as: (1) absence of an S wave below the TP–PR isoelectric line in > 2 leads that usually have a terminal S configuration (leads V1 to V3); or (2) ST J point amplitude > 50% of the R wave amplitude measured from the TP–PR baseline in > 2 of all other leads".[12] (*Figure 2*) Patients meeting the ST segment elevation

criteria but not the GI3 criteria were classified as having either GI1 or GI2.[17] (*Figure 3*) GI1 is defined as tall upright T waves without ST segment elevation; and GI2 is defined as ST segment elevation in >2 adjacent leads without terminal QRS distortion as described above. ST segment deviation was measured manually to the nearest 0.5 mm at the J point in 11 of the 12 ECG leads, excluding aVR, by using the TP segment as the isoelectric line. Alternatively, the PR segment was used if the TP segment was not distinct.

Angiographic data analysis: Coronary angiography was performed using the right femoral approach to determine the infarct related artery (IRA) and collateral channels. The collateral channels were graded according to a previously described method.[18] Grades of collateral filling from the contralateral vessel were: 0 = none; 1 = filling of side branches of the artery to be dilated via collateral channels without visualization of the epicardial segment; 2 = partial filling of the epicardial segment via collateral channels; 3 = complete filling of the epicardial segment of the artery being dilated via collateral channels. Quantitative coronary angiography was performed before and immediately after the procedure using the edge detection algorithm[19] and by selecting end-diastolic frames demonstrating the stenosis in its most severe and non-foreshortened projection. The reference lumen diameter (RLD) and lesion length were calculated with a contrast-filled guiding catheter used as the calibration standard. Large IRA is defined as having a RLD of ≥ 4.0mm and a long lesion of the IRA as a lesion length ≥ 15 mm using the criteria of type B lesions from the guidelines of the lesion morphology. In addition, the presence of an intraluminal thrombus in the IRA on the initial angiogram was assessed. High-burden thrombus formation have the following features: 1) an intraluminal thrombus with the greatest linear dimension ≥3 times the reference lumen diameter (RLD); 2) cut-off pattern (lesion morphology with a sudden cut-off without tapering proximal to the occlusion); 3) existence of accumulated thrombus (≥5mm of linear dimension) before the occlusion; 4) presence of floatingthrombus before the occlusion; 5) persistent contrast staining distal to the obstruction.

Percutaneous coronary intervention was performed as the reperfusion therapy in all patients whether with coronary stents or conventional balloon angioplasty. Optimal coronary intervention was performed after evaluation of the lesion morphology. The decision making for the PCI strategy was left to the discretion of the attending physician. The TIMI flow grade was evaluated on the initial and final angiogram after PCI and Myocardial Blush Grade (MBG) on the final angiogram,[7] and was determined by two other investigators who were also blinded from the initial ECG findings. The TIMI flow grades were defined as: 0, total occlusion of the IRA; 1, some penetration of contrast beyond the occlusion point but without distal vessel perfusion; 2, perfusion of the entire IRA into the distal coronary bed but with delayed flow compared with a normal artery; 3, full perfusion of the IRA with normal flow.[22] Myocardial Blush Grades were defined as follows: 0, no myocardial blush or contrast density; 1, minimal myocardial blush or contrast density; 2, moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral non–IRA; and 3, normal myocardial blush or contrast density, comparable with that obtained during angiography of a contralateral or ipsilateral non-IRA.[23] Angiographic slow/no-reflow during PCI is defined as (1) angiographic evidence of reopening of occluded coronary artery and successful stent placement with no evidence of flow-limiting residual stenosis (≤50%), dissection, spasm, or apparent thrombus; (2) angiographic documentation of a TIMI flow grade ≤ 2 or 3 with an MBG ≤ 1, at least 10 minutes after the end of PCI procedure.[6,7]

Clinical outcome analysis: In-hospital outcomes were determined during the course of the study. It included death and a composite secondary endpoint comprising of heart failure, malignant arrhythmia, hemodynamic instability, and stroke. Death was regarded as cardiac unless a non-cardiac cause of death was considered. Heart failure is defined as Killip Class ≥ 2 requiring use of diuretics. Malignant arrhythmias included sustained ventricular tachycardia or fibrillation, or high degree atrioventricular block. Hemodynamic instability is defined as development of hypotension requiring ≥ 1 inotropic agents. Stroke is defined as a

new focal neurological deficit of sudden onset lasting ≥ 24 hours with or without imaging evidence by computed tomography or magnetic resonance imaging.

Statistical analysis: Sample size computed was N = 68 based on 95% confidence level, relative error of 20% and assumed mortality of 22.6% based on the study by Vicente.[20] Data were summarized using mean and standard deviation. To determine homogeneity of patient characteristics with ECG Ischemia grading, T-test and chi-square test were used. To determine association of ECG ischemia grading with outcome, chi-square or Fisher Exact Test was used. Logistic regression analysis could have been used to adjust for probable confounders in determining association of ECG ischemia grade with the outcome however, due to small sample size the data did not fit into the model. To determine the predictive value of ECG in determining outcome, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were computed. Kappa test was used to determine the significance of agreement. A p-value of ≤ 0.050 was considered significant.

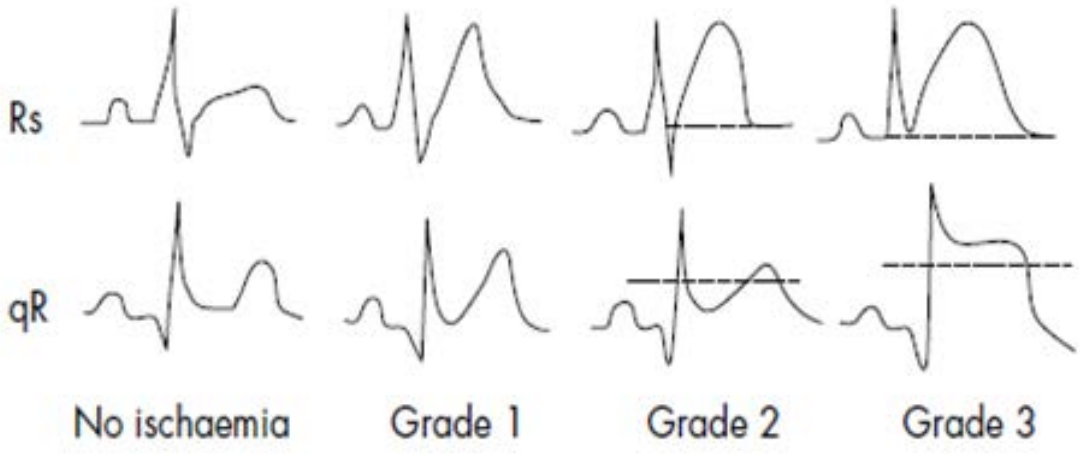


Figure 1. ECG Ischemia Grading System[12]

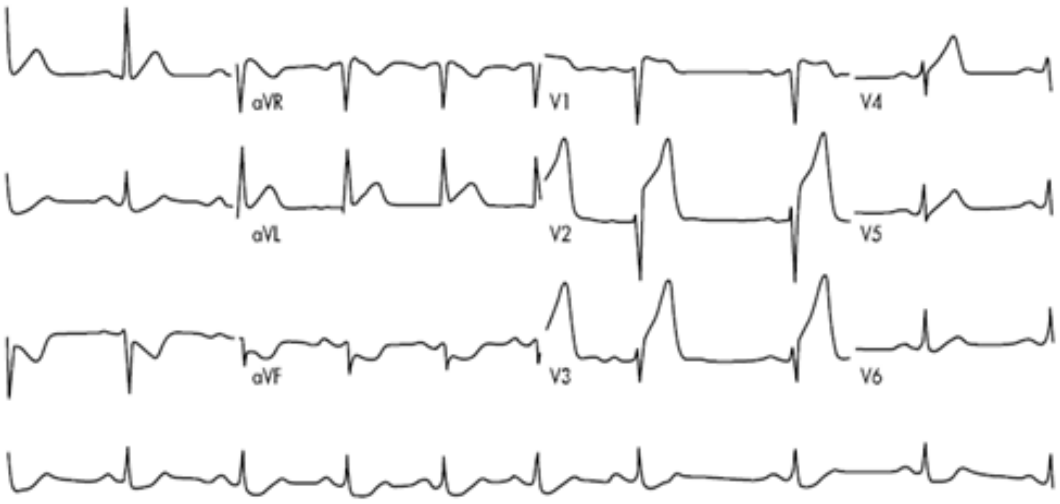


Figure 2. A patient with anterior acute myocardial infarction with grade II ischemia. There is ST elevation in aVL and V1–V4. The J/R ratio is less than 0.5 in aVL (a lead with qR configuration and ST elevation). The S waves in leads V1–V4 are preserved. [21]

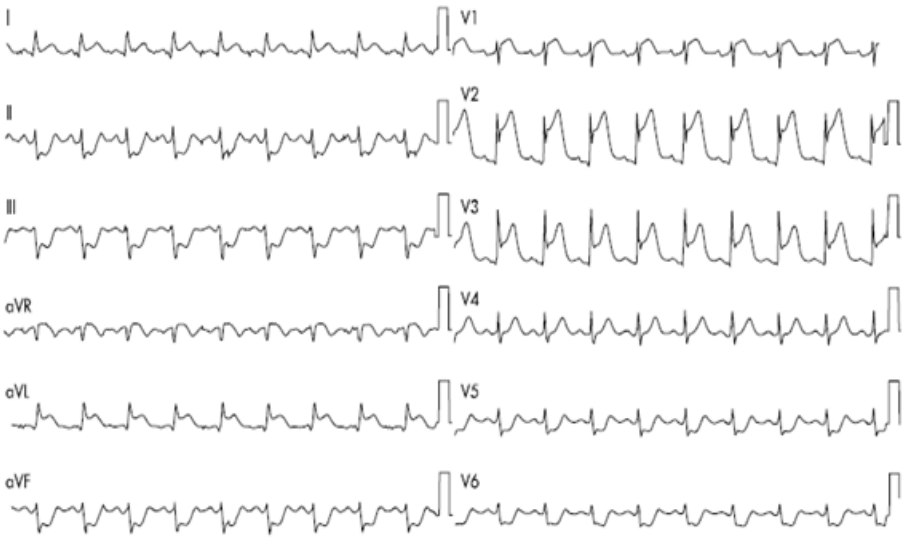


Figure 3. A patient with anterior acute myocardial infarction and grade III ischemia. There is ST elevation in leads I, aVL, V1–V3. There are no S waves in leads V2–V3.[21]

RESULTS

A total of 74 patients were included for initial evaluation in the study between April 2011 and December 2011. Primary PCI was performed in all these patients. However, six (6) patients were excluded from final analysis because of previous PCI (2 patients), planned rescue PCI after thrombolytic therapy (3 patients), and presence of a life-threatening disease (1 patient). ECGs of the 68 patients were assessed for ischemia grade. (*Figure 4)*

There were no significant differences in the baseline characteristics in terms of age, gender, and coronary artery risk factors between patients with GI3 and non-GI3. (*Table 1*) Anterior wall MI resulting from an acute LAD occlusion occurred more frequently than inferior wall MI resulting from either an acute RCA or LCx occlusion. Patients with inferior wall MI was found to have a higher percentage of GI3 on ECG while those with anterior wall MI have a higher percentage of non-GI3 ($p = 0.034$). Myocardial infarction presenting as Killip Class 3 and 4 occurred more frequently in patients with GI3 ($p = 0.001$) as they have significantly lower mean systolic and diastolic blood pressures ($p = 0.001$ and $p = 0.000$, respectively) and unexpectedly lower use of ACE inhibitors ($p = 0.003$). Incidence of cardiogenic shock was also higher among these patients (11 out of 12 cases) which subsequently necessitated use of IABP ($p = 0.006$). Mean value of WBC count and plasma glucose levels were also significantly higher in patients with GI3 ($p = 0.047$ and $p = 0.036$, respectively). Estimation of ischemic area at risk as measured by troponin level release on admission and time to treatment measured by door-to-balloon time was not significantly different between the two groups.

Table 2 shows the pre-revascularization angiographic characteristics of the eligible patients. Quantitative angiographic analysis demonstrated that patients with GI3 had longer lesion lengths ($p = 0.053$) compared to those with non-GI3, but did not differ in terms of incidence of the RLD of the IRA ≥ 4 mm ($p = 0.183$). The combined incidence of pre-revascularization TIMI ≤ 1 in the IRA was 63.2% but was found to be comparable between the two patient groups. The incidence of high-burden thrombus formation was observed in 58.8% of patients but likewise did not significantly differ between the two patient groups. However, it was found to occur in 71.4% of patients with combined GI3 and slow re-flow post-revascularization, and only in 58% of patients with non-GI3. In addition, patients with GI3 have an insignificant trend of having a higher percentage of multi-vessel coronary disease and poor collateral flow to the IRA ($p = 0.084$ and $p = 0.061$, respectively).

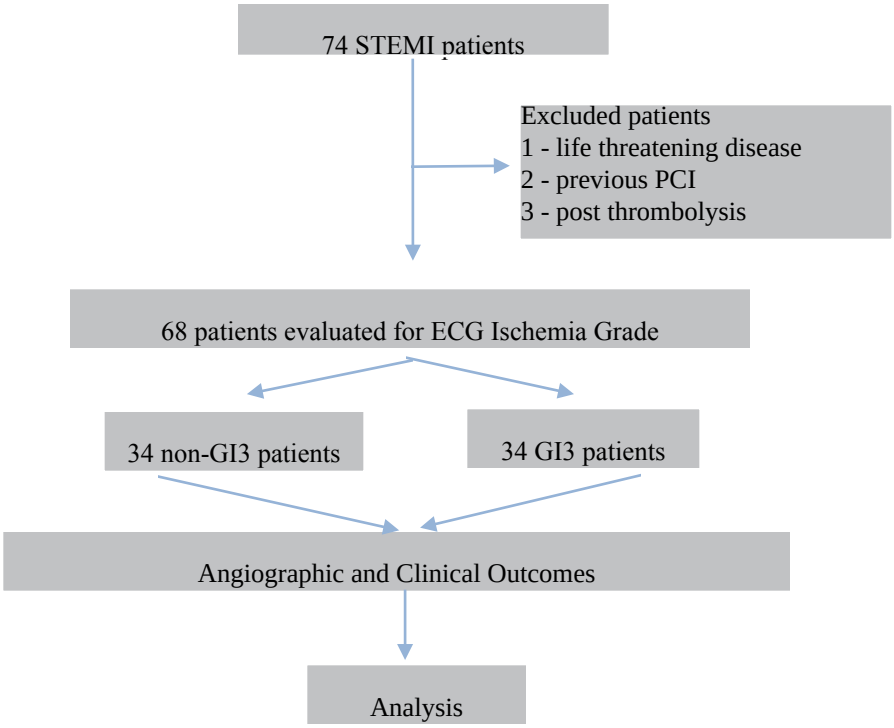


Figure 4. Study Flow Diagram

Table 3 lists the angiographic and in-hospital clinical outcomes after PPCI. Failure to gain re-flow in the IRA occurred in 58.8% (40 patients), including a combined 39.7% with TIMI ≤ 2 flow and 19.1% with TIMI 3 flow but MBG ≤ 1. Grade 3 ischemia is associated with a significantly higher incidence of angiographic no re-flow post-PPCI (p = 0.000). This translated to a higher in-hospital mortality among these patients compared with non-GI3 (26.5% vs. 2.9%, p = 0.013). More cardiac complications were also observed in patients with GI3 than those with non-GI3, particularly heart failure (p = 0.000), malignant arrhythmia (p = 0.000), hemodynamic instability (p = 0.000), and stroke (p = 0.001). The sensitivity, specificity, PPV, and NPV of GI3 were computed (*Table 4*) and showed significant agreement in predicting these outcomes.

DISCUSSION

No re-flow phenomenon is a known condition associated with impaired myocardial perfusion in the absence of a significant epicardial coronary artery obstruction seen in a significant proportion of patients presenting with STEMI undergoing PPCI. Based on some clinical trials, existence of this condition occurs with a prevalence ranging from 5% up to 50% according to the methods used to assess the phenomenon and to the population under study.[24] In our study, we used the angiographic TIMI flow grades and MBG to determine the adequacy of intervention among patients with STEMI. Using these two methods, the CADILLAC trial estimated the proportion of patients who get optimal myocardial reperfusion among those without cardiogenic shock undergoing PPCI was roughly 49%.[25] In our study, the proportion of patients who achieved a TIMI 3 with MBG of 2 or 3 was 41.2%. Successive clinical data have shown that no-reflow is associated with adverse clinical outcomes, opposing the possible benefit of PPCI.[26] Indeed, 60% of patients with no re-flow in our study exhibited early postinfarction complications (arrhythmias, early congestive heart failure, hemodynamic instability) and death. It is therefore imperative that detection, prevention, and ultimately treatment of no-reflow should be an important aspect in the management of STEMI patient undergoing PPCI. The pathogenesis of no re-flow is multifactorial and involves distal embolization, ischemia-reperfusion, and individual predisposi-

tion of coronary microcirculation to injury.[7] Several clinical parameters and biomarkers have been studied and shown to predict risk of no reflow that are related to these different mechanisms. Among these are high thrombus burden, longer time to reperfusion, large extent of ischemic region demonstrated by QRS score and wall motion score index, elevated neutrophil count, acute hyperglycemia, hypercholesterolemia, and lack of pre-infarction angina.[7] In our study, the presence of high thrombus burden, higher WBC count and plasma glucose levels were observed to be highly associated with adverse outcomes.

The ECG is considered to be an appropriate method for risk stratification in patients with reperfusion abnormalities. One of the parameters of interest is the Ischemia Grade, which determines the degree of distortion of the terminal portion of the QRS segment brought about by the amount of disturbance and prolongation in the electrical conduction in the Purkinje fibers in the ischemic region. The prolonged conduction reduces the extent of cancellation, resulting in augmented R wave amplitude in leads with terminal R wave and diminished S wave amplitude in leads with terminal S wave on the surface ECG.

Table 1. Baseline clinical characteristics of patients with STEMI included in the study according to ECG Ischemia Grade (PHC, 2012)

Clinical Characteristics	ECG Ischemia Grade		p-value
	GI1/GI2 (n=34)	GI3 (n=34)	
Age, years (Mean ± SD)	57 ±10	57.4 ± 10	0.146
Female gender (%)	4 (11.8)	10 (29.4)	0.132
Diabetes (%)	7 (20.6)	13 (38.2)	0.183
Arterial Hypertension	24 (70.6)	25 (73.5)	1.000
Smoker (%)	23 (67.6)	23 (67.6)	1.000
Systolic BP, mmHg (Mean ± SD)	128 ± 25	108 ± 21	**0.001**
Diastolic BP, mmHg (Mean ± SD)	81 ±15	68 ± 12	**0.000**
Heart rate, bpm ((Mean ± SD)	76 ±16	78 ± 23	0.777
Infarct localization			
Anterior (%)	28 (82.4)	19 (55.9)	**0.034**
Inferior (%)	6 (17.6)	15 (44.1)	
Killip Class			
1 (%)	23 (67.6)	13 (38.2)	**0.001**
2 (%)	8 (23.5)	4 (11.8)	
3 (%)	2 (5.9)	6 (17.6)	
4 (%)	1 (2.9)	11 (32.4)	
Troponin, U/L (Mean ± SD)	7.2 ± 14.3	11.4 ± 17.5	0.367
WBC count, /mm^3 (Mean ± SD)	12.8 ± 5.3	16 ± 6.8	**0.047**
Plasma glucose, mg/dL (Mean ± SD)	159 ± 69	210 ± 104	**0.036**
Door-to-balloon time, min (Mean ± SD)	196 ± 240	150 ± 89	0.292
Use of Intra-aortic balloon pump (%)	1 (2.9)	10 (29.4)	**0.006**
In-hospital medications			
Beta-blockers (%)	22 (64.7)	14 (41.2)	0.088
ACE-inhibitors or ARB (%)	32 (94.1)	21 (61.8)	**0.003**

The Purkinje fibers are less susceptible to ischemia than the viable myocytes, so for a distortion in the terminal portion of the QRS to occur, there should be a severe and extended period of ischemia involving the Purkinje fibers.[27] Grade III ischemia correlates positively with larger myocardial infarcts and less myocardial salvage than do non-GI3, resulting to a poorer left ventricular ejection fraction. This is related mainly to more severe regional dysfunction in the involved segments and less to the extent of involvement (size of the area at risk). Thus, the difference in infarct size between GI3 and non-GI3 patients can be explained by more severe ischemia and not by larger ischemic area, longer time to reperfusion, and lower rates of myocardial reperfusion.[28] This may partly explain despite the comparable troponin level release on admission, door-to-balloon time, baseline TIMI flow grade ≤1, and high thrombus burden between the two patient groups, patients with GI3 are associated with worse outcomes. Additionally, the absence of changes in the QRS complex during opening of the IRA may be an indication of myocardial protection despite prolonged ischemia (probably by persistent myocardial flow due to subtotal occlusion or collateral circulation, or due to myocardial preconditioning).[27] This explains how patients with GI3 show a higher proportion of multivessel coronary disease and poorer angiographic collateral flow grades.

Table 2. Baseline angiographic characteristics of patients with STEMI included in the study according to ECG Ischemia Grade (PHC, 2012)

Angiographic Characteristics	ECG Ischemia Grade		p-value
	GI1/GI2 (n=34)	GI3 (n=34)	
Infarct Related Artery			0.103
Left Anterior Descending	28 (82.4)	19 (55.9)	
Left Circumflex)	1 (2.9)	2 (5.9)	
Right Coronary	5 (14.7)	13 (38.2)	
High thrombus burden	18 (52.9)	22 (64.7)	0.460
TIMI flow grade ≤ 1 at baseline	21 (61.8)	22 (64.7)	0.329
Collateral flow grade ≤1	20 (58.8)	28 (82.4)	0.061
Multivessel coronary disease)	16 (47.1)	24 (70.6)	0.084
Lesion length ≥ 15mm	21 (61.8)	29 (85.3)	0.053
Initial reference vessel diameter ≥ 4mm	7 (20.6)	13 (38.2)	0.183

Table 3. Angiographic and clinical outcomes after Primary PCI of patients with STEMI included in the study according to ECG Ischemia Grade (PHC, 2012)

Outcomes	ECG Ischemia Grade		p-value
	GI1/GI2 (n=34)	GI3 (n=34)	
Angiographic Outcome (%)			
Reflow after PCI	22(64.7)	6 (17.6)	**0.000**
No re-flow after PCI			
TIMI flow ≤ 2	9 (26.5)	18 (52.9)	**0.000**
TIMI flow = 3 with MBG ≤ 1	3 (8.8)	10 (29.4)	
Clinical Outcome (%)			
Death	1 (2.9)	9 (26.5)	**0.013**
Composite Secondary Endpoint	7 (20.6)	23 (67.6)	**0.000**
Heart Failure	4 (11.8)	19 (55.9)	**0.000**
Malignant arrhythmia	4 (11.8)	19 (55.9)	**0.000**
Hemodynamic instability	5 (14.7)	22 (64.7)	**0.000**
Ischemic stroke	0	7 (20.6)	**0.011**

Table 4. Sensitivity, Specificity, PPV, and NPV of Grade 3 ECG Ischemia Grade in determining outcome of patients with STEMI included in the (PHC, 2012)

Outcome (%)	Sensitivity	Specifity	PPV	NPV	Kappa	p-value
No re-flow	70.0	78.6	82.4	64.7	0.471 ± 0.119	**0.000**
Death	90.0	56.9	26.5	97.1	0.235 ± 0.086	**0.000**
Heart Failure	82.6	66.7	55.9	88.2	0.441 ± 0.115	**0.006**
Arrhythmia	82.6	66.7	55.9	88.2	0.441 ± 0.115	**0.000**
Hemodynamic instability	81.5	70.7	64.7	85.3	0.500 ± 0.119	**0.000**
Stroke	100.0	55.7	20.6	100.0	0.206 ± 0.074	**0.004**

CONCLUSION

ECG ischemia grade on admission can be a predictive tool of adverse clinical and angiographic outcomes associated with abnormalities of myocardial reperfusion. It is possible that patients with GI3 who will undergo PPCI will benefit further if angiographic no re-flow can be prevented and treated.

REFERENCES

1. Canadian Cardiovascular Society; American Academy of Family Physicians; American College of Cardiology; American Heart Association, Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, Hochman JS, Krumholz HM, Lamas GA, Mullany CJ, Pearle DL, Sloan MA, Smith SC Jr, Anbe DT, Kushner FG, Ornato JP, Pearle DL, Sloan MA, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B, Tarkington LG, Yancy CW. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2008 Jan 15;51(2):210-47.
2. Morishima I, Sone T, Okumura K, Tsuboi H, Kondo J, Mukawa H et al. Angiographic no-reflow phenomenon as a predictor of adverse long-term outcome in patients treated with percutaneous transluminal coronary angioplasty for first acute myocardial infarction. J Am Coll Cardiol. 2000 Oct;36(4):1202-9.
3. Ito H, Maruyama A, Iwakura K, Takiuchi S, Masuyama T, Hori M et al. Clinical implications of the 'no reflow' phenomenon. A predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. Circulation. 1996 Jan 15; 93(2): 223-8.
4. Morishima I, Sone T, Okumura K, Tsuboi H, Kondo J, Mukawa H, et al. Angiographic no-reflow phenomenon as a predictor of adverse long-term outcome in patients treated with percutaneous transluminal coronary angioplasty for first acute myocardial infarction. J Am Coll Cardiol. 2000 Oct;36(4):1202-9.
5. Suenari K Shiode N, Shirota K, Ishii H, Goto K, Sairaku A, et al. Predictors and long-term prognostic implications of angiographic slow/no-flow during percutaneous coronary intervention for acute myocardial infarction. Intern Med. 2008;47(10):899-906.
6. Ndrepepa G, Tiroch K, Keta D, Fusaro M, Seyfarth M, Pache J, et al. Predictive factors and impact of no reflow after primary percutaneous coronary intervention in patients with acute myocardial infarction. Circ Cardiovasc Interv. 2010 Feb 1;3(1):27-33.
7. Niccoli G, Burzotta F, Galiuto L, Crea F. Myocardial no-reflow in humans. J Am Coll Cardiol. 2009 Jul 21;54(4):281-92.
8. Johanson P. Electrocardiogram dynamics for risk stratification in ST-segment elevation myocardial infarction--immediate and serially updated information on outcome. J Electrocardiol. 2006 Oct;39(4 Suppl) :S75-8.
9. Buber J, Gilutz H, Birnbaum Y, Friger M, Ilia R, Zahger D. Grade 3 ischemia on admission and absence of prior beta-blockade predict failure of ST resolution following thrombolysis for anterior myocardial infarction. Int J Cardiol. 2005 Sep 30;104(2):131-7.
10. Wolak A, Yaroslavtsev S, Amit G, Birnbaum Y, Cafri C, Atar S et al. Grade 3 ischemia on the admission electrocardiogram predicts failure of ST resolution and of adequate flow restoration after primary percutaneous coronary intervention for acute myocardial infarction. Am Heart J. 2007 Mar;153(3):410-7.
11. Ghaffari S, Ghaffari MR, Sorkhab SSF. Does Grade 3 Ischemia on admission electrocardiogram predict the ST segment resolution following thrombolysis in ST elevation myocardial infarction? J Cardiovasc Thorac Res 2010; 2(2):5-10.
12. Billgren T, Birnbaum Y, Sgarbossa EB, Sejersten M, Hill NE, Engblom H. Refinement and interobserver agreement for the electrocardiographic Sclarovsky-Birnbaum Ischemia Grading System. J Electrocardiol. 2004 Jul;37(3):149-56.

13. Birnbaum Y, Kloner RA, Sclarovsky S, Cannon CP, McCabe CH, Davis VG, et al. Distortion of the terminal portion of the QRS on the admission electrocardiogram in acute myocardial infarction and correlation with infarct size and long-term prognosis (Thrombolysis in Myocardial Infarction 4 Trial). Am J Cardiol. 1996 Aug 15;78(4):396-403.
14. Birnbaum Y, Herz I, Sclarovsky S, Zlotikamien B, Chetrit A, Olmer L, et al. Prognostic significance of the admission electrocardiogram in acute myocardial infarction. J Am Coll Cardiol. 1996 Apr;27(5):1128-32.
15. Lee CW, Hong MK, Yang HS, Choi SW, Kim JJ, Park SW et al. Determinants and prognostic implications of terminal QRS complex distortion in patients treated with primary angioplasty for acute myocardial infarction. Am J Cardiol. 2001 Aug 1;88(3):210-3.
16. Tamura A, Nagase K, Watanabe T, Nasu M. Relationship between terminal QRS distortion on the admission electrocardiogram and the time course of left ventricular wall motion in anterior wall acute myocardial infarction. Jpn Circ J. 2001 Feb;65(2):63-6.
17. Sejersten M, Birnbaum Y, Ripa RS, Maynard C, Wagner GS, Clemmensen P; DANAMI-2 Investigators. Influences of electrocardiographic ischaemia grades and symptom duration on outcomes in patients with acute myocardial infarction treated with thrombolysis versus primary percutaneous coronary intervention: results from the DANAMI-2 trial. Heart. 2006 Nov;92(11):1577-82.
18. Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. J Am Coll Cardiol. 1985 Mar;5(3):587-92.
19. Hermiller JB, Cusma JT, Spero LA, Fortin DF, Harding MB, Bashore TM. Quantitative and qualitative coronary angiographic analysis: review of methods, utility, and limitations. Cathet Cardiovasc Diagn. 1992 Feb; 25(2):110-31.
20. Vicente FR, Dy BY. In-hospital outcome after an acute myocardial infarction: The Primary Angioplasty with or without Stenting in Acute Myocardial Infarction (PASA-MI Study) Philippine Heart Center, 2000. [Unpublished work].
21. Birnbaum Y, Drew BJ. The electrocardiogram in ST elevation acute myocardial infarction: correlation with coronary anatomy and prognosis. Postgrad Med J. 2003 Sep;79(935):490-504.
22. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. N Engl J Med. 1985 Apr 4;312(14):932-6.
23. van't Hof AW, Liem A, Suryapranata H, Hoorntje JC, de Boer MJ, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Zwolle Myocardial Infarction Study Group. Circulation. 1998 Jun 16;97(23):2302-6.
24. Rezkalla SH, Kloner RA. Coronary no-reflow phenomenon: from the experimental laboratory to the cardiac catheterization laboratory. Catheter Cardiovasc Interv. 2008 Dec 1;72(7):950-7.
25. McLaughlin MG, Stone GW, Aymong E, Gardner G, Mehran R, Lansky AJ, et al. Prognostic utility of comparative methods for assessment of ST-segment resolution after primary angioplasty for acute myocardial infarction: the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. J Am Coll Cardiol. 2004 Sep 15;44(6):1215-23.
26. Gibson CM, Cannon CP, Murphy SA, Marble SJ, Barron HV, Braunwald E; TIMI Study Group. Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary intervention to long-term outcomes after thrombolytic administration in acute myocardial infarction. Circulation. 2002 Apr 23;105(16):1909-13.
27. Holland RP, Brooks H. The QRS complex during myocardial ischemia. An experimental analysis in the porcine heart. J Clin Invest. 1976 Mar;57(3):541-50.
28. Birnbaum Y, Criger DA, Wagner GS, Strasberg B, Mager A, Gates K, et al. Prediction of the extent and severity of left ventricular dysfunction in anterior acute myocardial infarction by the admission electrocardiogram. Am Heart J. 2001 Jun;141(6):915-24.

Conventional Coronary Stenting Versus Direct Coronary Stenting in Coronary Artery Disease Patients Undergoing Elective Percutaneous Transluminal Coronary Angioplasty: a Philippine Heart Center Experience

Dodee Niño V. Rigor, MD; Ronaldo H. Estacio, MD; Melquides Pua, MD

Background --- Coronary stent implantation is being performed in stenosed coronary artery with long term outcome improvements and improvement of the patency in treated vessels. Conventional coronary stenting includes standard balloon angioplasty (predilation) followed by stent deployment. Stenting without predilation with balloon is termed direct coronary stenting. This approach help reduce procedure time, cost, reduced risk of extended dissections, radiation exposure, reduce vessel trauma and lessen neointimal hyperplasia which can lower the incidence of subsequent restenosis. With these, direct stenting is now the primary therapeutic option for many coronary lesions.

Methods --- Patients with stable coronary artery disease (CAD) who underwent elective single stent implantation in a native coronary artery between January to November 2011 at the Philippine Heart Center were included in the study. In-hospital as well as 1 month follow-up of major adverse cardiovascular and cerebrovascular events (MACCE) were noted and compared between the two groups.

Results --- A total of 229 patients, 129 in the direct stent group and 100 for the conventional group, were included in the study. There was no significant difference in the demographic, angiographic, and procedural characteristics between the two groups except for stent stenosis before the procedure, stent length, and maximum inflation pressure. Adjustment for covariates between these three parameters did not show any significant difference in terms of outcome. Angiographic success based on residual stenosis was comparable between the two strategies. In-hospital and 1 month MACCE were similar in both groups.

Conclusions --- Compared to conventional stenting, direct stenting is a safe and feasible procedure in selected coronary lesions in terms of angiographic success based on residual stenosis and in-hospital and 1 month MACCE. ***Phil Heart Center J 2014;18(1):39-44.***

Key Words: Conventional Stent ■ Direct Stent ■ Coronary Artery Disease

Percutaneous Transluminal Coronary Angioplasty (PTCA) nowadays is being used for various coronary lesions.[1] An increasing number of coronary stent implantation is being performed in stenosed coronary artery lesions and several studies showed favorable results with this technique which includes long term outcome improvements and improvement of the patency in treated vessels.[1,2] However, overall procedural expenses and prolonged exposure time to radiation for both the operator and patients, and the increase in the amount of contrast agent used have raised some concerns about this procedure. Conventional coronary stenting includes standard balloon angioplasty (predilation) followed by stent deployment.[2,3] This is because of the large profile, limited securement, and low balloon burst pressure of early stent designs.[3] Simplification of this procedure is achieved by the availability of a low profile stent delivery system, better securement, and higher rated burst pressure, thereby avoiding the use of predilation.[2,3] Stenting without predilation with balloon is termed direct coronary stenting. This may help reduce procedure time, cost, reduced risk of extended dissections, and radiation

Finalist, Poster Presentation, 20thPHC Annual Research Paper Competition held on February 23, 2012 at Philippine Heart Center,
Correspondence to Dodee Niño V. Rigor, MD, Division of Adult Cardiology . Philippine Heart Center, East Avenue, Quezon City, Philippines 1100
Available at **http://www.phc.gov.ph/journal/publication** ISSN 0018-9034

exposure.[1-3] This could also reduce vessel trauma and lessen neointimal hyperplasia which can lower the incidence of subsequent restenosis.[3-5] A number of randomized studies have demonstrated that direct stenting is feasible in 28-72% of coronary lesions resulting in fewer use of resources and with note of early and late outcomes as compared with conventional stenting provided that careful lesion selection is done.[6] With these, direct stenting is now the primary therapeutic option for many coronary lesions.[1]

This study was done to compare the efficacy of direct coronary stenting as compared to conventional coronary stenting in patients with coronary artery disease undergoing PTCA.

METHODOLOGY

This is a prospective, cohort study done at the Philippine Heart Center involving consecutive patients who underwent PTCA with stent implantation in the Philippine Heart Center cardiac catheterization laboratory from January 2011 to November 2011. Included were male or female subjects aged 21 years and older with known coronary artery disease who underwent elective PTCA and with the following angiographic characteristics: coronary lesion with an obstructive lesion ≥ 70%; native coronary lesion with a diameter between 2.5 to 4.0mm; and native coronary lesion requiring only 1 stent. Excluded were those with: left main disease; acute and recent (<72 hours) myocardial infarction; evidence of lesion-associated thrombus; totally occluded lesions; marked tortuosity; in-stent restenosis lesion; previous history of revascularization; multi-vessel PCI and heavily calcified lesions.

Demographic data, angiographic and procedural characteristics were assessed using hospital records, peri-operative records, and electronic data. In-hospital major adverse cardiac and cerebrovascular event (MACCE) which includes death, acute myocardial infarction, post-procedural complications requiring emergency CABG (coronary perforation, cardiac tamponade etc.), acute thrombosis or restenosis and cerebrovascular disease were assessed. Follow-up assessment was done by OPD consults, clinic records, direct interview with their respective attending physician/angiographers, hospital records, and electronic data 1 month after hospital discharge.

Sample Size: Sample size computed was n=63 for each group or a total of 126 based on 95% CI (alpha=0.05), 80% power (beta=0.20), and assumed clinical end point of 16.7% with direct stenting and 40.8% with conventional stenting as presented in the paper of Okmen et. al.[8]

Statistical analysis: Data summaries were carried out using mean and standard deviation or frequency and percent. Comparisons of numerically continuous data were analyzed using independent T-test while Fisher exact test was utilized for categorical data. Analysis of COVARIANCE was used to determine the independent effect of the mode of stent delivery with the outcome. A two-tailed p-value of < 0.05 was considered statistically significant.

RESULTS

A total of 229 patients with stable coronary artery disease who underwent elective PTCA during January 2011 to November 2011 at the Philippine Heart Center were included in the study.

Baseline characteristics of the patients in the two groups were described in Table I. There was no significant difference in the mean age, gender, history of ACS, hypertension, diabetes, dyslipidemia, CVD, and smoking between the two groups. The population is composed predominantly of males with 75% (172) of the whole study population (229).

Angiographic and procedural characteristics were described in Tables 2 and 3. Single vessel diseased was the most number included in the study (88%). There was no significant difference in the number of diseased vessels between the two study population. LAD was the most common artery that was stented in this study followed by the RCA.

Proximal and the mid segment of the vessel was the most common site where the stent was deployed. However, there was no significant difference in terms of coronary artery stented and lesion site when compared between the two groups. Drug-eluting stents were used more often as compared to bare metal stents in this study. There was no significant difference in the stent size used between the two groups. The use of balloon to post dilate the deployed stent with residual stenosis showed no significant difference in both interventions. There was less severe preprocedural stenosis (78.91 ± 8.908% vs. 88.54 ± 9.091%, $p < 0.001$) in the direct stenting group. Residual diameter stenosis after stent deployment was similar between the two groups. No residual stenoses were noted on both groups after balloon dilatation post stenting. Longer stents were noted to be utilized more in the conventional stenting group (25.00 ± 7.569 mm vs. 21.46 ± 7.50 mm, $p = 0.001$). Maximal inflation pressure were also noted to be significantly different between the two groups (15.36 ± 2.915 atm vs. 14.36 ± 2.956 atm, $p = 0.011$).

Table 1. Baseline characteristics of patients included in the study

Characteristics	Direct Stenting N = 129	Conventional Stenting N = 100	p-value
Age, mean ± SD (yrs)	58.92 ± 10.915	59.015 ± 10.238	0.951
Gender			0.442
Male	94 (73)	78 (78)	
Female	35 (27)	22 (22)	
Medical History			
ACS	49 (38)	37 (37)	0.892
Hypertension	89 (69)	74 (74)	0.436
Diabetes	37 (29)	27 (27)	0.882
Dyslipidemia	70 (54)	45 (45)	0.184
CVD	6 (5)	3 (35)	0.725
Smoking	62 (48)	41 (41)	0.349

Table 2. Baseline Angiographic Characteristics of patients of the study population

Characteristics	Direct Stenting N %	Conventional Stenting N %	p-value
No. of diseased vessels			0.462
1	113 (88)	89 (89)	
2	11 (8)	5 (5)	
3	5 (4)	6 (6)	
Coronary artery stented			
LAD	85 (66)	65 (65)	0.999
LCx	9 (7)	10 (10)	0.561
RCA	27 (21)	21 (21)	0.880
Diagonal	0 (0)	0 (0)	0.000
OM	5 (4)	3 (3)	1.000
RPDA	0 (0)	1 (1)	0.437
RPL	3 (3)	0 (0)	0.259
Lesion site			0.858
Ostial	6 (5)	4 (4)	
Proximal	60 (46)	48 (48)	
Mid	57 (44)	41 (41)	
Distal	6 (5)	7 (7)	
Percent stenosis before procedure ± SD (%)	78.91 ± 8.908	88.54 ± 9.091	**0.00**

***LAD = left anterior descending artery; LCx = left circumflex artery; RCA = right coronary artery; OM = obtuse marginal; RPDA = right posterior descending artery; RPL = right postero-lateral branch

Table 3. Procedural Characteristics of the study population

Characteristics	Direct Stenting N % n=129	Conventional Stenting N % n=100	p-value
Stent type			0.780
DES	121 (94)	95 (95)	
BMS	8 (6)	5 (5)	
Stent Length ± SD (mm)	21.46 ± 7.509	25.00 ± 7.569	**0.001**
Stent Size ± SD (mm)	3.10 ± 0.450	3.32 ± 2.726	0.390
Maximal Inflation pressure Stent Length ± SD (atm)	15.36 ± 2.915	14.36 ± 2.956	**0.011**
Percent stenosis after stent ± SD (%)	3.10 ± 7.049	2.30 ± 5.835	0.288
Balloon dilatation after stenting	25 (19%)	16 (16%)	0.603

***DES** = drug-eluting stent; **BMS** = bare metal stent

Table 4. Post-Procedural Complications after PTCA

Characteristics	Direct Stenting N % n=129	Conventional Stenting N % n=100	p-value
Death			
In-hospital	0 (0)	2 (2)	0.190
1 month	2 (1.6)	1 (1)	1.000
Total	2 (1.6)	3 (3)	0.656
Myocardial Infarction			
In-hospital	0 (0)	0 (0)	
1 month	2 (1.6)	0 (0)	0.506
Total	2 (1.6)	0 (0)	0.506
Emergency CABG*			
In-hospital	0 (0)	0 (0)	
1 month	0 (0)	0 (0)	
Total	0 (0)	0 (0)	
CVD			
In-hospital	1 (0.8)	1 (0.8)	1.000
1 month	1 (0.8)	1 (0.8)	1.000
Total	2 (1.6)	2 (1.6)	1.000
Composite endpoints	4 (3.1)	4 (4.0)	0.732

- CABG = Coronary artery bypass graft
- *post procedural complications requiring emergency CABG
- CVD = cerebrovascular disease

Post-procedural complications after PTCA were described in Table 4. There were no in-hospital mortality noted in the direct stenting group as compared to the conventional stenting with two (2%) recorded fatalities. None of the patients in conventional group suffered from myocardial infarction during the admission and follow-up as compared to the direct stenting group who had two (1.6%) recorded event within the one month follow-up. However, there was no significant difference noted in mortality and risk for myocardial infarction between both groups during the hospital stay and within the 1 month follow-up. There was no reported case of patients requiring emergency CABG/ repeat PTCA during the whole study period. There is similar risk of developing CVD and composite endpoints between the two groups that were studied. Adjustments for covariates were analyzed between the significant variables (maximal inflation, diameter before, and stent length) and results did not show any significant difference between the two groups in terms of overall death, MI, CVD, and composite outcomes.

DISCUSSION

Direct stenting is a widely acceptable interventional approach in a wide spectrum of coronary lesions because of the availability of more deliverable stents, with improved stent designs, lower profile, and greater navigability which simplified the implantation procedure.[9-11] This approach was also noted to be feasible, safe, and effective.[12] Potential benefits of this interventional strategy includes avoidance of abrupt vessel closure after balloon predilatation, reduction of embolization of debris, and decreased restenosis rate due to reduced injury to the arterial wall.[13] Additional benefits include reduced length of ischemia, reduction in costs, less procedural time, and less radiation exposure.[2,11] Two potential risks of this procedure were incomplete stent expansion and stent dislodgement; however, due to the technological advancement in stent design and fixation by the balloon, the occurence of these events is very low.[14]

Procedural approach in this study was performed at the discretion of the interventional cardiologist/operator. Direct stenting group has a lower preprocedural stenosis in this study. This could reflect the concern of the operator that tighter stenosis may be more difficult to cross without balloon predilatation and thus may lead to a greater risk of stent dislodgement from the delivery balloon.[10] Thus, more operator preferred the conventional approach when dealing with tight lesion especially those with > 90% stenosis.

Direct stenting decreases the incidence of myocardial injury but this was not shown in this study. In fact, there are two patients who suffered myocardial infarction in this group as compared to the conventional group. However, this was noted to be not statistically significant.

The absence of effect of direct stenting on in-hospital and overall 30-day composite endpoint rate of 3.1% (4 events) is concordant with results of other previous studies (2.5%-5.1%).[13-15] This study also showed no difference in the angiographic and clinical parameters in between both treatment strategy making direct stenting strategy an acceptable approach to selected coronary lesions.

CONCLUSION

This study showed that in-hospital and 30-day clinical outcomes in patients undergoing elective PTCA are equivalent using the direct stenting approach as compared with the more conventional technique. Angiographic success based on residual stenosis was also comparable between the two strategies. This study also showed that direct stenting is a safe and feasible procedure in selected coronary lesions.

Limitations of the study: The selection of the interventional approach in this study was mostly based on operator's discretion/experience. Also, pre- and post-procedural (residual) stenosis was based on visual estimate and not on Quantitative Coronary Angiographic (QCA) Assessment. Furthermore, data for those patients who were initially planned to undergo direct stenting but converted to conventional approach due to intra-procedural difficulties were not noted making assumption for success rate of direct stenting difficult.

REFERENCES

1. Nazeri I, Nazeri A, Shokoufi-Moghiman S. Direct coro nary stenting without predilatation in selected patients with significant coronary artery disease. Arch Iranian Med. 2005;8(3):202-205.
2. Briguori C, Sheiban I, De Gregorio J, Anzuini A, Montorfano M, Pagnotta P, et al. Direct coronary stenting without predilation. J Am Coll Cardiol. 1999 Dec; 34(7):1910-5.
3. Baim DS, Flatley M, Caputo R, O'Shaughnessy C, Low R, Fanelli C, et al. Comparison of PRE-dilatation vs direct stenting in coronary treatment using the Medtronic AVE S670 Coronary Stent System (the PREDICT trial). Am J Cardiol. 2001 Dec 15;88(12):1364-9.
4. Kocum T, Yurtdas M, Ozcan T, Akcay B, Erol T, Camsari A, et al. Direct stenting versus predilatation and stenting technique when using paclitaxel-eluting stents. Int Heart J. 2008 Sep;49(5):545-52.
5. Baim, DS. Grossman's cardiac catheterization, angiograpy, and intervention. 7th ed. PA: LWW, 2005.
7. Loubeyre C, Morice MC, Lefèvre T, Piéchaud JF, Louvard Y, Dumas P. A randomized comparison of direct stenting with conventional stent implantation in selected patients with acute myocardial infarction. J Am Coll Cardiol. 2002 Jan 2;39(1):15-21.

8. Okmen E, Cam N, Sanli A, Yapici F, Uyarel H, Vural M et al. Effects of direct stent implantation and conventional stent implantation on minor myocardial injury. Angiology. 2004 Sep-Oct;55(5):485-91. 9.
Masood T, Sagheer T, Jan D, Qamar N, Faruqui AM. Experience of direct coronary stenting at National Institute of Cardiovascular Diseases. J Pak Med Assoc. 2002 Aug;52(8):338-41.
10. Wilson SH, Berger PB, Mathew V, Bell MR, Garratt KN, Rihal CS, et al. Immediate and late outcomes after direct stent implantation without balloon predilation. J Am Coll Cardiol. 2000 Mar 15;35(4):937-43.
11. Martínez-Elbal L, Ruiz-Nodar JM, Zueco J, López-Minguez JR, Moreu J, Calvo I, et al. Direct coronary stenting versus stenting with balloon pre-dilation: immediate and follow-up results of a multicentre, prospective, randomized study. The DISCO trial. DIrect Stenting of COronary Arteries. Eur Heart J. 2002 Apr;23(8):633-40.
12. Brueck M, Scheinert D, Wortmann A, Bremer J, von Korn H, Klinghammer L, et al. Direct coronary stenting versus predilatation followed by stent placement. Am J Cardiol. 2002 Dec 1;90(11):1187-92.
13. Rensing, B. Direct stenting study with the Orbus R stent Trial. The Director Trial. A controlled, Prospective, Multicenter registry Trial. Sint Antonius Ziekenhuis Nieuwegein, The Netherlands, May 2004
14. López-Palop R1 Pinar E, Lozano I, Carrillo P, Cortés R, Saura D, et al. [Comparison of intracoronary ultrasound expansion parameters in coronary stents implanted with or without balloon predilatation. A randomized intravascular ultrasound study].Rev Esp Cardiol. 2004 May;57(5):403-11.
15. Jsselmuiden A, Serruys P, Tangelder G, Slagboom T, van der Wieken R, Kiemeneij F, et al. Safety, efficacy and costs associated with direct coronary stenting compared with stenting after predilatation: A randomised controlled trial. Neth Heart J. Aug 2004; 12(7-8): 323–330.

Association of Severity of Sleep Apnea Syndrome with Driving Accidents

Irenee Faustina J. Casino, MD; Ma. Encarnita B. Limpin, MD; Aileen G. Banzon, MD;
Joseph Hope, Cal MD; Teresita Celestina S. Fuentes, MD

Background --- Sleepiness and reduced vigilance are important risk factors for road accidents. In the Philippines, accidents were caused by driver error, drunk driving, vehicle mechanical defects, speeding, and use of cell phone while driving represented the highest increase among causes of vehicular accidents. No data on sleep related disorder was presented as one of the causes of vehicular accidents. It is the goal of this paper to determine if the severity of sleep apnea is a factor contributing to the incidence of vehicular accidents among patients diagnosed with obstructive sleep apnea in Philippine Heart Center Sleep Clinic.

Methods --- A cross sectional study was done on patients diagnosed with sleep apnea syndrome from January 2005 up to December 2011 in the Philippine Heart Center Sleep Clinic through polysomnography. They were interviewed regarding driving and driving accidents.

Results --- There were 361 patient drivers included in the study. Among these patient drivers, 62 (17%) were noted to have mild sleep apnea syndrome, 63 (17.45%) were moderate SAS and 236 (65.37%) severe SAS patients. It was noted that the driving accidents tend to increase in number as the severity of SAS increases (mild SAS= 48.38% (30/58), moderate SAS=52.38% (33/63), severe SAS=58.47% (138/236). However, the incidence of driving accidents across the 3 groups of SAS did not differ significantly. Majority of the SAS patients gave "sleepiness" as the reason in 86.06% of the respondents. Other causes were "not following traffic rules" in 12.94%, alcohol intake (8.96%), attributed to other's fault in 6.97%, personal human error (4.97%) and cell phone use (0.5%). By statistical analysis, the reasons of driving accidents were not significantly associated to the severity of SAS.

Conclusions --- The study showed that driving accidents occurred more than 50% of SAS patients regardless whether the severity was mild, moderate or severe. The incidence of driving accidents tends to increase with increasing severity of SAS. This, however, was not statistically significant. ***Phil Heart Center J 2014;18(1):45-51.***

Key Words: Driving Accidents ■ Sleep Apnea Syndrome

Driving is a skilled task that requires sustained vigilance if accidents are to be avoided. Sleepiness and reduced vigilance are important risk factors for road accidents.[1-4.] The available data regarding the incidence of sleepiness vary considerably in different countries.[1,3] Risks for drowsy-driving crashes include sleep loss, nighttime or early morning driving, use of sedating medications, and untreated sleep disorders such as sleep apnea syndrome and narcolepsy.

In the Philippines, it was reported in the Philippine Daily Inquirer Archives-Metro Manila Accident and Analysis System (MMARAS 2010)[5] that the total number of vehicular crashes was 14,847 with 380 total number of fatal road accidents from January 2010-October 2010. The report included that the traffic accidents were caused by driver errors.

It is the goal of this paper to determine if the severity of sleep apnea is a factor contributing to the incidence of vehicular accidents among patients diagnosed with obstructive sleep apnea in Philippine Heart Center Sleep Clinic from January 2005-December 2011.

The total number of vehicular crashes in the Philippines from January 2010-October 2010

Finalist, Oral Presentation, 20th PHC Annual Research Paper Competition held on February 23, 2012 at Philippine Heart Center. Presented during the 31st Annual Chest Convention, Poster Presentation, Shangrila Hotel, March 2012. *Correspondence to* ***Dr. Irenee Faustina Casino,*** Division of Pulmonary and Critical Care Medicine. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication** ISSN 0018-9034

was 14,847 with 380 fatal road accidents as reported in the Philippine Daily Inquirer Archives -Metro Manila Accident and Analysis System (MMARAS 2010).[5] Accidents were caused by driver error, drunk driving, vehicle mechanical defects, speeding, and use of cell phone while driving that represented the highest increase among causes of vehicular accidents. No data on sleep related disorder was presented as one of the causes of vehicular accident.[5]

The National Center on Sleep Disorders Research (NCSDR) of the National Heart, Lung, and Blood Institute (NHLBI) of the National Institute of Health (NIH) and National Highway Traffic Safety Administration (NHTSA) Expert Panel on Driver Fatigue and Sleepiness in USA noted that untreated sleep disorders are risks for driving crashes.[5]

In a study by G. Maycock in 1997 among drivers, 7% of accident involvement was associated with tiredness and the accident liability is shown to be sensitive to daytime sleepiness.[6]

A survey by Ned Carter et al. on general population with regard to sleep habits and driving of motor vehicles showed the proportion of total accidents was higher among professional drivers as compared with males in the general population. When sleep study was done, quite a number (17%) of those examined received the diagnosis of obstructive sleep apnea.[7]

A cross-sectional study conducted in 2004 by Fabrio et al. supported by the Italian Ministry of Education among students 18-21 years old with 58% male reported that adolescent drivers were twice as likely to have a crash if they experienced sleepiness while driving (adjusted odds ratio 2.1) or reported having bad sleep (odds ratio 0.9). There were 80 out of 339 students who crashed at least once and 15% of them considered sleepiness to have been the main cause of the crash.[8]

In Canada, a study by Moller of University Health Network and University of Toronto Sleep Research Unit noted that driver fatigue contributes to death of Canadians every year. In 2005, through a survey, 1 out of 5 Canadians admitted to nodding off or falling asleep while driving at least once in the previous 12 months.[9]

Data from New Zealand showed that 370 heavy motor vehicle crashes in 1997 found that driver fatigue was listed as a contributing factor in 7% of accidents. In 2006, at least 40 people lost their lives while almost 1000 people were injured because they or the drivers were in fatigue.[10] An Australian study reported 20-30% of heavy vehicle crashes to be sleep-related.[11]

In Spain, Teran-Santos et al. showed that patients with apnea-hypopnea index of 10 or higher had an odds ratio of 6.3 (95% confidence interval, 2.4 to 16.2) for having a traffic accident, after adjusting for potential confounders such as alcohol consumption, visual-refraction, history pertaining to the traffic accidents, medications causing drowsiness, and sleep schedule of the drivers.[12]

Horstmann et al. studied sleepiness-related accidents in sleep apnea patients. They reported that patients with moderate to severe sleep apnea syndrome (SAS) with Apnea-Hypopnea Index (AHI) >34/hr) were more often involved in motor vehicle accidents than those with mild sleep apnea syndrome.[13].

METHODOLOGY

A cross sectional study was done on patient drivers diagnosed with sleep apnea syndrome from January 2005 up to December 2011 in the Philippine Heart Center Sleep Clinic through polysomnography. Excluded were patients below 18 years old and patients who had symptoms of sleep apnea but polysomnography result was normal. The sample size computed was $n > 87$ based on 95% confidence interval, relative error of 20% and assumed rate of accident among sleep apnea syndrome patients of 65.6% as presented in the paper of Teran-Santos.[12] In this study, a total of 361 patients was included. Baseline characteristics – name, age, sex, address, telephone number, civil status, occupation, smoking history, alcohol intake history, intake of caffeinated drinks, other medical conditions, Epworth Sleepiness Scale (ESS) were recorded. The patients and their significant other were contacted by telephone or personal interviews. Questions to be asked pertaining to driving and driving accident were

adapted and modified from the papers of G. Maycock[6] and Carter et al.[7] that included the type of vehicle used, number of years driving, number of driving hours per day, time of driving, sleepiness while driving, number of accidents the patient had before he was diagnosed with SAS. The questionnaire was piloted among patients diagnosed to have sleep apnea syndrome patients in the sleep clinic with utmost confidentiality observed. Outcome measured included incidence of driving accidents and its association with the severity of sleep apnea syndrome. Written informed consent was obtained from the patients, and the study was approved by the Institutional Ethics Review Board (IERB).

RESULTS

There were 361 patient drivers included in the study. Table 1 showed the baseline characteristics of patients by SAS severity. Among these patient drivers, 62 (17%) were noted to have mild sleep apnea syndrome, 63 (17.45%) were moderate SAS and 236 (65.37%) severe SAS patients. Majority were males (325/361) and married (293/361). Most of them had history of smoking (58%) and had co-morbidities (64.8%). The co-morbidities reported were hypertension, coronary artery disease, diabetes, aortic aneurysm, asthma, chronic obstructive lung disease and thyroid problems. More than half of them were taking caffeine-containing drinks. The average Epworth Sleepiness Score was 11.95 ± 5.27 in mild SAS, 13.62 ± 12.01 in moderate SAS and 13.64 ± 5.57 in severe SAS which is comparable across the 3 groups.

The other baseline characteristics of patients are comparable except for: (1) coffee drinking with patients with severe SAS drinking more coffee compared to those with lower SAS severity (p=0.005); (2) BMI with those with severe SAS having BMI compared to those with lower SAS severity (p=0.031); (3) neck circumference in which patients with higher severity having bigger neck circumference (p=0.024); and, (4) number of years driving with patients with severe SAS noted to have longer driving experience compared to those with mild or moderate SAS (p=0.055).

It was noted that the driving accidents tend to increase in number as the severity of SAS increases (mild SAS= 48.38% (30/58), moderate SAS=52.38% (33/63), severe SAS= 58.47% (138/236). However, the incidence of driving accidents across the 3 groups of SAS did not differ significantly. (*Table 1*)

The cause of driving accidents in the patients with SAS was tabulated in Table 2. Majority of the SAS patients gave "sleepiness" as the reason in 86.06% of the respondents. Other causes were "not following traffic rules" in 12.94%, alcohol intake (8.96%), attributed to other's fault in 6.97%, personal human error (4.97%) and cell phone use (0.5%). These reasons were however not mutually exclusive as some of the respondents answered that the accident was brought about by both alcohol intake and sleepiness.

By statistical analysis, the reasons of driving accidents such as sleepiness, not following traffic rules, alcohol intake, cell phone use while driving, and personal error were not significantly associated to the severity of SAS. (*Table 3)*

A univariate analysis was done to know the association of the severity of SAS with the driving accidents. There was no association between these variables with p=0.307. (*Table 4*) Multiple logistic regression analysis was performed in order to adjust for the effect of the confounders identified such as the BMI, neck circumference, coffee drinkers and number of years of driving. Table 5 showed that there was no significant association with these factors and driving accidents.

Table 1. Baseline Characteristics of Sleep Apnea Syndrome Patients in Philippine Heart Center From January 2005-December 2011

	Mild SAS (AHI 5-15) n = 62	Moderate SAS (AHI 16-30) n = 63	Severe SAS (AHI >30) n = 236	p-value
Age Mean (± SD)	48 ± 10	48 ± 9	50 ± 11	0.127
Sex:				
Males	55	56	214	
Females	7	7	22	0.851
Civil Status:				
Single	8	18	42	
Married	54	45	194	0.064
Non-smokers	21	23	66	
Past smoker	28	26	114	
Current smoker	13	14	56	0.696
Co-morbidities	38	39	157	0.646
Alcohol drinker	29	26	119	0.421
Coffee drinker	42	39	189	0.005*
Tea drinker	18	20	97	0.129
Soda drinker	32	32	138	0.414
Epworth Sleepiness Score (mean ± SD)	11.95 ± 5.27	13.62 ± 12.01	13.64 ± 5.57	0.237
Body Mass Index (mean ± SD)	30.22 ± 7.31	30.10 ± 6.41	32.40 ± 7.98	0.031*
Neck circumference (cm)	40.64 ± 4.37	40.97 ± 3.64	42.30 ± 5.41	0.24*
No. of years driving	24.95 ± 10.80	22.48 ± 10.65	26.56 ± 12.61	0.055*
No. of hours driving per day	2.38 ± 1.42	2.21 ± 1.88	2.45 ± 1.77	0.613
No. of drivers who had accidents	30 (48.38%)	33 (52.38%)	138 (58.47%)	0.307

Table 2. Cause of Accidents Among Sleep Apnea Syndrome Patients in Philippine Heart Center from January 2005-December 2011

Cause of Accident	Number	%
sleepiness	173	86.06
not follow traffic rules	26	12.94
alcohol intake	18	8.96
other ‘s fault	14	6.97
personal human error	10	4.97
cellphone use	1	0.5
vehicular defect	0	0

Table 3. Number of Driving Accidents According to the Cause of Accident and Severity of Sleep Apnea Syndrome

	Mild SAS (AHI 5-15)	Moderate SAS (AHI 16-30)	Severe SAS (AHI >30)	p-value
sleepiness	25	27	121	0.208
not follow traffic rules	5	5	16	0.913
alcohol intake	2	5	11	0.446
other ‘s fault	2	2	10	0.889
personal human error	2	3	5	0.510
cellphone use	1	0	0	0.089
vehicular defect	0	0	0	N/A

Table 4. Association of Severity of Apnea-Hypopnea Index and Epworth Sleepiness Score With Driving Accidents

Variables	(-) accident	(+) accident	p-value
Mild SAS	32	30	0.307
Moderate SAS	30	33	
Severe SAS	98	138	
Epworth Sleepiness Score (mean ± SD)	13.58 ± 8.56	13.15 ± 5.69	0.565

Table 5. Logistic Regression of Variables That May Affect in the Association of SAS Severity with Driving Accidents

Variables	Odds Ratio	95% CI	p-value
SAS Severity	1.19	0.91 to 1.58	0.220
BMI	1.01	0.95 to 1.05	0.331
Neck circumference	0.99	0.94 to 1.04	0.564
Years of driving	1.02	0.99 to 1.03	0.095
History of coffee intake	1.03	0.63 to 1.68	0.909

DISCUSSION

Sleep apnea syndrome is a disorder that involves cessation of airflow or significant decrease in airflow during sleep. Its symptoms are snoring, sleepiness and witnessed apnea as observed by the patient's bed partner. Other daytime manifestations are daytime somnolence, morning headache, excessive daytime sleepiness, daytime fatigue and tiredness, cognitive deficits, memory and intellectual impairment (short-term memory, concentration), decreased vigilance, morning confusion, personality and mood changes. Symptoms of excessive daytime sleepiness (EDS) begins as feeling of sleepiness during quiet activities such as reading and watching television and as the severity of SAS worsens, the patient may feel sleepy even in activities that requires alertness such as driving.

As reported by Teran-Santos et al, the odds ratio for having a traffic accident was 6.3 (95% CI, 2.4 to 16.2) in patients with apnea-hypopnea index of 10 or higher in Spain.[12] In the report of Horstmann et al., those with moderate to severe SAS with AHI>34/hr sleep were more commonly involved than those with mild SAS.[13] In our study, there was no association between the severity of SAS and occurrence of accidents (*Table 3*). It was important to note that all the causes, may it be sleepiness, not following traffic rules, alcohol intake, other's fault and personal error, each would have a perfect association with the occurrence of accidents. In other words, if the person was sleepy, accident may happen. As presented by Connor and Norton et al., there was a strong association between acute sleepiness and the sleep crash with eightfold increased for drivers who are sleepy but there was no significant increase with chronic sleepiness.[14] Majority of the drivers in our study pointed out that sleepiness was the cause of the accidents (*Table 2*). However, sleepiness per se, whether it was acute or chronic, may be difficult to assess. It was established that patients with SAS presents with increased daytime sleepiness.[14] The increase in daytime sleepiness brought about by sleep apnea syndrome may result to increased tendency of these patients to have driving accidents.

The subjective perception of sleepiness had been correlated with Epworth Sleepiness Score (ESS).[15] Subjective and objective methods had been employed to evaluate excessive daytime sleepiness. Objectively, the test considered as the gold standard to determine sleepiness is the

multiple sleep latency test (MSLT). The principle behind this was that the degrees of sleepiness can be measured by how quickly a person falls asleep (sleep latency) when given the opportunity to do so. However, because this test was costly and cumbersome, simple subjective scale such as the ESS was developed to reliably predict sleep latency. Studies had been pub lished to correlate whether ESS was associated with MSLT. A study by Bendabis et al, examined the association of ESS with MSLT that included 102 patients evaluated for daytime sleepiness.[15] They concluded that ESS is comparable to MSLT except in some parameters such as determining sleep latency wherein MSLT can give a more objective results. Furthermore, the subjective ESS and objective MSLT may evaluate different complementary aspects of sleepiness.[15] In contrast to the study by Chervin and Aldrich on the validity of ESS as a measure of sleepiness among patients who were suspected or confirmed to have obstructive sleep apnea syndrome, the ESS had a statistically significant association with self-rated problem of sleepiness. However, the ESS was not associated statistically with multiple latency sleep test or measures of sleep apnea severity.[16] In another study by Olson et al,[17] the ESS and the mean sleep latency (MSL) were correlated but not inter-changeable. It was found out that ESS was influenced by psychological factors but multiple latency test was not affected. The ESS cannot be used to demonstrate or exclude sleepiness as it is measured by MSLT. The information from these studies may explain our results. As presented in Table 1, the ESS scores of our patients were not significantly different across the groups whether mild, moderate or severe SAS. Furthermore, the ESS among our patients who had accidents was not significantly different (i.e. meaning higher ESS scores from those who did not have accidents) (*Table 4)*. Our study was parallel to the result of the study by Connor and Norton et al. who reported a population-based case-control study on driver's sleepiness and its risk of serious car injuries.[14] They reported that subjects who had ESS of 10-15 was associated with lower risk of accidents compared to drivers with ESS less than 10. Furthermore, an ESS of 16-24 with other factors were not associated with either significant increase or decrease in injury crash.[14] It is implied that ESS may not be a good predictor for classifying the severity of SAS nor is it a good predictor of occurrence of driving accidents but may help gauge the tendency of sleepiness among drivers.

The BMI and the neck circumference in our patients as grouped according to the severity of SAS was statistically significant and was noted to be greater among the severe SAS (*Table 1*). Neck circumference has been reported to correlate better with the presence of apnea than the BMI and recommended a thorough inquiry on history pertaining to sleep apnea symptoms when the neck circumference is more than 40cm.[18] Other study showed conflicting results otherwise and concluded that no single anthropometric value can predict the severity of SAS.[19]

Coffee consumption among our patients was statistically different among the groups. This was also reported in the study of Bardwell et al. that patients with obstructive sleep apnea had significantly greater caffeine consumption than those without sleep apnea and they consume more amount of caffeine.[20] This higher caffeine consumption among those with higher SAS severity may be indicative of the state of sleepiness of patients with sleep apnea that may otherwise be unnoticed by the patients.

The following were the limitations of the study. The patients were contacted by phone or personally visited through the address and telephone number given in the record. The recall bias can also be considered since the patients were asked about the driving accidents that could have happened several years ago. This was also the reason why a significant other of the patient was asked so as to compare the accuracy of the incidents that had happened. Another limitation of the study was the effect of other factors that might have contributed to the driving accident such as mechanical defects or alcohol intake, although careful extraction of the details on the incidence was done.

CONCLUSION

The study showed that driving accidents occurred in more than 50% of SAS patients regardless whether the severity was mild, moderate or severe. The incidence of driving accidents tends to increase with increasing severity of SAS. This, however, was not statistically significant. The most common cause of driving accidents among SAS patients was sleepiness comprising 86% of those who had accidents. The ESS score, a subjective measure of sleepiness, however, was not significantly different among the different severity groups of SAS patients. There was no difference in the ESS of those driver SAS patients who had accident and those who did not have driving accidents.

REFERENCES

1. Lyznicki JM, Doege TC, Davis RM, Williams MA. SleepiNess, driving, and motor vehicle crashes. Council on Scientific Affairs, American Medical Association. JAMA. 1998 Jun 17;279(23):1908-13.
2. Pack AI, Pack AM, Rodgman E, Cucchiara A, Dinges DF, Schwab CW. Characteristics of crashes attributed to the driver having fallen asleep. Accid Anal Prev. 1995 Dec;27(6):769-75.
3. Horne JA, Reyner LA. Sleep related vehicle accidents. BMJ. 1995 Mar 4;310(6979):565-7.
4. Dinges DF. An overview of sleepiness and accidents. J Sleep Res. 1995 Dec;4(S2):4-14.
5. MMARAS 2010 by MMDA Road Safety Unit (RSU) and Traffic Operations Center (TOC), World Health Organization, PNP Directorate for Investigation and Detective Management. [cited on 2014 Apr 15]. Available from: http://showbizandstyle.inquirer.net/sim/sim/view/20110219-321146/Numbers
6. Maycock G. Sleepiness and Driving: The experience of U.K. Car drivers. Accid Anal Prev. 1997 Jul;29(4):453-62.
7. Carter N, Ulfberg J, Nyström B, Edling C. Sleep debt, sleepiness and accidents among males in the general population and male professional drivers. Accid Anal Prev. 2003 Jul;35(4):613-7.
8. Pizza F, Contardi S, Antognini AB, Zagoraiou M, Borrotti M, Mostacci B, et al. Sleep quality and motor vehicle crashes in adolescents. J Clin Sleep Med. Feb 15, 2010; 6(1): 41-45.
9. Working Together to Understand Driver Fatigue: Report on Symposium Proceedings. [cited on 2014 Apr 15]. Available from: http://www.ibc.ca/en/Car_Insurance/documents/driver_fatigue/Understanding_Driver_Fatigue_HSR-Feb2008.pdf
10. Young T, Blustein J, Finn L, Palta M. Sleep-disordered breathing and motor vehicle accidents in a population-based sample of employed adults. Sleep. 1997 Aug;20(8):608-13.
11. Howard ME, Desai AV, Grunstein RR, Hukins C, Armstrong JG, Joffe D, et al. Sleepiness, sleep-disordered breathing, and accident risk factors in commercial vehicle drivers. Am J Respir Crit Care Med. 2004 Nov 1;170(9):1014-21.
12. Terán-Santos J, Jiménez-Gómez A, Cordero-Guevara J. The association between sleep apnea and the risk of traffic accidents. Cooperative Group Burgos-Santander. N Engl J Med. 1999 Mar 18;340(11):847-51.
13. Horstmann S, Hess CW, Bassetti C, Gugger M, Mathis J. Sleepiness-related accidents in sleep apnea patients. Sleep. 2000 May 1;23(3):383-9.
14. Connor J, Norton R, Ameratunga S, Robinson E, Civil I, Dunn R, Bailey J, et al. Driver sleepiness and risk of serious injury to car occupants: population based case control study. BMJ. 2002 May 11;324(7346):1125.
15. Benbadis SR, Mascha E, Perry MC, Wolgamuth BR, Smolley LA, Dinner DS. Association between the Epworth sleepiness scale and the multiple sleep latency test in a clinical population. Ann Intern Med. 1999 Feb 16;130(4 Pt 1):289-92.
16. Chervin RD, Aldrich MS. The Epworth Sleepiness Scale may not reflect objective measures of sleepiness or sleep apnea. Neurology. 1999 Jan 1;52(1):125-31.
17. Olson LG, Cole MF, Ambrogetti A. Correlations among Epworth Sleepiness Scale scores, multiple sleep latency tests and psychological symptoms. J Sleep Res. 1998 Dec;7(4):248-53.
18. Kryger MH, Thomas R, and , William CD. Principles and opactice of sleep medicine. 4th ed. PA: Elsevier, Inc., 2005. pp. 1043-1050.
19. Subramanian S1, Jayaraman G, Majid H, Aguilar R, Surani S. Influence of gender and anthropometric measures on severity of obstructive sleep apnea. Sleep Breath. 2012 Dec;16(4):1091-5.
20. Bardwell WA, Ziegler MG, Ancoli-Israel S, Berry CC, Nelesen RA, Durning A. Does caffeine confound relationships among adrenergic tone, blood pressure and sleep apnoea? J Sleep Res. 2000 Sep;9(3):269-72.

Predictors of Postoperative Pulmonary Complications in Children Undergoing Cardiothoracic Surgery at the Philippine Heart Center (PREdICt Phase I)

Maria Niña F. Banque, MD; Teresita S. De Guia, MD; Fernando G. Ayuyao, MD; Milagros S. Bautista, MD; Ma. Dulce Requiron-Sy, MD; Maria Nerissa Atienza-De Leon, MD

Background --- Postoperative pulmonary complication (PPCs) increases the morbidity of post cardiothoracic surgery patients especially of the lower age group. This study was done to determine the risk factors associated with postoperative pulmonary complications following cardiothoracic surgery in children 6 years old and below who underwent cardiothoracic surgery from November 1, 2010 - October 31, 2011 at the Philippine Heart Center.

Methods --- This is a prospective cohort study done in a total of 120 patients, 52 of whom performed tidal breathing analysis. Upon admission, data collection sheet was filled up with the demographic and clinical characteristics of patients included, the preoperative risk factors identified, the American Society of Anesthesiologists (ASA) physical status score, and the Risk Adjustment in Congenital Heart Surgery-I (RACHS-1) classification. Perioperatively, the surgical procedures done, cardiopulmonary bypass time and aortic cross clamp time were noted. Postoperatively, the total duration of postoperative mechanical ventilation, recovery room stay, intensive care unit stay, length of postoperative hospital stay and the condition on discharge were also noted. Patients were then evaluated for postoperative pulmonary complications. Primary outcome was development of PPCs. Secondary outcomes included the duration of postoperative mechanical ventilation, recovery room (RR) stay, pediatric intensive care unit (PICU) stay, overall length of postoperative hospital stay and mortality. For qualitative data, proportions/percentages were computed. For quantitative data, means and standard deviation were used. Comparisons of categories between with and without postoperative complications were done using Chi-square and independent T-test for all continuous variables at $\alpha = 0.05$ (5%). All variables that presented a p-value of ≤ 0.050 were considered independent predictors of postoperative pulmonary complications.

Results --- The rate of PPCs in this study was 73% with atelectasis, pneumonia and air leaks as the top three most common PPCs. Patients with PPCs had a longer duration of postoperative mechanical ventilation, longer RR and PICU stay and a longer overall length of hospital stay. There were 14 (12%) who died in the study, all with PPCs. There is the tendency that as the number of postoperative pulmonary complication increases, the rate of mortality also increases. Risk factors associated with PPCs were history of respiratory tract infection (RTI), preoperative mechanical ventilation, high pulmonary artery pressure (PAP), hypercarbia, hemoconcentration, lymphocytopenia, prolonged protime, hypoalbuminemia, complexity of cardiac surgery using the RACHS -1 scoring system and high ASA score. Logistic regression analysis however, only showed history of RTI and preoperative mechanical ventilation as independent risk factors for the development of PPCs.

Conclusions --- Incidence of PPCs in children 6 years old and below undergoing cardiothoracic surgery is high and is associated with need for prolonged mechanical ventilation and longer RR, PICU and hospital stay post-operatively. Therefore, identifying the risk factors to prevent its occurrence is of paramount importance. ***Phil Heart Center J 2014;18(1):52-67.***

Key Words: Children 6 Years Old and Below ■ Postoperative Pulmonary Complications

Management of patients with congenital heart disease (CHD) is an interplay of complexities. In taking care of the heart, one also has to consider the other organs of the body most especially the lungs as their pathologies are interrelated.[1] This subset of patients may

1st Place, Oral Presentation. 20thPHC Annual Research Paper Competition held on February 23, 2012 at Philippine Heart Center. Oral Presentation, 11th International Congress in Pediatric Pulmonology (CIPPXI), July, 2012 Bangkok, Thailand. *Correspondence to* ***Dr.*** Maria Niña F. Banque, Division of Pulmonary and Critical Care Medicine . Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication** ISSN 0018-9034

have limited ability for the heart to increase systemic and/or pulmonary blood flow, decrease arterial oxygen due to shunt lesions and inadequate delivery of oxygen to the tissues.[2] Children with congenital heart diseases therefore have profound alterations in respiratory functions even before a surgical intervention can be done. Despite enormous advances both in the care of the child with critical heart disease in the last decade and in surgical interventions for CHD, postoperative complications remain to be inevitable.

In a study by Ferguson, the most common form of postoperative morbidity experienced by pediatric patients who underwent surgical abdominal procedures, thoracotomy and cardiac surgical procedures are pulmonary complications.[3] A review article by Khan and Hussain in 2005 mentioned that postoperative pulmonary complications (PPCs) contribute significantly to morbidity and mortality in surgical patients and is more frequent than cardiac complications.[4]

It is given that the age and growth dependent changes in physiology and anatomy of the respiratory control mechanism, airway dynamics, and lung parenchymal characteristics have a profound influence on the pathophysiologic manifestations of the disease process. In younger children, they have smaller airways, a more compliant chest wall and poor hypoxic drive compared to their older counterparts.[5] The infant or young child is therefore an important population in the field of cardiothoracic surgery as they are more prone to develop post-operative complications than their older counterparts. Morbidity and mortality are also higher. Currently in our institution, children 6 years old and below comprise the majority of those who underwent palliative or corrective cardiothoracic surgery. For the year 2010, there were 669 cardiothoracic surgeries done among children 0-18 years old. Of these, 445 (66.5%) were among those younger than 6 years old.[6]

Most of the studies on determining risk factors of developing postoperative pulmonary complications after a cardiothoracic surgery were done on adults and older children. It includes pulmonary function test (PFT) as one of the variables. Adults and older children are more cooperative and therefore able to perform PFTs. Controversy exists whether abnormalities in pulmonary function can significantly associate or predict pulmonary complications. Punzal and colleagues noted that among adult patients, PFT can be an optional tool rather than an essential part of the preoperative assessment tool in cardiac patients undergoing heart surgery.[7] In 2009, Dela Cruz et al. studied the risk factors for developing PPCs among children above 6 years old.[8] Subjects included only those with PFT by spirometry. No study was done among children 6 years old and below and without any PFT. Hence, this study was done to identify the risk factors for developing PPCs among these age group and eventually propose a scoring system to predict these complications.

Children 6 years old and below have difficulty performing the PFT. The major differences in undertaking PFTs in younger children relate to sleep state, sedation, ethical issues, posture and the need to adapt equipment for measurements in small subjects who cannot be asked to undertake any special breathing maneuvers. In addition, infants are also preferential nose breathers, with nasal resistance representing approximately 50% of total airway resistance. These children are also difficult to sedate or are old to sedate but young to cooperate. Thus, infants and young children have been regarded as the dark ages of pediatric pulmonology in terms of assessing lung function.[9] For children who cannot follow instructions, the section of spirometry recommends the use of a tidal breathing analysis (TBA) where no cooperation is needed. Locally, TBA is done only in our institution. While this study would want to include TBA measures as one of the variables, doing so will neglect a significant portion of the population since tidal breathing analysis can only be performed at the pulmonary laboratory and limited to those patients who are stable enough for transport.

It is therefore the objective of this study to prospectively determine the risk factors associated with the development of PPCs in patients 6 years old and below undergoing cardiothoracic surgery and to determine how various risk factors could be combined to best predict the development of PPC.

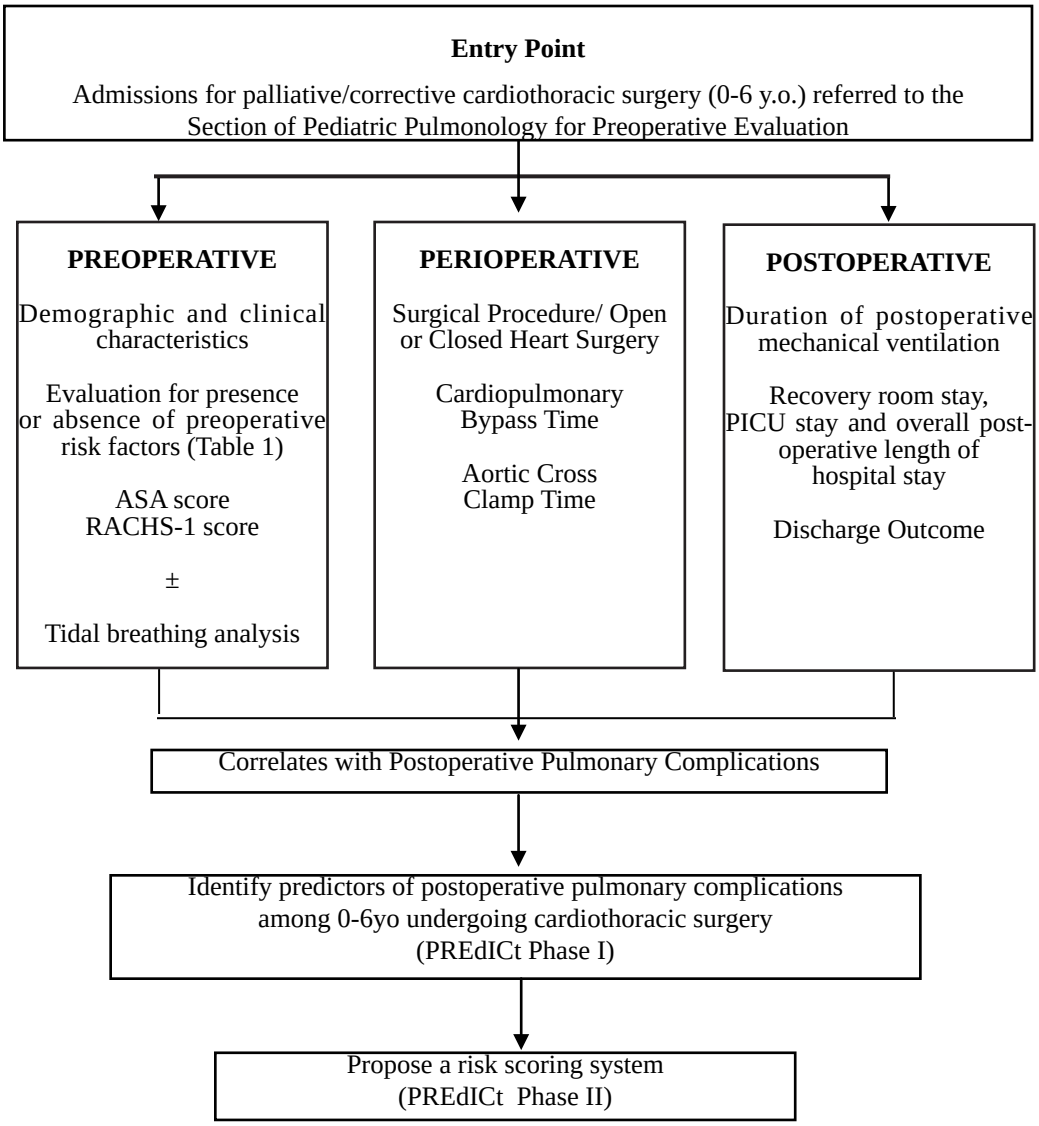


Figure 1. Conceptual model of study

METHODOLOGY

This is a prospective cohort study done among children 6 years old and below who underwent cardiothoracic surgery at the Philippine Heart Center from November 1, 2010 - October 31, 2011.

The study included all pediatric patients referred for preoperative evaluation to the Section of Pediatric Pulmonology aged 6 years old and below and admitted at the Philippine Heart Center from November 1, 2010-October 31, 2011 for palliative or corrective cardiothoracic surgery.

Risk factors: Criteria for selection of risk factors included in this study was based on various literatures on PPC in children and mostly from the Philippine Academy of Pediatric Pulmonology (PAPP) position statement on preoperative evaluation of pediatric patients for elective surgery[11] and the use of risk factors that were accessible to the institution in the preoperative, intraoperative, and immediate postoperative setting. Accessibility and identification of standard of care procedures were deemed important factors for selection in an attempt to build a model or a scoring system that would have clinical applicability to predict risk and guide pulmonary care in cardiothoracic

surgery. Risk factors and operational definitions are shown in Table 1.

Outcome measures: The primary outcomes are postoperative pulmonary complications with its specific definitions as shown in Table 2. Postoperative pulmonary complications were considered as pulmonary manifestations or problems noted within the 7th postoperative day or while the patient is still in the hospital.

Secondary outcomes were also assessed as to postoperative duration of mechanical ventilation, recovery room stay, postoperative pediatric ICU stay and overall postoperative length of hospital stay however there were no attempts made to differentiate between hours or days attributable to the PPC versus those that were not. Death was also considered in this study and was correlated with postoperative pulmonary complications.

Data collection: Upon admission, data collection sheet was filled up with the needed data to determine the demographic and clinical characteristics of patients included in the study as well as to identify the presence or absence of the preoperative risk factors identified in Table 1. Patients were also evaluated and scores were assigned as to their American Society of Anesthesiologist (ASA) physical status and Risk Adjustment in Congenital Heart Surgery-1 (RACHS-1) score. Perioperatively, the following variables were recorded: surgical procedure, cardiopulmonary bypass time and aortic cross clamp time. Immediately post op, the total duration of post-operative mechanical ventilation, duration of recovery room stay, PICU stay, overall postoperative length of hospital stay and outcome upon discharge were also be noted. For those who underwent tidal breathing analysis, despite the limited number, these were also recorded.

Patients were then evaluated for PPCs as defined in Table 2. Subjects were divided as those with PPCs and those without. Postoperative pulmonary complications were considered as pulmonary manifestations or problems noted within the 7th postoperative day or while the patient is still in the hospital.

Statistical analysis and sample size calculation: Sample size computed is $n \geq 51$ based on a 95% confidence level, 15% relative error. This is with an assumed postoperative pulmonary complication rate of 8.1% as found in the study by Borges et al.[10]

Data were presented in tabular and graphical forms. For qualitative data, proportions/percentages were computed. For quantitative data, means and standard deviation were computed. Comparisons of categories between with and without postoperative complications were done using Chi-square and independent T-test for all continuous variables using STATA 11. All independent variables were entered into a binary logistic regression model using full model technique. Beta coefficients and their corresponding odd ratios were used to determine the independent predictors of pulmonary complications. All variables that presented a p-value of ≤ 0.050 were considered independent predictors of postoperative pulmonary complications.

RESULTS

From November 1, 2010-October 31, 2011, a total of 336 (65%) out of 517 patients aged 6 years old and below underwent cardiothoracic surgery at the Philippine Heart Center. Of these, 120 patients were referred to the service of the pediatric pulmonology for preoperative evaluation and were included in the study.

The mean age is 2.18 years old, with majority belonged to the 1-3 years old age group. Forty seven out of the 120 patient [40%] were females and 73/120 [60%] were males. Seventy five of the 120 (63%) underwent open heart surgeries. Demographics and clinical characteristics of the subjects as well as the procedures are detailed in the table below (*Table 3*).

Cardiac diagnoses of patients included are in Table 4. The three most common lesions were Tetralogy of Fallot (TOF), Ventricular Septal Defect (VSD) and Patent Ductus Arteriosus (PDA).

Table I. Risk Factors of Interest for this Study

Age (in years)
Age classification (Neonatal 0-28 days; Infants 29 days old <1 year old; Toddlers 1-3 years old; Pre-schoolers 4-6 yeas old
Gender (Male or Female)
Weight (in kilograms)
History of prematurity (born less than 37 weeks age of gestation (AOG)
History of respiratory tract infection (RTI) - evidence active RTI within the past 30 days
History of reactive airway disease (asthma attack/note of wheezing or bronchospams within 4-6 weeks
History of tuberculosis (exposure, infection, disease, post-treatment defined according to the 2010 Tuberculosis of Infancy and Childhook Handbook
Presence of neurologic problem (cerebral palsy, epilepsy, global development delay)
Diagnosis (cyanotic/acyanotic)
Surgical procedure (palliative/corrective)
Preoperative intubation and mechanical ventilation (intubated and hooke to mechanical ventilation at least 24 hours prior to operation
Presence of pulmonary hypertension (mean pulmonary artery pressure of greater than or equal to 25mmHg at rest or greater than or equal to 30mmHg during exercise)
Pulmonary arterial pressure in mmHg (PAP from 2D echocardiogram taken most immediate to operation)
PAH classification (normal <25mmHg, mild 25-44mmHg, moderate 45-55mmHg, >55 severe)
Preoperative ABG (pH, p02, HCO3, BE, 02sat)-most immediate prior to operation
Preoperative complete blood count (CBC)-white blood count, hemoglobin, hematocrit, neutrophils, lymphocytes, platelet)-last determination prior to operation
Preoperative Protime (INR) - last determination prior to operation
Preoperative APTT (in seconds)-last determination prior to operation
Chest radiograph taken most recent prior to operation (normal vascularity, hypovascularity,hypervascularity, pneumonia, hyperaeration, scoliosis/deformity, congestion, atelectasis)
Preoperative serum albumin - last determination prior to operation
Bypass time in hours
Cross-clamp in hours
RACHS-1 Risk Adjustment in Congenital Heart Surgery classified as 1-6
American Society of Anesthesiologists (ASA) physical status - Class I-IV
Duration of postoperative mechanical ventilation (in hours)-
Tidal breathing analysis (TBA) - tidal volume (TV) which is the volume of air inspired and expired during normal quite breathing, time to peak tidal expiratory flow rato of total expiratory time (tPTEF/tE) and the volume to peak tidal expiratory flow ratio of total expiratory time (VPTEF/VE)
Positive studies / Negative studies
Patterns:
Normal: TV 6cc/kg and above, tPTEF/tE >30, VPTEF?VE>30
Restrictive: TV less than 6cc/kg
Obstructive: either tPTEF/tE or VPTEF/VE is less than 30
Mixed: TV less than 6cc/kg, tPTEF/tE

Table 2. Definitions of Postoperative Complications

Postoperative Pulmonary Complications
Pleural effusion - chest radiograph demonstrating blunting of the costophrenic angle, loss of sharp silhoutte of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures, or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows.
Pulmonary edema - as read on chest radiograph, as airspace opacification with diffuse or perihilar distribution ± frothy and/or bloody endotracheal tube (ET) secretions
Atelectasis (lobar) - lung opacification with a shift of mediastinum, hilum, or hemidiaphragm toward the affected area, and compensatory overinflation in the adjacent nonatelectatic lung
Diaphragmatic paralysis - elevation of one of the hemidiaphragms with (+) sniff test
Pulmonary hemorrhage - gross bleeding per ET tube not related to trauma
Air leaks - pneumothorax, pneumomediastinum, subcutaneous emphysema
Airway problem - bronchospasm, wheezing/stridor [newly detected expiratory wheezing treated with bronchodilator
Pneumonia - a new or progression of localized infiltrates on CXR with fever and leukocytosis >10,000/mm3 ± findings of crackles not due to congestion, (+) growth on sputum/NTA/ETA/plueral CS
Pulmonary hypertensive crisis - PAP that ≥ systemic arterial pressure that is associated with significant deterioration in hemodynamic status-unexplained desaturation, tachycardia and hypotension, high atrial pressure[12]

Table 3. Demographics, Clinical Characteristics and Procedures of Children Ages 0-6 Years Old Included in this Study (PHC, 2012)

Charateristics	With complications N = 88	Without complications N = 32	p-value
Age (years) Mean ± SD	2.04 ± 2.065	2.64 ± 2.164	0.167
Age (classification)			
0-28 days old	7	3	
29 days ≤1 years old	30	5	0.272
1-3 years old	27	13	
4-6 years old	24	11	
Sex			
Male : Female ratio	52 : 36	20 : 12	0.834
Weight (kg)			
Mean ± SD	8.574 ± 4.807	9.972 ± 5.2354	0.174
History of prematurity	11 (13)	3 ()	0.758
History of RTI	64 (73)	13 (41)	0.002**
History of Reactive Airway Disease	50 (57)	13 (14)	0.149
History of TB	13 (15)	2 (6)	0.349
History of Neurologic Disease	8 (9)	4 (13)	0.731
Preoperative mechanical ventilation	22 (25)	0 (0)	0.002**
Use of bypass	56 (64)	19 (59)	0.670
Type of lesion			0.215
Acyanotic	41 (47)	19 (59)	
Cyanotic	47 (53)	13 (41)	

Table 4. Cardiothoracic Abnormalities of Children Ages 0-6 Years Old Included in this Study (PHC, 2012)

Cardiothoracic abnormality/Heart Lesion, n (%)	No. = 120
Tetralogy of Fallot	27 (23)
Ventricular Septal Defect	23 (19)
Patent Ductus Arteriosus	16 (13)
D-Transposition of the Great Arteries	11 (9.2)
Double Outlet Right Ventricle	8 (6.7)
Pulmonic Valve Atresia	6 (5)
Tricuspid Valve Atresia	6 (5)
Atrioventricular Septal Defect	5 (4.2)
Atrial Septal Defect	5 (.4.2)
Total Anomalous Pulmonary Venous Return	4 (3.3)
Hypoplastic Left Heart Syndrome	1 (.83)
Interrupted Aortic Arch	1 (.83)
Double inlet, double outlet single ventricle	1 (.83)
Aortopulmonary window	1 (.83)
Truncus arteriosus	1 (.83)
Redundant mitral valve	1 (.83)
Congenital heart block	1 (.83)
Parachute mitral valve	1 (.83)
Massive pericardial effusion	1 (.83)

Table 5. Cardiothoracic Abnormalities of Children ages 0-6 Years Old Included in this Study (PHC, 2012)

Pulmonary Complications	No. = 170
Atelectasis, n (%)	41 (24)
Pneumonia, n (%)	37 (22)
Air leaks, n (%)	27 (16)
Airway problem, n (%)	22 (13)
Pulmonary edema, n (%)	14 (8)
Pleural effusion, n (%)	13 (7.6)
Pulmonary hypertensive crisis, n (%)	10 (6)
Diaphragmatic paralysis, n (%)	5 (3)
Pulmonary hemorrhage, n (%)	1 (0.6)

Table 6.1. 2D echocardiography and Chest Radiograph of Children ages 0-6 Years Old Included in this Study (PHC, 2012)

Test	With complications	Without complications	p-value
No. of patients	n=88	n=32	
PAH on 2D echocardiography	37 (42)	9 (28)	0.388
PAP (mmHg ± SD	26.86 ± 33.754	13.88 ± 23.693	0.021**
PAH classification			
No hypertension	51 (58)	23 (72)	
Mild	0	3 (9)	0.006**
Moderate	15 (17)	2 (6)	
Severe	22 (25)	4 (12)	

Table 6.2. Pulmonary Function Test using Tidal Breathing Analysis of Children ages 0-6 Years Old Included in this Study (PHC, 2012)

Test	With complications	Without complications	p-value
No. of patients	n=35	n=19	
Abnormal TBA result	28 (80)	14 (74)	0.594
Type of TBA Abnormality			
Normal	7 (20)	5 (26)	
Obstructive	24 (69)	9 (47)	0.424
Restrictive	1 (3)	1 (5)	
Mixed	3 (8)	4 (21)	
Tidal Volume (mean ± SD)	9.473 ± 2.6775	8.784 ± 2.9835	0.396
tPTEF%tE (mean ± SD)	25.882 ± 8.9715	30.611 ± 12.3225	0.117
VPEF%VE (mean ± SD)	28.1 ± 7.3903	32.021 ± 10.2073	0.116

Table 6.3. Other Laboratory Parameters of Children Ages 0-6 Years Old Included in this Study Group (PHC, 2012)

Test	With complications	Without complications	p-value
No. of patients	n=88	n=32	
Arterial Blood (mean ± SD)			
ph	7.36 ± .15	7.39 ± .044	0.128
pCO2	39.06 ± 11.97	35..41 ± 6.49	0.036**
p02	67.89 ± .54.18	82.88 ± 84.07	0.255
HC03	22.06 ± 5.69	20.84 ± 3.16	0.145
BE	-1.552 ± 7.4883	-1.583 ± 3.31	0.975
O2sat	74 ± 25.26	75.72 ± 26.9	0.762
CBC (mean ± SD)			
WBC	8.29 ± 8.01	5.281 ± 7.03	0.063
Hgb	92.16 ± 72.668	62.76 ± 67.25	0.048**
HCT	0.59 ± .78	0.89 ± .79	0.072
neutrophils	44.77 ± 18.855	39.28 ± 13.45	0.082
lymphocytes	41.89 ± 17.804	50.03 ± 12.6	0.007**
platelet	281 ± 143	303.94 ± 102.5	0.346
Protime (INR) (mean ± SD)	1.16 ± .24	1.08 ± .16	0.048**
APTT (seconds) (mean ± SD)	37.451 ± 9.09	36.41 ± 4.51	0.408
Albumin (g/L) (mean ± SD)	35.48 ± 12.3	40.38 ± 11.927	0.05**

Table 6.4. ASA and RACHS-1 Scoring of Children Ages 0-6 Years Old Included in this Study (PHC, 2012)

Test	With complications	Without complications	p-value
	n=88	n=32	
RACHS-1			
1	21	13	
2	32	14	0.010**
3	24	4	
4	11	1	
5	0	0	
6	0	0	
ASA			
1	2	5	
2	33	16	0.003**
3	46	11	
4	7	0	
5	0	0	

Table 6.5. Perioperative Characteristics of Children Ages 0-6 Years Old Included in this Study (PHC, 2012)

Test	With complications	Without complications	p-value
No. of patients	n=88	n=32	
Mean Bypass Time (hrs) ±SD	1.37 ± 1.225	1.08 ± 1.136	0.24
Mean Cross Clamp Time (hrs) ±SD	1.67 ± 6.692	0.78 ± .869	0.454

Table 7. Preoperative Factors Associated with Postoperative Complication of Children ages 0-6 Years Old Included in this Study (PHC, 2012)

Risk Factors	Odds ratio	[95% conf. interval]		p-value
History of RTI	4.74128	1.22576	18.34024	0.024**
Preoperative mechanical ventilation*	omitted			
High preoperative PAP (mmHg)	1.024175	0.9984728	1.050538	0.065
High pC02	1.02187	0.9287577	1.124317	0.657
Hemonoconcentration	1.008637	0.9939698	1.02352	0.250
Lymphocytopenia	0.9148435	0.8173545	1.02396	0.122
Protime (INR)	3.977041	0.112431	140.6805	0.448
Serum albumin	0.9812228	0.925562	1.040231	0.525
ASA	0.9293152	0.3224874	2.678017	0.892
RACHS-1	1.678835	0.7439713	3.788433	0.212

* Preoperative ventilation was omitted because of collinearity; it predicts success perfectly

Table 8. Outcome Characteristics of Children ages 0-6 Years Old Included in this Study (PHC, 2012)

Test	With complications	Without complications	p-value
No. of patients	n =88	n=32	
Duration of Postop Mech Vent (hours) ±SD	115.97 ± 287.693	14.34 ± 12.19	0.001**
RR stay (hours) ±SD	35.23 ± 22.48	20.22 ± 13.08	0.001**
Postoperative PICU stay (days) ±SD	10.24 ± 20.21	2.84 ± 2.7	0.042**
Length of postoperative hospital stay (days) ±SD	20.62 ± 21.58	10.28 ± 4.43	0.008**
Death, No. (%)	14(16)	0(0.0)	0.020**

Table 9. Association of the Number of Pulmonary Complications as to Outcome of Children ages 0-6 Years Old Included in this Study (PHC, 2012)

No. of postoperative pulmonary complications per patient	Discharge Outcome		
	Discharged Improved n(%)	Expired n(%)	p-value
0	30	0(0.0)	
1	39	4(9.3)	0.003**
2	18	5(21.9)	
3	13	2(13.3)	
4	4	1(20.0)	
5	1	0(0.0)	
6	1	2(66.7)	
Total	106	14(11.7)	

Of the 120 subjects, 73% (n=88) developed postoperative complications, 12% (n=14) died, all of whom are with postoperative pulmonary complications. Atelectasis is the most common complication followed by pneumonia and air leaks. Table 5 shows the different pulmonary complications.

Table 6.1-6.5 summarized the univariate analysis of the risk factors. Table 6.1 showed that a higher pulmonary artery pressure and the presence of PAH are significantly associated with PPCs.

Table 6.2 compared the lung function measures among those who developed complications and without complications. There is no significant difference between the two groups.

For the other laboratory parameters, the development of carbon dioxide retention or hypercarbia (p=0.036), hemoconcentration (p=0.048), prolonged protime (p=0.048) and hypoalbuminemia (p=0.05) are associated with PPCs.

Both the ASA score and complexity of cardiac surgery using the RACHS-1 scoring system are associated with postoperative pulmonary complications. More complications are seen as the score increases though there were no subjects who scored 5 and 6 for RACHS-1 and 5 for ASA.

Though statistically insignificant, those with PPCs have longer bypass time (1.37±1.225 vs. 1.08±1.136) and aortic cross clamp time (1.67±6.692 vs. 0.78±.869). All factors with $p \leq 0.05$ in the univariate analysis were entered into logistic regression analysis to see the individual effects of these factors on the outcome (*Table 7*).

PPCs were significantly associated with a longer duration of postoperative mechanical ventilation, longer RR stay, postoperative PICU stay and longer overall length of postoperative hospital stay. Mean duration of postoperative mechanical ventilation was 115.97h (SD± 287.693) in patients with PPCs, and 14.34h (SD±12.19) in patients without PPCs. Mean length of stay in the RR was 35.23h (SD±22.48) in patients with PPCS and 20.22h (SD±13.08) in patients without PPCs. Mean length of stay in the PICU postoperatively was 10.24h (SD±20.21) in patients with PPCs and 2.84h (SD±2.7) in patients without PPCs. Mean length of postoperative hospital stay was 20.62h (SD±21.58) in patients with PPCs and 10.28h (SD±4.43) in patients without PPCs. There were 14 patients who died in the study, all with PPCs, attaining a statistical significance of p=0.020.

An in-depth analysis of those who died revealed that there is the tendency that as the number of postoperative pulmonary complication increases, the rate of mortality also increases. Due to the small size for those with 4 or more complications per patient, the trend however cannot strongly be demonstrated (*Table 9*).

DISCUSSION

Postoperative pulmonary complications following cardiothoracic surgery can never be undermined. In the study of Healy et al., children with congenital heart diseases already have high incidence of pulmonary complications even before repair.[1] Locally in our institution, the study of Damian in 2010 showed a high incidence of postoperative pulmonary complications following cardiothoracic surgery at 75%,[13] a somewhat higher incidence compared to the study of Dela Cruz et al.[8] in 2008 (64.5%) and AM Reyes et al. in 2001, (63%).[14] These numbers were all taken from a higher age group of 6-18 year olds. But what about in the lower, much vulnerable age group of the pediatric population (6 years and below) who constitutes the majority of the cardiothoracic surgeries in the institution? Studying the lower aged group is also deemed essential as most of the congenital heart diseases are best corrected earlier in life and that doing surgery at a later age would only mean delay in the diagnosis and treatment. It is in this light that this study was done and found out a high incidence of 73%, almost the same as in the study of Damian of the older pediatric age group.[13] This is far from studies done in a university hospital in Brazil where wherein they reported a very low incidence of postoperative pulmonary complication at 8.1%.[10] In some international studies, Felcar et al.[15] reported a 34% incidence rate, with pneumonia as the most common one at 14.8%, while Linhua et al.,[16] whose study included children up to 1 year old reported an incidence rate of 21.5% for pneumonia alone. The lower percentage of PPCs in these literatures as compared to our study could be attributed to the retrospective nature of their studies, where documentation plays a very important role. The present study and the study of Damian are both prospective cohort studies.

In the present study, the most common complication is atelectasis followed by pneumonia and air leaks. While atelectasis was found to be the most common postoperative pulmonary complication both in a cardiac and non-cardiac surgery, pneumonia was not a common complication in both the studies of Dela Cruz and Damian which were also done in the same institution. The increase rate of pneumonia postoperatively among the subjects could be attributed to the ongoing renovation of the operating room (OR) complex at the time the study was done. Major changes including the change in the preoperative antibiotics (from Cefuroxime to Cefazolin plus Gentamicin) and more vigilant infection control monitoring were done.

PPCs are associated with the need for prolonged mechanical ventilation, RR stay, PICU stay and overall postoperative hospital stay. While this is self-explanatory, this indicates a bigger impact when it comes to cost, both for the patient's finances as well as the hospital's budget as many patients in our institution are charity patients. Identifying the risk factors of developing PPCs is therefore of great importance. Notably, with the 12% mortality rate found in the present study, all were found to have pulmonary complications, however no attempt was made to differentiate between deaths attributable to the PPC versus those that were not but what is certain is that as the number of PPCs increases per patient, mortality is most likely.

Predictors of PPC

Among the patient's demographics and clinical characteristics, the history of respiratory tract infection and preoperative use of mechanical ventilation were found to be significantly associated with postoperative pulmonary complications. This is similar to the studies cited in the PAPP position statement on the preoperative evaluation of pediatric patients for elective surgery,[11] the presence of both upper and lower respiratory tract infections increase the risk of airway complications by 5.28 times. Several studies have also shown that children who have a recent (within 1 month) or active URI are more likely to have respiratory complications including breath holding, oxygen desaturation, and severe coughing.[17] Results of the current study show that children with active and recent URIs (within 4 weeks) are at ncreased risk for adverse respiratory events, particularly if they have a history of reactive airway disease, require surgery involving the airway, have a history of prematurity, are exposed to environmental tobacco smoke, have nasal congestion or copious secretions, or

require placement of an endotracheal tube; thus, an algorithm was proposed to guide clinicians in their management. Although there is paucity of literatures pointing to the need of mechanical ventilation as predictor of PPCs, Shi et al. noted in their study that prolonged mechanical ventilation is associated with high postoperative morbidity and mortality. It is also associated with nosocomial pneumonia and extubation failure.[18]

While the age and age classification, sex, weight, history of prematurity, history of reactive airway disease, history of TB, history of neurologic disease, use of bypass/open heart surgery, type of lesion whether cyanotic or acyanotic, and type of procedure as to palliative or corrective were not statistically associated with postoperative pulmonary complications, PPCs in our patients were mostly seen in those patients with the following risk factors: history of prematurity (13% vs. 9%), history of reactive airway disease (57% vs. 41%), and the use of bypass or open heart surgery (64% vs. 59%).

Several studies mentioned history of prematurity and history of reactive airway disease as risk factors of PPCs. According to the National Institute for Clinical Excellence, there are two common concerns with former preterm infants and that is the presence of bronchopulmonary dysplasia and possibility of postoperative apnea.[19] On the other hand, as to the history of reactive airway disease, several studies have reported higher number of respiratory complications associated with anesthesia and asthma exacerbation in these group of patients.[20] It has been recommended by Black and Milenkovic[21] that elective surgery should be done 4-6 weeks after an asthma attack to prevent complications such as coughing and bronchospasm. It was also mentioned in the September 2010 issue of the Lancet that the following are associated with perioperative respiratory complications: wheeze during exercise, wheeze >3x in the past year, nocturnal dry cough and family history of asthma, rhinitis and eczema.[22] Increasing the sample size of this study will probably illumine the true value of the aforementioned risk factors as predictors of postoperative pulmonary complications.

While it was an ambitious attempt to associate a certain type of congenital heart disease with occurrence of postoperative pulmonary complication, it was however difficult to do so as the cardiac lesions included in the study are varied. The top 3 cardiac lesions included in the study are TOF, VSD and PDA. As to whether the lesion was cyanotic or acyanotic, it was not statistically significant that it was associated with postoperative pulmonary complications.

For the preoperative laboratory characteristics, the following were considered to be associated with postoperative pulmonary complications: (1) high pulmonary artery pressure, with more pulmonary complications associated with the severe type (PAP >55mmHg as measured during 2D echocardiogram), (2) higher pCO2 on arterial blood gas, (3) hemoconcentration and lymphocytopenia on CBC, (4) elevated protime using international normalized ratio (INR) and (5) hypoalbuminemia. The elevated white blood cell (WBC) count (p =0.063), high hematocrit value (p=0.072), and high neutrophilic count (p=0.082) were almost as close to being statistically significant. Further studies or adding more subjects will evaluate its true relevance.

Pulmonary hypertension can result from a broad spectrum of cardiac and pulmonary diseases and like producing a domino effect, children with pulmonary arterial hypertension can have hypertensive crises precipitated by a rapid increase in pulmonary vascular resistance (PVR) in response to stimuli including: hypercarbia, acidosis and hypoxia. If PVR increases to the point where pulmonary artery pressure exceeds systemic blood pressure, right ventricular diastolic and systolic function decrease acutely and can rapidly progress to right ventricular failure, arrhythmias, syncope and death.

The most common pCO2 abnormality seen among those with PPCs is acute respiratory acidosis. Pulmonary congestion/edema, pooling of secretions, bronchospasm and bronchoconstriction result to inefficient ventilation and thereby CO2 retention. A state of respiratory acidosis if uncorrected will lead to more pulmonary complications as alveolar hypoventilation ensues leading ultimately to respiratory

failure. In patients with cardiac problems especially those with pulmonary hypertension, it will lead to pulmonary vasodilatation and incites a hypertensive crises event.[1]

Hemoglobin is also one factor associated with postoperative pulmonary complications. As an oxygen carrier, its role in oxygen transport is vital such that a deficiency will compromise the respiratory status of patients.[23] In various literatures, preoperative hemoglobin determination is never considered routine unless the contemplated surgical procedure is associated with considerable blood loss[24] and cardiothoracic surgery especially those requiring cardiopulmonary bypass is one of them. Patel et al. also recommends preoperative hemoglobin determination among those infants less than 1 year old[25] while the American Academy of Pediatrics recommends preoperative hemoglobin determination in those less than 6 months old because the physiological nadir of red blood cell production may cause the hemoglobin level to decrease as low as 7g/dL and in those ex prematures because of the higher risk of postoperative apnea in these group.[26] It was however unexpected that a high hemoglobin and hematocrit count was significantly associated with postoperative pulmonary complications. Hemoconcentration is mostly seen among patients with cyanotic type of congenital heart disease where preoperatively, some may even require phlebotomy. A hemoconcentrated blood is a thicker blood, much more difficult to transport to other systems of the body and therefore oxygenation is most likely to be compromised. It is therefore important to have a normal or acceptable level of hemoglobin prior to subjecting these group of patients to cardiothoracic surgery.

The inclusion of lymphocytes (more likely lymphocytopenia) as a risk factor for developing PPC was also somewhat surprising. There were limited literatures to support this claim. Meguid et al.[27] and Leite el al.[28] noted in their studies that lymphocyte count 3,000 per uL3 may signify malnutrition and increased perioperative risk. Although patient's weight were considered non-significant risk factor of developing postoperative pulmonary complications, it would have been better to use body mass index or wasting/stunting as a measure of nutritional status in this study although it was also noteworthy that both the study of Dela Cruz[8] and Damian[13] who used the presence or absence of wasting as marker of nutritional status in their studies, did not show any association with postoperative pulmonary complication.

Deranged bleeding parameters like prolonged INR also pose a risk of developing postoperative pulmonary problems. Two of the patients in the study developed pulmonary hemorrhage and both were with deranged bleeding parameters. Postoperative bleeding was one of the indications why patients' chest were kept open for a time, decreasing further the tensile strength of the muscles of respiration and further decreasing lung compliance. Furthermore, patient's were kept intubated longer and noted to have more pulmonary complications.

Hypoalbuminemia was also found to be associated with postoperative pulmonary complications. Hypoalbuminemia disturbs the Starling forces (hydrostatic and oncotic pressures) that dictate the flow of water between the capillaries and the alveoli posing risk of developing pulmonary edema.[1] Children with congenital heart problems especially those with congestive heart failure is often hypoalbuminemic. Malnutrition which may also manifests as hypoalbuminemia, may contribute to the problem.

In our country, the PAPP uses ASA as method of risk stratifying patients who will undergo any kind of surgery needing general anesthesia. Patients who are in ASA classes I and II are frequently considered appropriate for minimal, moderate or deep sedation but those in classes III and IV, "children with special needs, and those with anatomic airway abnormalities or extreme tonsillar hypertrophy present issues that require additional and individual consideration, particularly for moderate and deep sedation."[11] ASA scoring in this study is found to be associated with PPCs. ASA scoring, therefore, can also be used in risk stratifying patients for cardiothoracic surgery as well. Classifying patients according to the complexity of cardiac surgery using RACHS-1 scoring system has been used since the year 1997 by panel of experts. It has been used to correlate with

in-house mortality among pediatric patients undergoing cardiac surgery such that the higher the score, the higher the incidence of mortality.[29] In our study, the RACHS-1 scoring system is also associated with PPCs. The higher the ASA and the RACHS-1 score, the more likely PPCs tend to occur.

The present study did not show an association between the bypass time and the aortic cross clamp time with postoperative pulmonary complications, although there is a tendency that the longer the bypass and aortic cross clamp time, PPCs are more likely. The study will need more subjects to qualify this claim as it has been well documented also in literatures that in patients with CHD undergoing cardiopulmonary bypass, systemic inflammatory responses contribute to pulmonary edema and resultant mechanical and gas exchange abnormality thereby increasing the risk of developing PPC.[1]

Pulmonary function test is considered vital in doing preoperative evaluation, that is why in the institution only those children who were able to do spirometry were included in the study of Dela Cruz and Damian. The present study made use of the infamous tidal breathing analysis to evaluate pulmonary function in the lower pediatric age group where not much cooperation is needed to perform the test. Because of the limited number of patients that were able to visit the pulmonary laboratory to do the procedure, only 52 patients were able to do the test, thus the subset analysis. Among those who performed the test, whether an abnormal TBA result, type of TBA abnormality, tidal volume, tPTEF%tE and VPEF%VE, it did not show any statistically significant association with postoperative pulmonary complications. This is in agreement with the study of Punzal et al[7] done in the same institution but among adult patients wherein he found out that pulmonary function testing is not a prerequisite of doing preoperative pulmonary evaluation. It has also been a statement of the PAPP that routine pulmonary function tests are not indicated for healthy patients prior to surgery.[15] Lawrence et al. have shown that clinical findings are more predictive of pulmonary complications than spirometric results.[30] It further showed that FEV1, FVC and FEV1/FVC where nearly identical among patients with or without pulmonary complications and no spirometric value was associated with postoperative pulmonary risk. Pulmonary function test may be done in those who will undergo thoracic surgery for prognostication and for patients with pulmonary symptoms that is unexplained after clinical evaluation. However, in the PEDIARISM study of De la Cruz et al, FVC<80 is considered a risk factor of developing postoperative pulmonary complications.[8] However it is important to note that in our study, both the mean tPTEF%tE (25.882±8.9715) and VPEF%VE (28.1±7.3903) of those with PPCs were below the normal value of 30, indicating that small airways' disease could be associated with PPCs.

Among the risk factors that were considered significant ($p \leq .05$) in the univariate analysis were then entered into binary logistic regression model using full model technique and it identified the history of RTI and preoperative mechanical ventilation as independent predictors of PPCs. All patients intubated and mechanically ventilated preoperatively who underwent cardiothoracic surgeries developed postoperative pulmonary complications, the reason why this factor was omitted but nevertheless considered significant.

The present study is considered phase I of Preoperative Risk Scoring System for Infants and Young Children Undergoing Cardiothoracic Surgery (PREdICt). After identifying these risk factors, enrollment of more subjects as well as collection of data will continue and will hopefully be able to develop a scoring system to risk stratify in terms of developing postoperative pulmonary complications those patients 6 years old and below who will undergo cardiothoracic surgery in the future.

CONCLUSION

The present study identifies the predictors of postoperative pulmonary complications among children 6 years old and below who underwent cardiothoracic surgery in the institution. One hundred twenty patients were included in the study, majority of which are males and mostly belonged to the 1-3 year old age group. There

were 63% who underwent cardiopulmonary bypass, and underwent mostly corrective procedures. TOF, VSD and PDA were the top three congenital heart diseases included in the study.

Overall, the incidence of postoperative pulmonary complications in this study is as high as 73% with atelectasis followed by pneumonia and air leaks as the most common postoperative pulmonary complications.

Patients with PPCs had a longer duration of postoperative mechanical ventilation, longer RR and PICU stay and a longer overall length of hospital stay. There were 14 (12%) who died in the study, all with PPCs. There is the tendency that as the number of postoperative pulmonary complication increases, the rate of mortality also increases. Risk factors associated with PPCs were history of respiratory tract infection (RTI), preoperative mechanical ventilation, high pulmonary artery pressure (PAP), hypercarbia, hemoconcentration, lymphocytopenia, prolonged protime, hypoalbuminemia, complexity of cardiac surgery using the RACHS -1 scoring system and high ASA score. Logistic regression analysis however, only showed history of RTI and preoperative mechanical ventilation as independent risk factors for the development of PPCs.

Tidal breathing analysis was not found to be significantly associated with postoperative pulmonary complications among those tested. With the incidence of PPCs remaining to be high especially in the lower pediatric age group, knowing the risk factors of its occurrence is of paramount importance.

RECOMMENDATIONS

A much larger sample population might reveal more significant results as a lot of those risk factors being studied showed trending towards significant results. Although this study already included 35 risk factors being considered, future studies can still include nutritional status in terms of BMI or percent wasting, blood transfusion and its contribution to lung injury, duration of operation and the type/site of incision.

Preoperatively as an out patient, this study recommends to do pulmonary function test using tidal breathing analysis for the lower pediatric age group to be able to achieve and thereby analyze a large number of patients and will therefore evaluate and utilize its full use as pulmonary function evaluation among these age group, as in the whole country, tidal breathing analysis machine can only be found in this institution.

Limitation of the study:

In an ideal setting wherein a study deals with different age group with different reference normal values, it is best to do analysis for age, however the author cannot find a standard normal values for age per age group for CBC and ABG results.

To assess the true value of tidal breathing analysis in the preoperative evaluation prior to a cardiothoracic surgery, it is ideal to do this test among all the subjects, however, this study was not able to do so because in the real setting, more than 50% of the subjects were direct to ICU admissions and are critically ill therefore doing tidal breathing analysis was an impossibility.

Furthermore, another limitation of our study is the fact that it reflects a single-center experience, which may limit its generalizability.

But despite all these, this study has allowed us to identify the risk factors that will predict PPCs in this subset of patients and will hopefully create a lay-out for the phase II of this study wherein we will propose a scoring system to predict development of PPCs in patients 6 years old and below who will undergo cardiothoracic surgery in the future.

REFERENCES

1. Healy F, Hanna BD, Zinman R. Pulmonary complications of congenital heart disease. Paediatr Respir Rev. 2012 Mar; 13(1):10-5.
2. Nichols DG, Ungerleider RM, Spevall PJ (eds): Critical heart disease in infants and children. 2nd ed. Philadelphia, PA: Mosby; 2006
3. Ferguson MK. Preoperative assessment of pulmonary risk. Chest. 1999 May;115(5 Suppl):58S-63S.
4. Khan MA, Hussain SF. Pre-operative pulmonary evaluation. J Ayub Med Coll Abbottabad. 2005; 17(4):82-6.
5. Kliegman RM, Stanton BF, Schor NF, St. Geme JW, Behrman RE. Nelson's textbook of pediatrics. 18th ed. PA: Elsevier. 2007.
6. Pediatric Cardiology Logbook of OR/RR admissions, Phil. Heart Center, 2010.
7. Punzal P, De Guia T, Tan J. A comparison of pre-operative risk assessment tool with and without the use of pulmonary function testing among patient who underwent valvular heart surgery. Phil Heart C J. 2006;12(3):48-51.
8. Dela Cruz BD, De Guia TS, De Leon NA, Bautista MS, Requiron-Sy DE. Pediatric risk stratification method (PediaRISM) for predicting postoperative pulmonary complication for cardiothoracic surgery. CHEST [abstract]. 2009 [cited 2009 Nov 3]. Available from: http://www.meeting.chestpubs.org.
9. Chernick V Boat TF, Wilmott RW, Bush A (eds). Kendig's disorders of the respiratory tract in children.7th ed. PA:Elsevier. 2006.
10. Borges DL, Sousa LRT, Silva RT, Gomes CDR, Ferreira FMM, Lima WL, et al. Pulmonary complications in pediatric cardiac surgery at a university hospital. Rev Bras Circ Cardiovasc. 2010: 25(2):234-237.
11. Sua C, Avendano C, De Leon A, Sanchez M, Manuel R. Preoperative evaluation of pediatric patients for elective surgery. Phil Academy of Pediatric Pulmonologists position statement. January 2011.
12. Lake CL, Booker PD. Pediatric cardiology anesthesia. 4th ed.USA: LWW, c2005. p. 544.
13. Damian M, Dela Cruz BD, De Guia TS, De Leon NA, Bautista MS, Requiron-Sy DE et al. Pediatric risk stratification method (PEDIARISM) for post-operative pulmonary complications for cardio-thoracic surgery: a validity study at the Philippine Heart Center, 2010. [Unpublished work]
14. Reyes, AMA. Preoperative evaluation of pulmonary risk for complication in children and adolescents with atrial septal defects and ventricular septal defects. Phil Heart Center, 1998 (Unpublished paper)
15. Felcar JM, Guitti JCS, Marson AC, Cardoso JR. Fisioterapia preoperatoria na prevancao das complicaoes pulmonares em cirurgia cardiac pediatrica. Rev Bras Cir Cardiovasc. 2008; 23(3): 383-8.
16. Linhua T. Tan L, Sun X, Zhu X, Zhang Z, Li J, Shu Q. Epidemiology of nosocomial pneumonia in infants after cardiac surgery. Chest. 2004;125(2):410-7.
17. Budic I, Simic D. Risk factors for respiratory adverse events during general anesthesia in children. Facta Universitatis Series: Medicine and Biology. 2004;11 (3):118-122.
18. Shi SS, Zhao ZY, Liu XW, Shu Q, Tan LH, Lin R, et al. Perioperative risk factors for prolonged mechanical ventilation following cardiac surgery in neonates and young infants. Chest 2008;134(4):768-74.
19. Preoperative Tests: The use of routine preoperative tests for elective surgery [Internet].Editors National Collaborating Centre for Acute Care (UK). London: National Collaborating Centre for Acute Care (UK); 2003 Jun. National Institute for Health and Clinical Excellence: Guidance.
20. Roy WL, Lerman J, McIntyre BG. Is preoperative hemoglobin testing justified in children undergoing minor elective surgery? Can J Anaesth 1991;38: 700-3.
21. Milenkovic A, Ivanisevic V. Pediatric anesthesia. In: Anesthesiology. Lalevic P.Ed Zavod za udzbenike I nastavna sredstva, Beograd, 1999: 111-129.
22. von Ungern-Sternberg BS, Boda K, Chambers NA, Rebmann C, Johnson C, Sly PD, Habre W. Risk assessment for respiratory complications in paediatric anaesthesia: a prospective cohort study. Lancet. 2010 Sep 4;376(9743):773-83.
23. Hsia C. Respiratory function of hemoglobin. Review Article. N Engl J Med. 1998 Jan 22;338(4):239-47.
24. Institute for Clinical Systems Improvement (ICSI). Preoperative evaluation. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2008 Jul. p. 32. URL: Available at http://www.ICSI.org.
25. Patel RI, DeWitt L, Hannallah RS. Preoperative laboratory tests in children: J Clin Anesth. 1997; 9:569-575.
26. Zuckerberg AL, Maxwell LG. AAP Textbook of Pediatric Care. Chapter 62: Preoperative Assessment. Available at https://www.pediatriccareonline.org 27.
Meguid MM, Campos AC, Hammond WG. Nutritional support in surgical practice: part I. Am J Surg. 1990; 159:345-58.

28. Jenkins K, Gauvreau K, Newburger JW, Spray TL, Moller JH, Iezzoni L. Concensus-based method for risk adjustment for surgery for congenital heart disease. J. Thorac Cardiovasc Surg. 2002; 123: 110-8.
29. Leite JF, Antunes CF, Monteiro JC, Pereira BT. Value of nutritional parameters in the prediction of postoperative complications in elective gastrointestinal surgery. Br J Surg 1987;74:426-9.
30. Lawrence VA, Dhanda R, Hilsenbeck SG, Page CP. Risk of pulmonary complications after abdominal surgery. Chest.1996;110:744-750

The Accuracy of Hounsfield Unit CT Attenuation in Differentiating Transudative From Exudative Pleural Effusion Based on Light's Criteria

Allan P. Celi, MD; Harold L. Tan, MD

Background --- A non-invasive technique, such as CT scan, to determine whether pleural effusion is transudative or exudative would aid in therapeutic management especially in cases when thoracentesis is contraindicated. Aside from the financial advantage, this method would benefit patients with CHF and concomitant transudative effusion (comprising approximately half of all patients with pleural effusion), since these patients usually do not require thoracentesis, hence preventing the complications inherent to thoracentesis. This study is done to determine the accuracy of Computed Tomography (CT) in characterizing pleural fluid into transudative and exudative based on attenuation values (Hounsfield Units), a non-invasive technique not being used for this purpose at this time.

Methods --- This is a criterion-reference based cross-sectional study. Patients with pleural effusion who had thoracentesis and chest CT done within 7 days of each were evaluated retrospectively over a 4 year period. Effusions are classified as transudates or exudates using Light's criteria. The mean Hounsfield unit (HU) of an effusion is determined and a receiver operating characteristic (ROC) curve was constructed to determine threshold values for classification on the basis of mean HU and to examine overall accuracy, using the area under the curve (Az).

Results --- Of the 110 exudates and 158 transudates, the mean attenuation of exudates (25.99 HU; [SD] 9.3 HU; range, 12–45 HU) was significantly higher than transudates (11.89 HU; 2.5HU; range, 5-19 HU), (p = 0.00). The overall accuracy of attenuation values for identifying exudates was high, Az = 0.981, standard error = 0.007, with the largest limitation being the overlap of exudates in the 16 to 18 HU range, which constituted 13% (35/268) of the total effusions measured.

Conclusions --- The mean attenuation of exudates is significantly higher than transudates as their accuracy is high. However, pleural effusions with HU's between 16 to 18 represent a gray area where clinical correlation is required prior to thoracentesis. ***Phil Heart Center J 2014;18(1):68-74.***

Key Words: Plueral Effusion ■ Light's Criteria ■ CT Scan ■ Thoracentesis, exudate; transudate

Pleural effusion is excess fluid within the pleura, and when excessive, may impair breathing by limiting the volume of inspiration. Pleural effusion is generally classified into transudates or exudates depending upon the concentration of protein within the fluid itself. The formation of transudates is dependent on an imbalance of hydrostatic and osmotic forces, whereas exudates are due to pleural disease. This damaged pleura leads to leakage of protein and lactate dehydrogenase with ensuing elevated specific gravity.[1] As a result of the greater amount of protein content in exudates, there is a consequential increase in its density. This increased density may potentially demonstrate greater attenuation values on computed tomography, as measured with Hounsfield Unit (HU), and be noninvasively differentiated from a less dense transudative type of pleural effusion.

Once the presence of a pleural effusion is established, the cause should be elucidated and thoracentesis is frequently the first-line invasive diagnostic procedure. Although thoracentesis is used routinely in this institution, the procedure carries small but occasionally hazardous risks such as pneumothorax and re-expansion pulmonary edema. A method to characterize pleural

Finalist, Oral Presentation, 20th Annual Research hilippine College of Radiology held on February 7, 2012 at SMX Convention Center, Pasay City. *Correspondence to* ***Dr. Allan P. Celi,*** Nuclear Medicine Division. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100
Available at **http://www.phc.gov.ph/journal/publication** ISSN 0018-9034

fluid would be valuable in guiding therapy and avoiding these potential dangers. Furthermore, the financial impact of an ultrasound guided thoracentesis (total costs of which in private institutions amount to a minimum of 15,000 pesos) requiring approximately 30 to 60 minutes depending on degree of difficulty and volume of fluid removed, is far greater than that of a plain chest CT scan (costing 6,000 pesos and lasting just under 1 minute).

Some contraindications to thoracentesis include minimal fluid volume (at least 60 mL is required for diagnostic studies), internal septa, pulmonary disease severe enough to make complications life threatening and predisposi tion to hemorrhage.[2] However, there are two conditions in which diagnostic thoracentesis are usually not compulsory: when there is a small amount of pleural fluid and a definite clinical diagnosis; or when there is clinically apparent congestive heart failure (CHF) without atypical features. Some of these atypical features include: a unilateral or asymmetric effusion, pleurisy, fever, normal cardiac silhouette on chest radiograph, an echocardiogram that is inconsistent with heart failure and an effusion that does not resolve with heart failure therapy.[3]

The characterization of pleural fluid aids to determine the underlying pathologic process and therefore governs clinical management. Light's criteria has been found to be the most accurate test to differentiate an exudate from a transudate, and is as follows: pleural fluid is transudative if none of the following are met:[4]

1. Ratio of pleural fluid and serum protein levels is greater than 0.5,
2. Ratio of pleural fluid and serum (LDH) levels is greater than 0.6, and
3. Pleural fluid LDH level more than two thirds the upper limits for serum LDH levels

The review of related literature with regards to HU and pleural effusion remains conflicting with no steadfast range developed to differentiate the two types of effusion. Several authors believe that CT is rarely helpful in their differentiation[5] and recognize its limited value in distinguishing transudate from exudates.[6] Other researchers showed a difference in attenuation but are correlated to the gross appearance of the fluid itself. Warakaulle and colleagues cites that pleural effusions with Hounsfield units of 12 to 20 are suggestive of serosanguineous fluid while pleural effusions with an attenuation of 30 HU suggests the presence of blood or purulent fluid.[7] In a similar study by Arenas-Jimenez et al. in 2001, simple pleural effusion was observed to have a density below 15 HU, while pleural fluid rich in protein, such as empyema, had an HU over 30.[8] Other techniques employ the use of intravenous contrast administration to help demonstrate evidence of an inflammatory process (exudative) such as the split pleura sign, which is enhancement and thickening of parietal pleural.[9] A majority of the previous studies regarding computed tomographic characteristics of pleural effusion were done more than a decade ago, and the equipment used were not modern Multi-detector CT examinations. Earlier studies have not assessed the accuracy of attenuation values in assessing pleural fluid. In addition, the author is not aware of any local research, which has attempted to determine the diagnostic yield of this examination.

The significance of this study aims to show that attenuation values have a potential clinical value in the characterization of pleural fluid, especially when thoracentesis is contraindicated and/or when the volume of effusion is minimal in an otherwise asymptomatic patient. In addition, these findings may also help reduce the number of unnecessary thoracentesis particularly in patients with transudative pleural effusion secondary to CHF, since approximately 20 percent of these effusions present unilaterally or asymmetrically[10] (an indication for thoracentesis). Most importantly, this knowledge could also help to corroborate or be an adjunct when history and physical examination already point to a possible etiology. This study aims to determine the accuracy of CT in characterizing pleural fluid into exudate and transudate based on HU.

METHODOLOGY

This is a criterion-reference based cross-sectional study done at the Philippine Heart

Center Radiological Sciences Division. Included were adults over a 4 year period (January 2007 - December 2010) with CT and thoracentesis performed within 7 days of each other and with available laboratory parameters (pleural fluid protein, serum protein, pleural LDH and serum LDH). Excluded were those with hemothorax or history of trauma.

Patients from the author's previous research paper entitled "The Utility of Ultrasound in Differentiating Transudative from Exudative Pleural Effusion" were rescreened to determine if a CT scan of the chest or upper/whole abdomen was performed within 7 days of the thoracentesis. These patients included in the said study have had pleural fluid analysis (pleural fluid protein, serum protein, pleural LDH and serum LDH) with determination of exudative or transudative pleural effusion using Light's criteria.

The computed tomography scans of the patients who fulfils the abovementioned conditions were retrieved. The CT scans were reviewed by the Consultant Adviser blinded to the laboratory results. The three slices with the greatest amount of fluid, determined by the largest anteroposterior distances of the effusion were used. A round to oval region of interest were positioned encompassing the largest possible fluid collection on each slice and the mean Hounsfield units (HU) values of the three slices were recorded and averaged.

Sample size and statistical analysis: The sample size computed was n >268 based on 95% confidence level, 10% relative error and assumed overall accuracy of CT in identifying exudates of 77.5% as presented in the paper of Nandalur KR et al.[11]

The fluid analyses were then compared to the HU values taken from the patients CT scan. The data were evaluated statistically. An ROC curve were constructed to determine threshold values for classification on the basis of mean HU and to examine overall accuracy, using the area under the curve (A_z). The overall accuracy for identifying exudates were then determined with its subsequent confidence interval. The optimal threshold value was also determined providing the range of HU to help differentiate an exudate from a transudate.

Definition of terms:
Hounsfield Unit (HU) - the numerical information contained in each pixel of a CT image. It is related to the composition and nature of the tissue imaged and is used to represent the density of tissue. Each pixel is assigned a value on a scale in which air has a value of -1000; water, 0; and compact bone, +1000.[12]

Exudate - any fluid that filters from the circulatory system into lesions or areas of inflammation. Its composition varies but generally includes water and the dissolved solutes of the main circulatory fluid such as plasma proteins, white blood cells, platelets and red blood cells.

Transudate - Extravascular fluid with low protein content and a low specific gravity (< 1.012). It has low nucleated cell counts and results from increased fluid pressures or diminished colloid oncotic forces in the plasma.[4]

RESULTS

In the Philippine Heart Center, between July 2008 and December 2010, a total of 268 patients underwent thoracentesis and plain chest CT within 7 days of each other who had sufficient laboratory data to characterize their effusion according to Light's criteria. Plain CT was performed on all patients using 40-MDCT scanner (Brilliance, Philips Healthcare). In this population of 268 patients (*Table 1*), there were 143 male and 125 female patients with ages ranging from 19 to 91 years old (mean age 53.9 years). The 5 most common co-morbidities were congestive heart failure (24.9%), pulmonary tuberculosis (11.9%), community acquired pneumonia (9.2%), hepatic cirrhosis (8.0%) and lung carcinoma (6.5%). A large minority of the patients had a history of smoking (40.6%).

According to Light's criteria, 59% of the 268 pleural effusions were transudates and 41% were exudates. The mean attenuation of exudates (25.99 HU; Std Deviation 9.3 HU) was twice as high as that of transudative pleural effusion (11.89 HU; Std Deviation 2.5 HU). The attenuation of exudates ranged from 12 to 45 HU while the attenuation of transudates ranged from 5 to 19 HU. (*Figure 1*)

Among the patients with exudative pleural effusion, the most common causes were due to malignant disease, pulmonary tuberculosis and pneumonia while the most common causes of transudate pleural fluid were congestive heart failure and hepatic cirrhosis (*Figure 2*). Table 3 summarizes the different causes of pleural effusions and their respective mean attenuation in Hounsfield units. There was no significant difference in HU among the different causes of transudates or exudate, although malignant pleural effusion was found to have the highest HU (probably because of its hemorrhagic component). There is no previous study to the author's knowledge that has compared the HU among the different causes of exudative pleural effusion.

An ROC curve for the accuracy of attenuation values in the identification of exudates was constructed and is depicted in Figure 4. The overall accuracy for identifying exudates using HU is high (A_z = 0.981; Std error = 0.007). There was an overlap in the optimal threshold value for exudates which was determined to be 16 to 18 HU, which constituted 13% of effusions. At 16 HU the sensitivity is 84.1% with a specificity of 92.9%, at 17 HU the sensitivity is 76.6% with a specificity of 96.1 and at 18 HU the sensitivity was found to be 72.9% and specificity of 98.7 % (*Table 2*).

Table I. Baseline Characteristics of Patients with Pleural Effusion Included in the Study (PHC, 2011)

Variables	No. (%)
Age	19-91 y/o (mean 53.9)
Sex	
Male	143 (53.3)
Female	125 (46.6)
Smoking History	108 (40.6)
Co-morbidities:	
Congestive Heart Failure	67 (24.9)
PTB	32 (11.9)
Pneumonia	22 (9.2)
Cirrhosis	21 (8.0)
Lung Carcinoma/metastasis	17 (6.5)

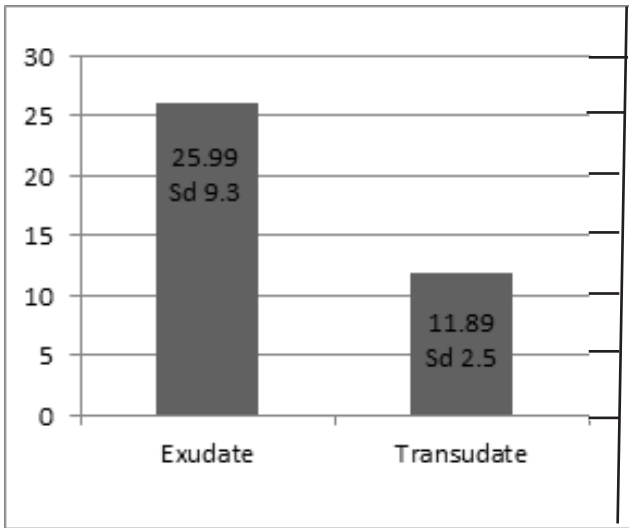


Figure 1. Average HU of exudates vs. transudates (PHC. 2011)

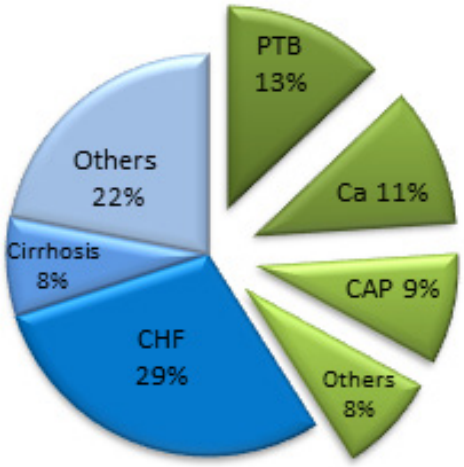


Figure 2. Most common comorbidities encountered among patients with transudates (clumped together) and exudates (separated). (PHC, 2011)

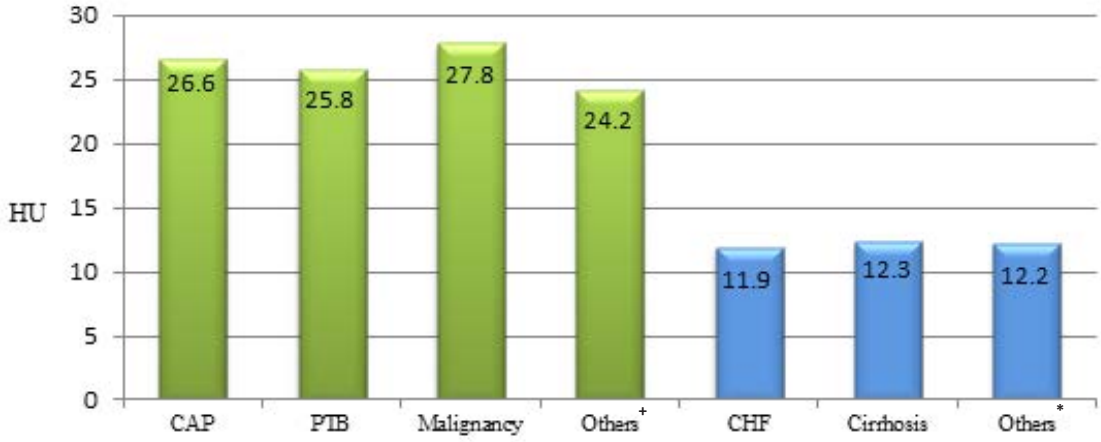


Figure 3. Summary of average HU for the most common causes of exudates and transudates. Other causes of exudates+ include SLE, Pancreatitis, Appendicitis, and Pulmonary Embolism. Other causes of transudates* include Schistosomiasis, Nephrotic Syndrome, ESRD, Myxedema, SVC Syndrome and Hepatitis. (PHC, 2011)

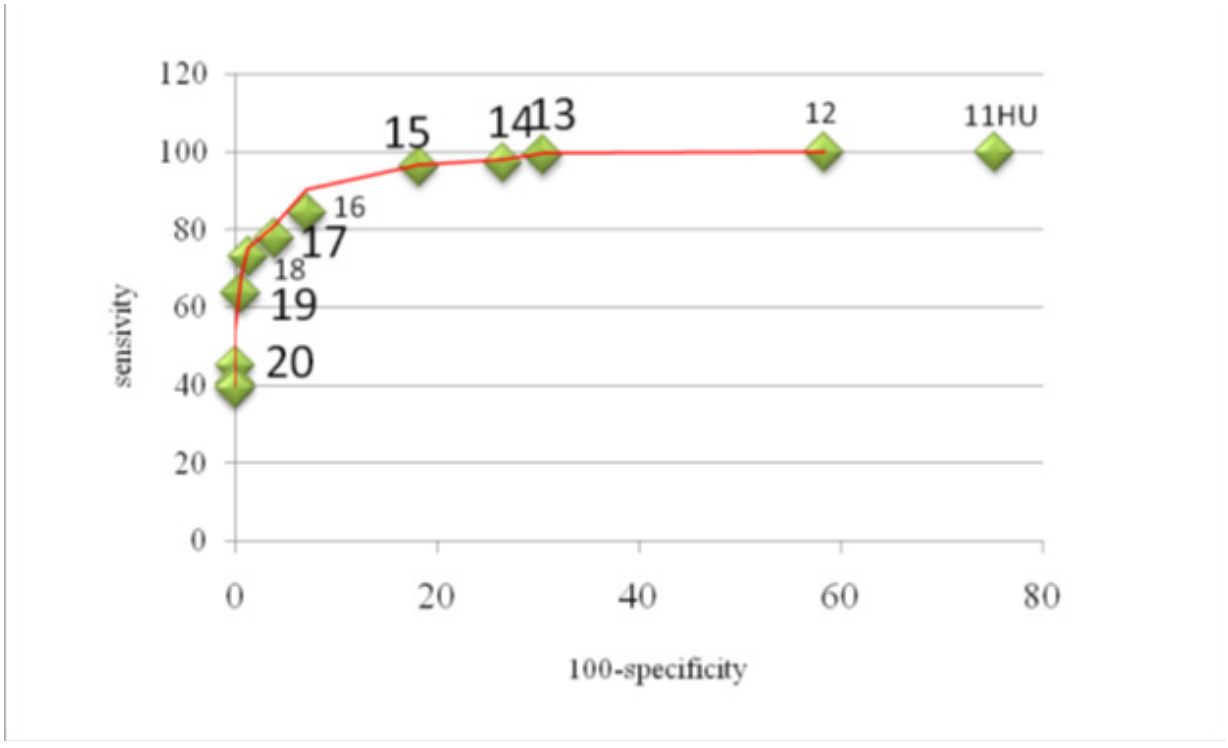


Figure 4. Graph shows receiver operating characteristic (ROC) curve plotting 100 – specificity (x axis) against sensitivity (y axis). Overall accuracy was high, with area under ROC curve of 0.981 and standard error of 0.007. (PHC, 2011)

Table 2. Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of CT Findings for Diagnosis of Exudative Versus Transudative Pleural Effusions. (PHC, 2011)

100.0	24.7	48.0	100.0	0.212 ± 0.038
100.0	41.6	54.3	100.0	0.368 ± 0.048
99.1	69.5	69.3	99.1	0.643 ± 0.058
97.2	73.4	71.7	97.4	0.673 ± 0.059
96.3	81.8	76.6	96.9	0.755 ± 0.061
84.1	**92.9**	**89.1**	**89.4**	**0.776 ± 0.062**
77.6	**96.1**	**93.3**	**86.0**	**0.756 ± 0.061**
72.9	**98.7**	**97.5**	**84.0**	**0.744 ± 0.060**
63.6	99.4	98.6	79.7	0.665 ± 0.059
44.9	100.0	100.0	72.7	0.490 ± 0.053
40.2	100.0	100.0	70.6	0.442 ± 0.051
39.3	100.0	100.0	70.3	0.433 ± 0.051

Ninety nine (99) patients underwent thoracentesis before CT and 169 underwent CT before thoracentesis (both within 7 days). The mean attenuation of patients in whom thoracentesis preceded the CT was slightly lower (14.9 HU compared with 15.6 HU).

DISCUSSION

Pleural effusion occurs "whenever the rate of fluid formation exceeds the rate of its removal.This occurs either because of an elevated net hydrostatic pressure gradient (transu dation) or because of an increased permeability of the pleural vessels (exudation)."[14] Thoracentesis is routinely performed in our institution, often on a daily basis. Although thoracentesis is considered a relatively safe procedure, it is associated with its own risks and contraindications. Finding an efficient non-invasive technique to help characterize pleural effusions would be clinically and financially beneficial for many patients whose effusion is secondary to Congestive Heart Failure (the most common cause of pleural effusion in this study) since these patients often respond to diuresis.

In the study of 145 patients by Nandalur et al,[11] it was found that the average attenuation of exudates was 17.1 HU while the average attenuation for transudates was 12.5 HU. The mean difference between exudates and transudates is smaller in this previous study but there is a moderately measureable difference between the two. Although this study and the study of Nandalur were done with similar methodology, there is no definitive explanation for the definitive explanation for the different attenuation values between the two studies. One possible explanation is that the quality and the resolution of the CT images in this study were probably higher thus elevating sensitivity. Another explanation is the number of effusions in The Philippine Heart Center is largely due to congestive heart failure and pulmonary tuberculosis. The densitometry of these two disease entities are theoretically on the opposite sides of the HU spectrum pulling the average HU of exudates and transudates further apart accordingly giving a larger mean difference. The study of Nandalur was performed in the United States where PTB is a rarity, found predominantly in AIDs patients.

"Prior to this study, it was expected that because exudative fluid contains high levels of protein, LDH, and bilirubin, this could potentially show increased attenuation (HU) on CT scan."[14] Only a few clinical studies done about a decade ago have been published in an attempt to prove this. The present research performed with a modern Multidetector CT scan concurs with these previous studies showing that the Hounsfield Unit of exudates are indeed higher than transudates, more than previously reported. In our study, mean attenuation of exudates was 25.99 HU compared with 11.89 HU for transudates, and the overall accuracy for identifying exudates was high ($A_z = 0.981$). The usefulness of identifying exudates and transudates was also evaluated by calculating the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each Hounsfield Unit. The value for p attained is 0.00 which is considered significant.

In determining the actual HU cut-off to differentiate an exudate from a transudate, 3 HU levels, namely 16, 17 and 18, provided the most sensitive and specific values with no significant advantage of one over the other. This gray area represented 13% of the pleural effusions encountered in this study, 71% of which were exudates (9 due to PTB, 8 due to pneumonia, 8 due to lung neoplasm/metastasis and 1 due to pulmonary embolism). The rest (29%) were transudative namely 8 patients with congestive heart failure (1 patient of which had rheumatic

heart disease) and 2 due to liver cirrhosis. At all HU levels between 16 and 18 exudates predominated, at 16 HU 70% were exudates, at 17 HU 66% were exudates and at 18 HU 80% were exudates. One explanation for this may due to different etiologies of pleural effusion in a single patient, for example, a patient with PTB who developed concomitant congestive heart failure would theoretically have a HU in the mean area. Another possibility is due to the effects of treatment such as antibiotics, heparin or diuresis which may affect effusion biochemistry and hence altering CT attenuation.[13]

CONCLUSION

In conclusion, the Hounsfield Unit exposes a potential clinical value in the stratification of pleural fluid. The results of the present study should encourage physicians to apply this tool in the management of patients with pleural effusion. However, when the CT attenuation of pleural fluid ranges from 16 to 18 HU, clinical correlation as well as assessment for cardiac configuration, parenchymal masses and infiltrates on CT images should be weighed. Nevertheless, CT should not replace thoracentesis when the latter is indicated and the etiology remains in question.

RECOMMENDATION

The limitation of this study was that it is retrospective study, and the thoracentesis and CT scans were not performed at the same time in a majority of patients. Diuresis as well as antimicrobial treatment may influence biochemistry of pleural fluid or CT appearance.[13] To minimize the effect of this limitation a prospective study prior to any form of treatment may be warranted.

REFERENCES

1. Bartter T, Santarelli R, Akers SM, Pratter MR. The evaluation of pleural effusion. Chest. 1994 Oct;106(4):1209-14.
2. Collins TR, Sahn SA. Thoracocentesis. Clinical value, complications, technical problems, and patient experience. Chest. 1987 Jun;91(6):817-22.
3. Sahn SA. State of the art. The pleura. Am Rev Respir Dis. 1988 Jul;138(1):184-234.
4. Light RW, Macgregor MI, Luchsinger PC, Ball WC Jr. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med. 1972 Oct;77(4):507-13.
5. Rubins J. Pleural effusion. [Internet]. WebMD; [updated 2014 Sept 5]. cited 2014 Oct 24. Available from: http://emedicine.medscape.com/article/299959-overview
6. Lee J, Sagel S, Stanley R. Computed body tomography with MRI correlation. Vol. I. 3rd ed. NY: LWW, 1998. p449.
7. Warakaulle DR, Traill ZC. Imaging of pleural disease. Imaging 2004 Oct;16(1):10-21.
8. Arenas-Jiménez J, Alonso-Charterina S, Sánchez-Payá J, Fernández-Latorre F, Gil-Sánchez S, Lloret-Llorens M. Evaluation of CT findings for diagnosis of pleural effusions. Eur Radiol. 2000;10(4):681-90.
9. Peek GJ, Morcos S, Cooper G. The pleural cavity. BMJ. 2000 May 13;320(7245):1318-21.
10. Porcel JM, Light RW. Diagnostic approach to pleural effusion in adults. Am Fam Physician. 2006 Apr 1;73(7):1211-20.
11. Nandalur KR, Hardie AH, Bollampally SR, Parmar JP, Hagspiel KD. Accuracy of computed tomography attenuation values in the characterization of pleural fluid: an ROC study. Acad Radiol. 2005 Aug;12(8):987-91.
12. Dahnert W. Radiology Review Manual. 5th ed. Baltimore: Williams & Wilkins, 2003. p56.
13. Shinto RA, Light RW. Effects of diuresis on the characteristics of pleural fluid in patients with congestive heart failure. Am J Med. 1990 Mar;88(3):230-4.
14. Abramowitz Y, Simanovsky N, Goldstein MS, Hiller N. Pleural effusion: characterization with CT attenuation values and CT appearance. AJR Am J Roentgenol. 2009 Mar;192(3):618-23.

A Comparison of Patient-Controlled Analgesia (PCA) with Nurse-Administered Analgesia (NAA) in Post-Operative Pain Control Among Open Heart Surgery Patients at the Philippine Heart Center

Juffey Tabingan, MD; Carina Dipasupil, MD; Veronica Durante, MD

Background --- Intravenous Patient Controlled Analgesia (PCA) was compared to a round the clock Nurse Administered intravenous Analgesia regimen (NAA) to determine if the PCA was advantageous in terms of pain scores and satisfaction ratings among post cardiac surgery patients.

Methods --- Eighty patients, 22 to 76 years of age, undergoing cardiac surgery under sternotomy approach were randomly assigned to receive Tramadol HCl either by PCA or by NAA for 24-hours after admission to the recovery room. Minimum and maximum doses were standardized. Pain intensity was tested four times a day and satisfaction ratings were obtained on the 24th hour after admission to the recovery room.

Results --- There was no difference in pain scores obtained between both groups ($p > 0.05$) in spite of greater analgesic usage by the PCA group ($p = 0.000$). Satisfaction ratings were higher among the PCA group. ($p = 0.000$)

Conclusions --- In using Tramadol HCl at 150 to 300mg per day, PCA and NAA methods are equally effective in treating post cardiac surgery pain. However, patients are significantly more satisfied with using the PCA pump. ***Phil Heart Center J 2014;18(1):75-79.***

Key Words: Cardiac Surgery ■ Patient Controlled Analgesia

Of utmost importance to every preoperative patient is the management of post-operative pain. However, inadequate treatment of acute post-operative pain has been well documented and probably still persists today.[1]

Effective opioid analgesia is maintained by sustaining adequate plasma opioid concentrations and avoiding the pitfalls of so called "peaks" and "troughs".[2] *(Figure 1)* Peaks happen immediately after an IV bolus of an opioid wherein serum concentrations of the opioid suddenly increases, sometimes above effective serum concentrations. It is at these concentrations where opioid side effects such as nausea, vomiting, pruritus and even respiratory depression or hypotension may occur.[1] Troughs on the other hand happen when due to pharmacokinetics, serum opioid concentration falls, sometimes below effective serum analgesic concentration. This usually happens when dosaging schedules are scheduled too far apart. Troughs are when patients could experience inadequate pain relief.[1] In our current practice of Nurse Administered Analgesia (NAA), wherein pain medications are given by an attending nurse on a scheduled dosage (e.g. Tramadol HCl 50mg IV every 8 hours), patients may experience pain in between dosing schedules.

Intravenous Patient-Controlled Analgesia (PCA) is an alternative modality used for the management of pain after major surgery.[1] In general, Grass loosely defines patient-controlled analgesia (PCA) to imply an on-demand, intermittent, IV administration of opioids under patient control (with or without a continuous background infusion).[1] This technique is based on the use of a sophisticated microprocessor-controlled infusion pump that delivers a preprogrammed dose of opioid when the patient pushes a demand button.[1]

Finalist, Poster Presentation, 20th PHC Annual Research Paper Competition held on February 23, 2012 at Philippine Heart Center
Correspondence to ***Dr. Juffey Tabingan,*** Dept. Cardiovascular Anesthesia. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100
Available at **http://www.phc.gov.ph/journal/publication** ISSN 0018-9034

Austin et al[3] has demonstrated that when analgesia starts to wane after an initial dose, even small increments of opioids could produce adequate pain relief. The least serum concentration at which pain was relieved was termed the "minimum effective analgesic concentration" (MEAC). (*Figure 2*) The maintenance of MEAC while avoiding serum opioid concentration peaks and troughs is the theoretical advantage of using PCA. This is the reason why we postulate that employing PCA would translate to better patient pain scores and satisfaction ratings as compared to NAA.

Although the use of the PCA has been extensively studied, almost all of the data obtained was from foreign centers.[4] The authors have not found any local data pertaining to the use of PCA in post-cardiac surgery. We therefore performed a prospective randomized controlled open label study to compare pain scores and satisfaction ratings between post cardiac surgery patients managed with PCA and NAA.

METHODOLOGY

A randomized controlled open label clinical study involving 80 patients from 22 to 76 years old undergoing cardiac surgery by the sternotomy approach at the Philippine Heart Center was conducted from November 2010 to January 2011. They were allocated by block randomization into Group 1 (PCA) and Group 2 (NAA). Group 1 post-op pain was managed by means of a PCA pump, which was set to give an initial bolus of 50mg Tramadol HCl followed by a continuous infusion of 4.2mg of tramadol per hour (100mg/24 hours). On demand boluses of 10mg Tramadol HCl was programmed with a lock out time of 10 minutes with a maximum allowable on demand dose of 40mg per hour. Group 2 post-op pain was managed by the NAA method with 50mg of Tramadol HCl IV every 8 hours with an additional 25mg of Tramadol HCl intravenously (IV) given every 4 hours as needed for pain scores of 4 and above. In both groups, the minimum amount of Tramadol HCl was set at 150mg/day and the maximum dose per patient was standardized at 300mg per day. Pain management was started within the first 15 minutes upon admission at the post-anesthesia care unit (PACU or recovery room). Visual Analog Scores (VAS) for pain were recorded at 1, 6, 12 and 24 hours after the patient was admitted at the PACU and satisfaction ratings using a four point scale were obtained 24 hours after admission at the PACU.

The study protocol was approved by the Institutional Ethics Review Board (IERB) of the hospital. A signed consent was obtained from the patients. Data was analyzed using the mean, standard deviation, t-test, Mann-Whitney test and Friedman Test.

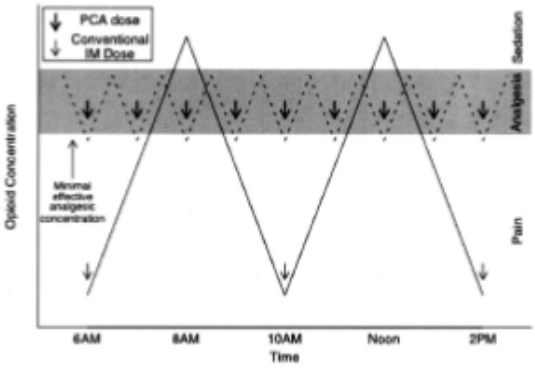


Figure 1. This representation shows serum opioid concentrations given by intermittent boluses showing "peaks and troughs" as shown in the straight line (NAA). Maintenance of effective serum concentrations with frequent small doses are indicated by the dotted lines (PCA). The shaded area is the target analgesic concentration. Adapted from Ferrante and Covino.[2]

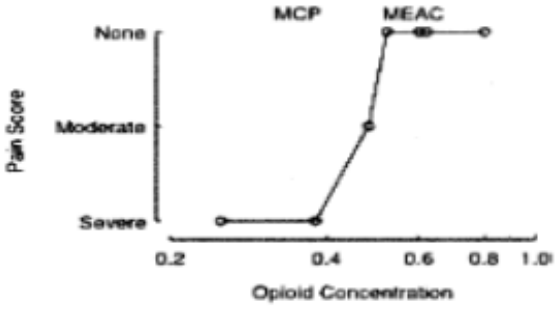


Figure 2. A figure showing that a minimal increase in opioid concentration could result in significant pain relief as long as the minimal effective analgesic concentration is reached. Adapted from Austin et al.[3]

RESULTS

Eighty patients were included in the study and randomly allocated into 2 groups. Each group was comparable in age, weight, sex and operations performed. (*Tables 1 and 2*)

There was no statistical difference between pain scores among both groups however, patients enrolled at the PCA Group had significantly higher total 24 hour Tramadol dosage (PCA 250 ± 28.53mg vs. NAA 209.72 ± 44. 832mg, p = 0.00). (*Tables 3 and 4*)

Patients enrolled in the PCA group also had significantly better satisfaction ratings than the NAA group (PCA 3.66 ± 0.591, NAA 3.06 ± 0.583, p = 0.00). (*Table 5)*

In both groups, there was a significant increase in reported pain scores between the first hour VAS and the 24th hour VAS (PCA2.29 ± 2.066 to 3.74 ± 1.336; NAA 1.89 ± 1.817 to 3.69 ± 1.600). (*Table 3*)

Table 1. Demographic Comparison Between the Treatment Groups

	(PCA) n=40 Mean ± SD	(NAA) n=40 Mean ± SD	p-value
Age	55.94 ± 12.139	50.36 ± 13.764	0.075
Weight	67.33 ± 12.394	67.17 ± 13.919	0.959
Gender, Male	34 (85)	28 (70)	

Table 2. Comparison of Operations Done on the Treatment Groups

Operations done	(PCA) n=40	(NAA) n=40
CABG	28 (70)	24 (60)
Valve	11 (28)	11 (28)
Others (Congenital)	1 (2)	5 (12)

Table 3. Comparison of Pain Scores Using Visual Analog Scores (VAS) According to Treatment

VAS Scores taken after admission at the Recovery Room	(PCA) n=40 Mean ± SD	(NAA) n=40 Mean ± SD	p-value
1 hour	2.29 ± 2.066	1.89 ±1.817	0.438
6 hours	3 ± 1.698	3.11 ± 1.801	0.967
12 hours	3.31 ± 1.530	2.72 ± 1.427	0.082
24 hours	3.74 ± 1.336	3.69 ± 1.600	0.787

Table 4. Total Analgesic Dosage During First 24 Hours Post-op According to Treatment Groups

	(PCA) n=40 Mean ± SD	(NAA) n=40 Mean ± SD	p-value
Total 24 hour Tramadol dose (mg)	3.66 ± 0.591	3.06 ± 0.583	0.000

Table 5. Comparison of Satisfaction Ratings According to Treatment Group

	(PCA) n=40 Mean ± SD	(NAA) n=40 Mean ± SD	p-value
Satisfaction rating 1 day post operation	3.66 ± 0.591	3.06. ± 0.583	0.000

DISCUSSION

Our results agree with the conclusions from foreign centers[4,6-8] that PCA does not confer additional pain relief regardless of significantly increased analgesic doses compared to NAA. However, most of these foreign studies employed morphine as the analgesic, while our study used Tramadol HCl. Two studies reported significantly lower pain scores using PCA but in these studies, piritamid and ketobemidone were used as the analgesic.[9,10] Tramadol was used in our study because it does not interfere with platelet function as compared to NSAIDs and it carries a low risk of respiratory depression, tolerance and dependence as compared to other pure opioid agonists such as morphine.[11] Tramadol was demonstrated to be safely used via PCA[1,12] and it also the most commonly used analgesic given to post operative patients in our institution. It is possible that some analgesics are more efficacious when given by PCA as opposed to be given by NAA.

Our results also showed that there was a significantly increased pain score on the 24th hour as compared to the baseline pain score on the first hour after admission at the PACU. Two factors may have contributed to this phenomenon. The first is that opioids given intraoperatively may still have conferred some pain relief up to the 12th hour of pain scoring but not up to the 24th hour. This is probable since the trend in anesthetic management in adult cardiovascular surgery is by the "fast track method" wherein the total dosage of intraoperative opioids are decreased. The second possibility is that the Tramadol dosage given was suboptimal leading to an increased pain score on the 24th hour. Marcou et al. reported that the ED50, or the dose of Tramadol wherein 50% of patients report pain relief is 86mg,[13] while a follow up study by Thevenin et al showed that the ED80 or the dose of Tramadol to confer pain relief in 80% of patients was 260mg.[11] However, Lehman clarified that the minimum effective analgesic concentration of tramadol varies greatly.[12] On average in this study, patients reported mild to moderate pain. As such, the researcher recommends an increase in the initial bolus of Tramadol to a dose higher than the ED50 and that the total 24 hour dosage should be adjusted according to the patient's weight, pain status and age in case of the geriatric population.

This study is at an intellectual impasse since it states that even though the PCA group received significantly greater amounts of analgesic, there was no significant difference in pain scores between the two groups and even if there was no difference in pain scores, satisfaction ratings were higher with the PCA group. There are several possible explanations to this dilemma. First is that the patients themselves may not have reported significant pain such as with York et al. wherein in their study, less than half the participants always communicated their experience of pain to nurses.[5] Another possibility is that this study assessed pain status four times in 24 hours, which may not be a true reflection of the patient's overall pain condition. As such, an explanation to this predicament, which was not tackled by available related literature, is that pain scores in the NAA group may have been understated due to the actual timing of pain scoring in relation to the timing of analgesic administration. For a better assessment of the patients pain status, at the

very least, pain scores should have been collected at baseline, 2 hours after dosing since this is the time of peak effect of tramadol,[14] and immediately prior to giving the next dose of Tramadol by NAA since this is theoretically the time of least serum concentrations and maximum pain.

In summary, the PCA and NAA methods have been shown to be equally effective in treating post-op pain but several factors such as the type of analgesic used, analgesic dosage and timing of administration together with intra-operative opioid usage may alter these findings.

CONCLUSION

In using Tramadol HCl at 150 to 300mg per day, PCA and NAA methods are equally effective in treating post cardiac surgery pain, however, patients are significantly more satisfied with using the PCA pump.

REFERENCES

1. Grass JA. Patient-controlled analgesia. Anesth Analg. 2005 Nov;101(5 Suppl):S44-61.
2. Ferrante FM, Covino BG (ed). Patient-controlled analgesia: a historical perspective. UK: Blackwell Science Ltd, 1990. p3–9.
3. Austin KL, Stapleton JV, Mather LE. Relationship between blood meperidine concentrations and analgesic response: a preliminary report. Anesthesiology. 1980 Dec;53(6):460-6.
4. Bainbridge D, Martin JE, Cheng DC.Patient-controlled versus nurse-controlled analgesia after cardiac surgery--a meta-analysis. Can J Anaesth. 2006 May; 53(5):492-9.
5. Yorke J, Wallis M, McLean B.Patients' perceptions of pain management after cardiac surgery in an Australian critical care unit. Heart Lung. 2004 Jan-Feb; 33(1):33-41.
6. O'Halloran P, Brown R. Patient-controlled analgesia compared with nurse-controlled infusion analgesia after heart surgery. Intensive Crit Care Nurs. 1997 Jun;13(3):126-9.
7. Myles PS, Buckland MR, Cannon GB, Bujor MA, Langley M, Breaden A et al. Comparison of patient-controlled analgesia and nurse-controlled infusion analgesia after cardiac surgery. Anaesth Intensive Care. 1994 Dec;22(6):672-8.
8. Tsang J, Brush B. Patient-controlled analgesia in post-operative cardiac surgery. Anaesth Intensive Care. 1999 Oct;27(5):464-70.
9. Pettersson PH, Lindskog EA, Owall A Patient-controlled versus nurse-controlled pain treatment after coronary artery bypass surgery. Acta Anaesthesiol Scand. 2000 Jan;44(1):43-7.
10. Boldt J, Thaler E, Lehmann A, Papsdorf M, Isgro F. Pain management in cardiac surgery patients: comparison between standard therapy and patient-controlled analgesia regimen. J Cardiothorac Vasc Anesth. 1998 Dec;12(6):654-8.
11. Thévenin A, Beloeil H, Blanie A, Benhamou D, Mazoit JX. The limited efficacy of tramadol in postoperative patients: a study of ED80 using the continual reassessment method. Anesth Analg. 2008 Feb;106(2):622-7.
12. Lehmann KA, Kratzenberg U, Schroeder-Bark B, Horrichs-Haermeyer G. Postoperative patient-controlled analgesia with tramadol: analgesic efficacy and minimum effective concentrations. Clin J Pain. 1990 Sep;6(3):212-20.
13. Marcou TA, Marque S, Mazoit JX, Benhamou D. The median effective dose of tramadol and morphine for postoperative patients: a study of interactions. Anesth Analg. 2005 Feb;100(2):469-74.
14. Tramadol [online]. [cited on 2014 June 16]; Available from: URL: http://www.drugs.com/tramadol.html.

Case Report

Familial Interstitial Lung Disease in a Family With Familial Juvenile Idiopathic Arthritis

Charo N. Francisco, MD

Background --- Interstitial lung disease (ILD) includes a large, heterogeneous group of mostly rare pulmonary conditions that cause derangements of the alveolar walls and loss of functional alveolar capillaries. It is a complex disease. Familial ILD is a rare type of hereditary disease and a thorough evaluation of the root cause is needed. It becomes explicitly rare and multifaceted when the main cause is another familial type of disease, familial juvenile idiopathic arthritis.

Case --- We present a case of an 8 year old girl who presented with difficulty of breathing, swelling of fingers, ankles and knees and respiratory distress when she was 2 years old. She was diagnosed initially to have miliary tuberculosis. Workups done included Chest CT scan and open lung biopsy. RF factor was extremely high, and anti-dsDNA was equivocal. Her eldest sister died of respiratory distress when she was 1 year and 4 months old. Her third sibling was diagnosed with systemic lupus erythematosus (SLE), juvenile idiopathic arthritis (JIA) at 3 years old. There is a familial history of ILD among the sisters, with one unaffected younger sister. She is presently maintained on corticosteroids, and sildenafil for the pulmonary hypertension.

Conclusion --- The diagnosis of interstitial lung disease is challenging. In this report, we describe a rare type familial ILD in Filipino children. Searching for the known etiology of such disease requires a thorough history and a complete physical examination. Since cases are under-reported and often misdiagnosed, vigilance is imperative to decrease morbidity and mortality among these children. ***Phil Heart Center J 2014;18(1):80-89.***

Key Words: Familial Interstitial Lung Disease ■ Familial Juvenile Idiopathic Arthritis ■ Fibrosing Alveolitis

Interstitial lung disease (ILD) comprises a large, diverse group of rare pulmonary conditions, sharing common histologic features, with resultant derangement of alveolar walls and loss of functional alveolar capillary units.[1] Aside from the alterations in the alveolar walls and spaces, the distal airways are commonly affected.[2] The prevalence of childhood ILD (chILD) is not well-known, probably due to under diagnosed and under-reported cases. It is certainly rare among children and involves only a small percentage of cases seen by pediatric pulmonologists worldwide.[1]

The clinical criteria for chILD must include the presence of at least 3 of the 4 common clinical manifestations for at least a month: symptoms of impaired respiratory functions (cough, breathlessness, exercise intolerance; evidence of impaired gas exchange (hypoxia or hypercapnia either at rest or induced by exercise); diffuse or patchy radiological chest abnormality on CXR or CT scan; and adventitious sounds on auscultation (crepitations or wheeze).[3]

ILD is a complex disorder and the exact definition, causes and spectrum of such disease is difficult to identify. Once the syndrome of chILD is recognized, a pursuit for a more precise diagnosis should be considered. Although, no classification is completely sufficient, classifications for chILD of known and unknown etiologies and of conditions that are unique to infants are identified.[1] (*Table I*) Clinical expression of the disease is influenced by several factors such as host susceptibility, genetics and environmental aspects. Considering these factors plus clinical heterogeneity makes the identification and classification of ILD in children difficult.[4]

1st Place, Poster-Case Report, 20th PHC Annual Research Paper Competition held on February 23, 2012 at Philippine Heart Center. Finalist, 18th Annual Congress of the Asian Pacific Society of Respirology (ASPR 2013), November, 2013. Yokohama, Japan. *Correspondence to* ***Dr. Charo Francisco,*** Division of Pulmonary and Critical Care Medicine. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication** ISSN 0018-9034

Familial interstitial lung disease is identified by verifying the presence of the disease in two or more members of the same family. Establishing an exact familial disease phenotype is difficult since different subtypes of ILD can be found in the affected family.[5] Familial clusters of seemingly similar cases have been identified. Sandoz made the first description of familial idiopathic interstitial fibrosis in twin sisters in 1907. Others hypothesized that the familial clustering may be secondary to exposure to shared environmental factors.[6] However, Peabody and associates in 1950 reported a case of familial idiopathic pulmonary fibrosis in twin sisters who have been separated geographically for 25 years, uncovering that a genetic analysis of the disease was involved.[7] Knowledge on the clinical features of hereditary ILD is essential to determine significant patients for genetic analysis in clinical practice. Study of genetics provide insight into the pathogenesis of these diseases.[4] A thorough way of searching the familial or genetic causes of ILD in any child should be done when the following are noted: severe unexplained lung disease in the newborn period; diffuse disease involving the entire lung on HRCT; histopathology that demonstrates alveolar proteinosis, DIP, or chronic pneumonitis of infancy; and electron microscopic findings of abnormal or absent lamellar bodies.[1] Familial cases account for 0.5-2% of idiopathic pulmonary fibrosis and occur as an autosomal dominant disorder with variable penetrance.[7]

Although distinct entities of ILDs are identified, only a few numbers of cases are encountered clinically. The most common form of ILD seen in practice is the idiopathic pulmonary fibrosis, also called as the cryptogenic fibrosing alveolitis, accounting for approximately 25% to 35% of ILD cases.[8] The most common histopathologic form of childhood ILD is lymphoid interstitial pneumonia.[1]

Clinical evidence of pulmonary involvement in rheumatoid disorders is not uniform and often insidious. The manifestations of the disease are always immunologically mediate; however, there are reports of genetic predisposition in some cases. The clinical manifestations maybe triggered by infectious or environmental influences.[1]

Rheumatoid arthritis-ILD is common among adult counterpart. However, lung involvement is rare in JRA and it is limited to children with systemic onset. The first case of ILD secondary to rheumatoid arthritis was first described in 1948.[1] Though cases of familial ILD were reported,[9,10] only two cases of familial juvenile rheumatoid arthritis causing fibrosing alveolitis was described in literature. One case involved identical twin sisters presenting with familial fibrosing alveolitis with rheumatoid arthritis; while the other case involved a family, with a father and six of his children inflicted with this familial disease.[6]

In view of the rarity of this familial association, we present a case of one family with familial chILD, probably the first case in the Philippines, given that it is not common in our settings or possibly some are not reported or are misdiagnosed. This is a case of familial childhood interstitial lung disease secondary to juvenile idiopathic arthritis. This case involved three out of four sisters wherein the eldest died and the youngest sibling is presently unaffected.

Table 1. Classification of Pediatric interstitial Lung Disease*

Interstitial Lung Disease of Known Etiology	Interstitial Lung Disease of Unknown Etiology
Aspiration syndromes	**Primary Pulmonary Disorders**
Infectious or post infectious lung disease	Desquamative interstitial pneumonia (DIP)
Drug or radiation-induced lung disease	Lymphoid interstitial pneumonia (LIP) and related disorders
Hypersensitivity pneumonitis	Nonspecific interstitial pneumonia (NSIP)
Lysinuric protein intolerance	Cryptogenic organizing pneumonia
Lysosomal storage disorders	Acute interstitial pneumonia
Neurocutaneous syndromes	Alveolar hemorrhage syndromes
Surfactant dysfunction mutations	Pulmonary infiltrates with eosinophilia
	Bronchiolitis obliterans
	Pulmonary alveolar proteinosis
	Pulmonary vascular disorders (proliferative and congenital)
	Pulmonary lymphatic disorders
	Pulmonary microlithiasis
	Systemic Disorders with Pulmonary Involvement
	Connective tissue disease
	Malignancies
	Histiocytosis
	Sarcoidosis

*Adapted from Kendigs, Disorders Of The Respiratory Tract In Children, 7th ed.

Case

This is a case of an 8 years old female who was admitted for difficulty of breathing. She was delivered full term to a 20 years old G2P1 (1001) mother at home, assisted by a midwife. She had good cry and activity, and with no note of respiratory distress. She was brought to a private pediatrician the following day, given vitamin K and diagnosed as well baby. Perinatal history showed that her mother had regular prenatal checkup and had UTI on the 6th month age of gestation.

At 1 month old, Bacillus Calmette-Guerin (BCG) was given at a local health center and was diagnosed as accelerated BCG reaction. She was started on triple anti-tuberculosis medications. Since 2 months of age, she had recurrent respiratory tract infections.

At 8 months old, she was brought to her pediatrician for cough and fast breathing. She was diagnosed to have Pneumonia and a congenital heart disease due to presence of murmur. 2Decho done revealed pulmonary regurgitation, mild, patent foramen ovale (PFO) and slightly elevated pulmonary artery pressure. Her parents were advised that the lesion will close spontaneously and to repeat 2Decho after a year. Repeat 2Decho done revealed a closed PFO and a mild pulmonary artery hypertension; however no medications were given. She also had recurrent knee joint swelling since she was 1 year old.

When she was 2 years and 2 months old, she was diagnosed to have miliary tuberculosis, based on her chest x-ray at a local hospital. She was transferred to Philippine General Hospital (PGH) where the impression was Pneumonia, to consider miliary tuberculosis, rule out interstitial lung disease. She was given unrecalled IV antibiotics, nebulizations, and quadruple therapy (INH, Rifampicin, Pyrazinamide, and Ethambutol). Purified Protein Derivative (PPD) and gastric acid fast bacilli (AFB) were negative. Interstitial lung disease was considered based on Chest CT scan. Quadruple anti-Kochs therapy was discontinued. Barium enema was done to rule out aspiration but revealed normal results. Repeat 2D echocardiography revealed pulmonary artery pressure of 72mmHg by PAT and with good LV function. She was given prednisone unrecalled dose and beraprost. Her parents were advised to do lung biopsy once her condition stabilizes. She completed IV antibiotics for 14 days and was discharged thereafter. She was started on Oxygen 0.5 to 1LPM for episodes of cyanosis when she is in distress and fatigue. Due to frequent attacks of pneumonia, the lung biopsy was always deferred.

She was regularly seen at PGH-OPD from 2005 to 2008 and was maintained on the following medications: salmeterol plus fluticasone inhaler, prednisone and beraprost, which was shifted to chloroquine. Referral to geneticist was done and impressions were Hamman-Rich syndrome and desquamative interstitial lung disease. They were advised to do immunologic workups but failed to comply. She had episodes of bilateral swelling of wrists, knees and ankles as well as respiratory distress when prednisone was tapered and discontinued. She became oxygen-dependent since she was 4 years old.

She was referred to Philippine Heart Center in 2008 and was regularly seen at our OPD. Initial physical examination showed the presence of moon facie, truncal obesity, and clubbing of nails but with no cyanosis. 2D echo (January 2010) revealed that her estimated PA pressure was 30 mmHg by TR jet and 74 mmHg by PAT. Chest CT scan revealed an impression of pulmonary lymphangiomyomatosis, rule out interstitial lung disease. Tidal Breathing Analysis done in May 2010 revealed restrictive lung disease. She was maintained at Oxygen 0.5 LPM and increased to 2 LPM when in distress. She was started on bosentan and iloprost, and shifted to sildenafil. She continued her salmeterol plus fluticasone and prednisone. She was referred to TCVS for lung biopsy. However, due to financial constraints, biopsy was deferred.

Ten days prior to admission, she developed distressing cough and colds with no fever noted. She was given salbutamol nebulization and clarithromycin at 6mg/kg/dose BID. Oxygen requirement was increased to 4LPM when in distress. She had gradual improvement after completion of antibiotics for 7 days. Three days prior to admission, there was recurrence of distressing cough, noted to be productive, accompanied with moderate grade fever. Nebulizations were resumed and paracetamol at 12mg/

kg/dose was given. She had episodes of cyanosis during bouts of cough. Oxygen support was maintained at 4LPM. Clarithromycin was resumed. Two days prior to admission, her fever subsided but she had worsening of cough. Persistence of her symptoms, accompanied with difficulty of breathing prompted consultation and subsequent admission.

Figure 1 shows her family pedigree. Her parents are not related by consanguinity. Pertinent family medical history showed that two younger brothers of her maternal grandmother died of an unknown cause. Both have a history of bronchial asthma and diabetes mellitus. On the paternal side, one of her uncle had psoriasis and one died of unknown kidney disease. Both parents have history of hypertension in the family. There was no history of any other connective tissue disease in their family.

Her eldest sister presented with respiratory distress and chest x-ray finding of miliary tuberculosis when she was 1 year and 3 months old; she died at 1 year and 4 months old. Her third sibling, presently 5 years old, was diagnosed with SLE with overlapping JIA at 3 years old. She presented with respiratory distress at 4 years old and she had similar chest x-ray finding with her older sibling. Chest CT scan showed interstitial lung disease. (*Figure 2*) Her mother observed presence of pectus excavatum on her first and 3rd daughter. Presently, her sibling is maintained on Naproxen sodium and on oxygen support at 1-2 LPM, when in distress.

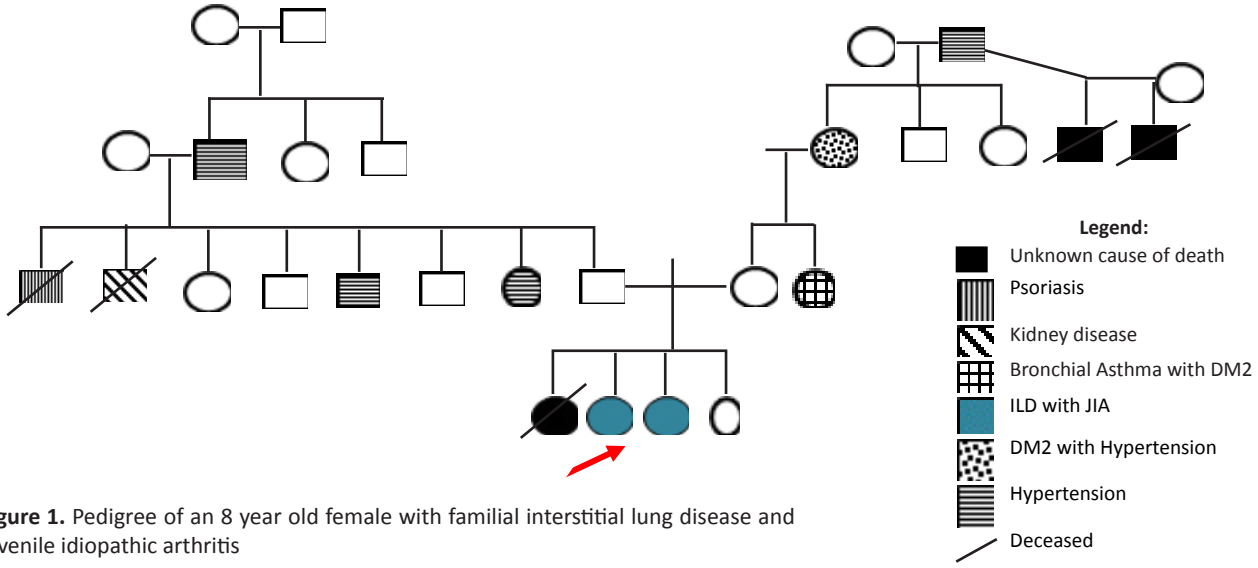


Figure 1. Pedigree of an 8 year old female with familial interstitial lung disease and juvenile idiopathic arthritis

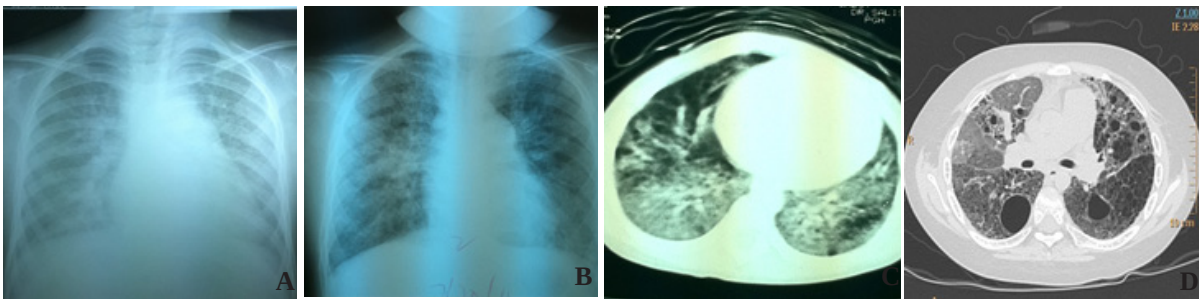


Figure 2. Chest X-ray and CT scan of sisters with familial interstitial lung disease. Chest x-ray of her younger sister (A) showed haziness on both lungs; while the patient's chest xray (B) showed reticulonodular and hazy infiltrates. Interstitial lung disease was considered for the Chest CT scan of her younger sister (C) and of the patient (D).

On admission, she was tachypneic, in respiratory distress, with tight air entry and oxygen saturation of 94% at 4 LPM. She had leukocytosis, respiratory acidosis and mild hypoxemia. Her chest xray showed infiltrates on the right lower lobe (*Figure 3*). She was started on Cefuroxime at 100mg/kg/day q8h and Amikacin at 15 mg/kg/day OD. Sildenafil at 0.8 mg/kg/day, prednisone at 1mg/kg/day and salmeterol plus fluticasone inhaler were continued. However, there was progression of infiltrates (*Figure 4)* accompanied with recurrence of her fever. Her antibiotics were shifted to Piperacillin plus tazobactam at 300mg/kg/day q6°, Fluconazole 6 mg/kg/day OD and her amikacin was continued. Her condition improved and she was referred for lung biopsy. She had recurrence of fever and leukocytosis on the 11th hospital day, and her antibiotics were shifted to Meropenem 120 mg/kg/day q8°.

On the 15th hospital day, a repeat Chest CT scan (*Figure 5*) was done with an impression of interstitial lung disease, cannot rule out pulmonary lymphangiomyomatosis. Repeat 2D echo, showed pulmonary arterial hypertension, with PA pressure of 52-56mmHg from previous of 74mmHg. She was cleared by infectious and cardiology service and scheduled for lung biopsy on 21st hospital day. She underwent posterolateral thoracotomy and right wedge lung biopsy of the right upper and lower lobes.

The histopathology report showed fibrosing alveolitis (interstitial pulmonary fibrosis) of varied etiologies (systemic disease, dusts, inhalants, drugs, infections, miscellaneous diseases, familial conditions or cryptogenic in nature). (*Figure 6*)

She tolerated the procedure and was discharged improved on the 30th hospital stay. She had regular follow-up at our OPD in Pediatric Pulmonology and PAH-clinic. She is maintained on oxygen support at 3 LPM when in distress and decreased to 1.5 LPM when asleep. Anti-dsDNA was equivocal and rheumatoid factor (512umol) was markedly increased. She was advised referral to a pediatric rheumatologist. She is advised monitoring of PA pressure by 2D echocardiography, and repeat 6 minute walk test and tidal breathing analysis. She was maintained on sildenafil, prednisone and salmeterol plus fluticasone.

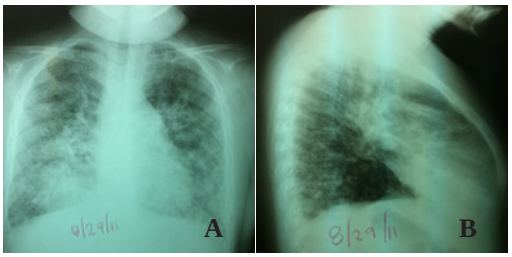


Figure 3. Chest x-ray on admission of an 8 year old female with familial interstitial lung disease.

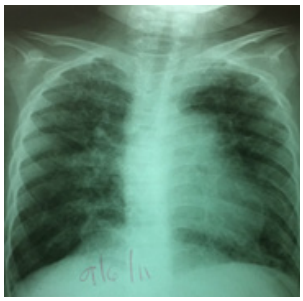


Figure 4. Chest x-ray of an 8 year old female on the 4th hospital day showed progression of infiltrates on both lung fields

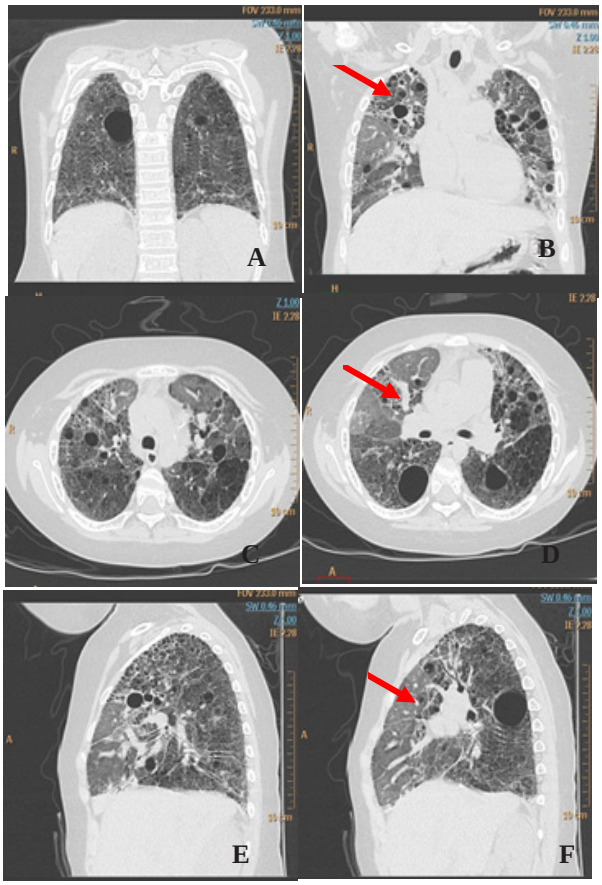


Figure 5. Chest CT scan done of an 8 year old female with interstitial lung disease on admission. There are reticular and linear pattern due to fibrosis. (A,B) with note of 1-2 cm air containing cysts (A, D, F). There are ground glass pattern seen in the middle lobes (D,F)

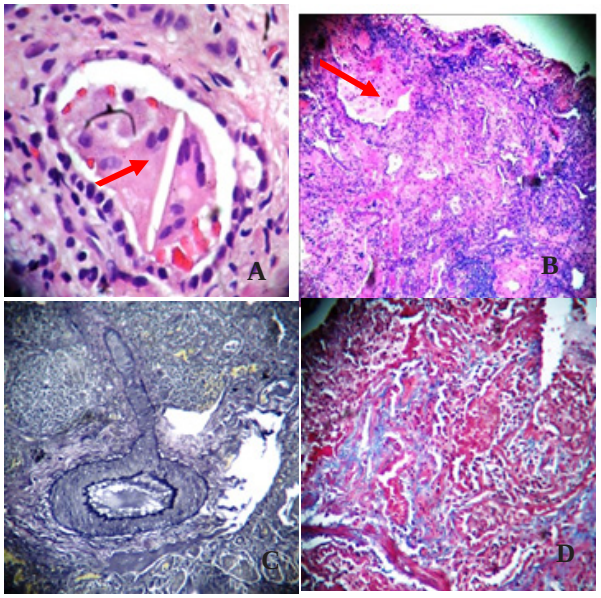


Figure 6. Microscopic section of the right lung from an 8 year old female with interstitial lung disease. A. foreign-body type giant cells are associated with crystalline material,(probably cholesterol crystals (arrow); B. Few dilated bronchioles filled with numerous foamy macrophages, edema fluid, scant fibrinous material, and inflammatory cells. The air spaces (alveoli) are compressed, slit like to irregular, and mostly lined by metaplastic cuboidal cells with the interstices widened by cellular infiltrates composed of lymphocytes, plasma cells, some eosinophils and neutrophils. C. Masson's trichrome stain highlights the increase in collagenous fibers within the interstitium and alveolar walls. D. Elastic (von Gieson) stain shows rare small arteries with mild medial thickening

DISCUSSION

Interstitial lung disease (ILD) represents a heterogeneous group of chronic respiratory disorders associated with morbidity and mortality rate of 15% in the pediatric age group.[10] The spectrum of ILD is described as varying morphology of inflammatory interstitial diseases, of unknown cause, with no definite diagnoses, and probably related to immunity.

There are important differences between ILDs in adults and chILD.[3] ILDs in adults are more common than chILDs, which can occur in the context of the maturing lung. They may share similar etiology, however, they may present differently histologically. There are also some specific forms of ILD that are only seen in children. ILDs in children are more difficult to manage.

Cases of idiopathic ILD have been documented, although they may be linked to some systemic disorders. Recently, genetic causes of ILD were considered.[4,5,9] Although rare in children, there have been reported cases of hereditary types. Although there have been cases of systemic disorders causing familial type of ILD in children that were identified, these are rare, especially in our setting. Among these systemic disorders that are related to ILD, there is little information available on the relationship of connective tissue disease (CTD) causing ILD in children.

Juvenile idiopathic arthritis (JIA), representing heterogeneous group of disorders characterized by a chronic inflammatory arthritis, is the most common rheumatic disease in childhood. It is characterized by inflammatory arthritis with symptoms lasting for at least a week and presenting by 16 years of age.[12] It is a diagnosis exclusion and its current terminology of JIA was developed by the International League of Associations for Rheumatology to create an international consensus on the diagnosis of persistent childhood arthritis.[13] Etiology of JIA remains to be unknown; however, there have been association with some infectious agents. It is considered an autoimmune disease, with possible genetic connection. Patients with JIA have a positive history of RA.[13] JIA, which is more common in females than males, has an incidence of 5–18 per 100,000, and prevalence of approximately 1 per 1,000 children in USA.[12] Recently, the reported prevalence of JIA ranges from 0.07 to 4.01 per 1,000 children, and the annual worldwide incidence varies from 0.008 to 0.226 per 1,000 children.[14]

The risk of developing JIA is thought to be influenced by a combination of multiple genes and environmental factors. In one cohort study on the multi-ethnic influence on the risk of developing JIA, European descent and native of North America were at a higher risk of developing JIA. Those of black origin, Asians and Indian subcontinent origin had a statistically significantly lower likelihood of developing such illness.[15] Patients of European ancestry present at an earlier age, had an increased risk of developing all subtypes of JIA, with the exception of the RF-positive polyarticular JIA and systemic JIA.[14] This study states that predisposing genetic factors exist and that the European ancestry is an important factor for the development of JIA.

Environmental factors, such as breastfeeding, infections and maternal smoking, were associated with the risks of JIA.[14,16] In individuals who were HLA-DR4 negative (i.e. those that do not carry this aspect of genetic predisposition to polyarticular JIA) breastfeeding for greater than three (3) months has a protective effect on the development of RF positivity. (OR 0.18; 95% CI 0.04, 0.99; P=0.049).[16] Certain infections, particularly Epstein-Barr Virus (EBV), human parvovirus 19 and streptococcus, were associated with risk of JIA development.

The diagnosis of Familial JIA requires the identification of a genetic component. The cumulative incidence of the disease in family members would justify genetic predilection.[14,17-21] Muaz and colleagues[17] identified a family with non-consanguineous parents in which JIA was identified in three out of four male siblings. Both the clinical and radiological presentation of these patients was compatible with polyarticular type of JIA. There is also a report of a familial occurrence in five out of seven siblings, with the parents being distantly related. Their symptoms were similar with monoarticular and oligoarthritis course of JIA.[18] In one study involving the largest cohort of JIA affected sibling pairs (ASP), there is concordance of the disease onset and type among these siblings.[19] Prahalad and co-workers estimated the degree of familial aggregation of JIA.[20] The risk was increased among the first- and third-degree relatives of children with JIA and recurrence risk was highest among first degree relatives and substantially lower among third-degree relatives. There was an increased risk of JIA for various levels of type 1 DM. The concordance rate among monozygotic twins is 25%, suggesting prevalence ~250 times than the population prevalence. On the other hand, Zeft and colleagues[21] showed that there were differences in the prevalence of autoimmune (AI) diseases among maternal and paternal relatives of children with JIA. Overall the prevalence of AI diseases was significantly increased among maternal second degree relatives as compared to that of controls (14% vs. 4.3%; p <0.001). The prevalence of AI diseases among mothers of JIA cases was three times that of fathers (32.3% vs. 11.4%; p <0.0001). The prevalence of AI diseases was significantly higher among all maternal second-degree relatives of children with JIA than that of all paternal second-degree relatives [14% vs. 7.9%; p<0.004]. These results demonstrate that maternal relatives of children with JIA have an increased prevalence of autoimmunity compared to paternal relatives, suggesting that there might be maternal parent of origin effect in JIA.[14]

Heritable component to JIA risk mainly contributed from twin and family studies, showed an increased prevalence of JIA in twins and siblings of JIA probands. About 20-30 % of concordance rates were seen in monozygotic twins.[22] The concordance rates quoted above are far from 100%, stating that certain environmental factors that the twins are individually exposed to must also contribute on the JIA risk.[23] Studies reported that in siblings, they tend to develop JIA at the same age of onset rather than the same calendar year.[20] Kwoh et al. states that probands from multiplex families have a 1:1 male to female ratio and have a younger age of onset as compared to the probands from simplex families. In addition, one third of families that appear to have familial cases may actually involve the chance occurrence of two sporadic cases within the same family.[12]

With regard to its pathogenesis, abnormal reparative process triggered by an acute inflammatory process as a response against infectious and exogenous agents, may result in structural remodeling, scarring and fibrosis.[3.24] The involvement at the alveolar level may manifests as significant impairment in gas exchange. In chILD, these processes occur in an organ that is still developing, further complicating the pathophysiology. The impairment in gas exchange may result to pulmonary hypertension and vascular remodeling. Honeycombing, which are a result of replacement of portions of the lung by fibrotic septae, are seen in end stage of ILD. These changes may also result to reduction in lung compliance, causing an increase in the energy expenditure for breathing.[24]

In CTDs, the systemic inflammation may affect the different components of the respiratory system. It was theorized that the lung fibrosis seen in RA was initiated by an initial cellular inflammatory process and a secondary fibroproliferative process. Once the fibroproliferative process begins, the clinical course and gene expression profile become similar to those of

idiopathic pulmonary fibrosis (IPF), the prototypical fibrosing lung disease, and the disease becomes unresponsive to immunosuppression.[25]

In a case series by Takastuki and co-workers,[26] three children presenting with pulmonary arterial hypertension were subsequently found to have auto-antibodies. There is subtlety in the manifestation of PAH and is usually part of the initial presentation of childhood connective tissue disease (CTD).[26]

Several diagnostic examinations are warranted in the management of ILDs. They may include imaging, bronchoalveolar lavage, and biopsy. Chest radiograph is nonspecific and nondiagnostic. There are four radiographic patterns usually seen: reticular, reticulonodular, reticulogranular and ground-glass patterns. In advanced cases, honeycombing is seen. In some children, the chest radiograph maybe normal.[4] On the other hand, high resolution computed tomography (HRCT) is more sensitive than chest x-ray in capturing the early stages of alveolar wall thickening. It is useful in assessing disease severity as well as identifying the most suitable site for biopsy. Chest CT is more accurate (66% correct diagnoses) compared with that of chest radiography (45% correct diagnoses) in the diagnosis of chILD.[2]

The diagnostic yield of bronchoalveolar lavage (BAL) in the context of ILD in the otherwise normal host is poor. However, it is diagnostic in a few specific conditions (IPH, LCH, PAP and lipoid pneumonia due to aspiration of oily medications). It is usually carried out in the most affected area. In diffuse involvement, it is performed in the right middle lobe, or for infants, in the lower lobe.[2] Bronchoalveolar lavage has also been used to diagnose alveolar proteinosis, lysosomal storage disorders, histiocytosis, and surfactant protein deficiency in children.[1]

Majority of chILD will require a biopsy for diagnosis, and this should not be delayed unless there is a realistic prospect that lesser procedures will obviate the need for this invasive procedure. There are several types of lung biopsy: open lung biopsy (OLB) with limited thoracotomy; video-assisted thoracoscopic (VAT) biopsy; transbronchial biopsy (TBB); and percutaneous lung biopsy with HRCT scan of the chest.

Percutaneous biopsy would seem the least invasive of the possible transthoracic approaches and has been reported in one series to have a high success rate with minimal complication. Another group reported a diagnostic yield of only 14/24 patients (58%) despite using CT guidance and 17% subsequently required OLB This procedure may have a role but needs further evaluation.[1]

Video-assisted biopsy can be safely performed even in small children. In one study involving 36 children, histological diagnosis was obtained in 97%, therapy was directly affected in 83% and there were no postoperative complications.[27] The procedure may not be suitable in the smallest patients because of the size of the trocar involved and in certain chILD, where high proportions of the patients are infants (12/27 in the present series).[28]

On the other hand, transbronchial biopsy (TBB) is usually performed to obtain a tissue diagnosis for a variety of conditions, such as tumors, chronic infiltrative diseases, and infections, and for lung transplant monitoring. The pieces of tissue are too small to be useful in the context of an undiagnosed interstitial process Furthermore, TBB is contraindicated when there is pulmonary hypertension. Complications associated with the procedure were minimal and the results of the biopsy sample enabled each child to be treated ppropriately.[29,30]

Open lung biopsy in the diagnosis of chronic ILD in children, carries a low risk of morbidity (3%) and mortality (1%).[29] It provide a specific histological diagnosis in a high proportion of patients (93%) and help initiate or change management (56%), with few complications related directly to the biopsy procedure (11%). In another study of children with ILD,[29] a specific diagnosis was provided by OLB in 53%, but there was a lower diagnostic yield in children aged 2 yrs.[24,29] The in-hospital mortality rate was 20%. Reserved for patients in whom a diagnosis that might change therapy is suspected and the underlying condition does not have a high mortality, it was least successful in making a definitive diagnosis in immunocompromised

children. (5 of 43, 28%; p 1.024) It is most successful in the patients with some element of pulmonary hypertension (17 of 18, 94%; p=0.006). The risk of the procedure is highest in patents requiring mechanical ventilation (15 of 19, 65%; p=1024) or ECMO support (6 of 8, 75%; p=0.007).[29]

One study compared the diagnostic yields of TBB, VAT and OLB in immunocompetent children.[2] Rothenberg et al. reported on the safety and efficacy of VAT lung biopsies in a series of infants and children with ILD.[3]

Having described these possibilities, it has been found that a positive serological diagnosis is rare in chILD. DNA tests for mutations in SPB, SPC and ABCA3 are only available at specialist centers.[1]

The management of ILD depends on its underlying cause. In some cases wherein no cause has been identified, a therapeutic trial with systemic steroids is prudent. The dose and duration of steroid therapy depends on the severity of illness and therapeutic response. It can be given initially at a high dose with gradual tapering or as a pulse therapy using IV methylprednisolone.[4] Other forms of immunosuppressive and immunomodulating treatments, such as cyclophosphamide, azathioprine, methotrexate, hydroxychoroquine, and chloroquine, have all been tried with varying success. Post-infectious organizing pneumonia usually responds to corticosteroids.[4] Hydroxychloroquine has anecdotal success in ILD and alveolar hemorrhage syndromes.[3] Methotrexate and cyclophosphamide has a dose-limiting pulmonary toxicity, limiting its use. In one study in 2010, azithromycin treatment resulted in clinical improvement in children with ILD with surfactant metabolism disorder.[32] In all forms of ILD, if medical therapy has failed, lung transplantation can be tried.[3]

On the other hand, several treatment modalities are available for those with JIA. Some of these may be given to patients with ILD as well. According to Haines and colleagues, nonsteroidal anti-inflammatory drugs (NSAIDS), intraarticular steroids, tumor necrosis factor-alpha (TNF-α), and autologous stem cell transplant can be given to patients with JIA.[33]

Moreover, clinicians utilized biomarker in ILD to predict responsiveness and progression of disease. They provide prognostic information that may help clinicians in the management of patients with ILD.[34]

With regards to survival, Fan and co-workers devised a severity of illness scoring system, which has been shown to be a predictor of survival. The scoring included the following parameters: presence of symptoms, hypoxemia at rest, hypoxemia during exercise and presence of pulmonary hypertension. The following parameters, on the other hand were not associated with decreased survival: family history of ILD, age of onset, weight, presence of clubbing, crackles and duration of illness. Those with lower scores had higher survival probabilities. However, there is a need for further investigation to determine whether the changes in the score over time is associated with disease progression.[35]

SUMMARY

In summary, we presented a case of an 8 years old female, who initially presented with recurrent cough and colds, and eventually had swelling of joints and pulmonary hypertension. She had a family history of death due to unknown cause in the family and SLE with overlapping JIA and ILD. She was found to be rheumatoid factor (RF) positive. A consideration of possible ILD was noted on her chest CT scan. Lung biopsy revealed idiopathic fibrosing alveolitis. On further evaluation, a diagnosis of juvenile idiopathic arthritis was established.

Hereditary forms should always be considered when one or two of the family members were presented with such disease. We should always remember that the adult type of ILD is markedly different from the pediatric type. Children with ILD should be treated as such and not as small adults, since the classification of the adult-ILD is different from pediatric patients.

In this report we describe a rare kind of illness, a familial ILD in a Filipino child. Searching for the known etiology of such disease requires a thorough history, complete physical examination and prudent laboratory

examinations. Once diagnosed, clinicians should always be vigilant since this disease entails a higher morbidity and mortality rate.

REFERENCES

1. Chernick V, Kendig, EL. Kendig's Disorders of the respiratory tract In children. 7th ed. Philadelphia (PA) : Elsevier, c2006.
2. Paiva MAS, Amaral SMM. Chronic interstitial lung diseases in children. J Bras Pneumol. 2009;35(8):792-803.
3. Shaheen M. Clinical approach for childhood interstitial lung disease child: journey to solve the mystery. Egypt J Bronchol. 2011;5(1):55-79.
4. Hartl D, Griese M. Interstitial lung disease in children – genetic background and associated phenotypes. Respir Res 2005:6(1);32.
5. Grutters JC, du Bois RM. Genetics of fibrosing lung diseases. Eur Respir J. 2005; 25: 915–927.
6. Hilton RC, Pitkeathly DA. Familial association of rheumatoid arthritis and fibrosing alveolitis. Ann Rheum. Dis.1974:33;191-195.
7. Allam JS, Limper AH. Idiopathic pulmonary fibrosis: is it a familial disease? Curr Opin Pulm Med. 2006 Sep; 12(5):312-7.
8. Ryu JH, Daniels CE, Hartman TE, Yi ES. Diagnosis of interstitial lung diseases. Mayo Clin Proc. 2007 Aug; 82(8):976-86.
9. Kim HB, Lee SY, Kim JH, Jang JY, Huh J, Park SJ, Hong SJ. Familial interstitial lung disease in two young Korean sisters. J Korean Med Sci. 2005 Dec; 20 (6): 1066-9.
10. Clement A, Eber E. Interstitial lung diseases in infants and children. Eur Respir J. 2008 Mar;31(3):658-66.
11. Prahalad S, Ryan MH, Shear ES, Thompson SD, Glass DN, Giannini EH. Twins concordant for juvenile rheumatoid arthritis. Arthritis Rheum. 2000 Nov; 43 (11):2611-2.
12. Jordan A, McDonagh JE. Juvenile idiopathic arthritis: the paediatric perspective. Pediatr Radiol. 2006 Aug; 36(8):734-42.
13. Olson JC. Juvenile idiopathic arthritis: an update. WMJ. 2003;102(7):45-50.
14. Youn-Soo H, Joong-Gon K. Pathogenesis and clinical manifestations of juvenile rheumatoid arthritis. Korean J Pediatr. Nov 2010; 53(11): 921–930.
15. Saurenmann RK, Rose JB, Tyrrell P, Feldman BM, Laxer RM, Schneider R, Silverman ED. Epidemiology of juvenile idiopathic arthritis in a multiethnic cohort: ethnicity as a risk factor. Arthritis Rheum. 2007 Jun;56(6):1974-84.
16. Ellis JA, Munro JE, Ponson AL. Possible environmental determinants of juvenile idiopathic arthritis. Rheumatol. 2010;49:411-425.
17. Shafi S, Muaz A, Ahmed S, Salim A, Siddika MM, Deb B. Family of juvenile idiopathic arthritis: case report. Bangladesh J Child Health 2010; 34 (1): 31-33.
18. Yodfat Y, Yossipovitch Z, Cohen I, Shapira E. A family with a high incidence of juvenile rheumatoid arthritis. Ann. Rheum. Dis. 1972; 31:92-94.
19. Moroldo MB, Chaudhari M, Shear E, Thompson SD, Glass DN, Giannini EH. Juvenile rheumatoid arthritis affected sibpairs: extent of clinical phenotype concordance. Arthritis Rheum. 2004 Jun;50(6):1928-34.
20. Prahalad S, Glass DN. Is juvenile rheumatoid arthritis/ juvenile idiopathic arthritis different from rheumatoid arthritis? Arthritis Res. 2002; 4 (suppl 3):303-310
21. Zeft A, Shear ES, Thompson SD, Glass DN, Prahalad S. Familial autoimmunity: maternal parent-of-origin effect in juvenile idiopathic arthritis. Clin Rheumatol. 2008 Feb;27(2):241-4.
22. Prahalad S. Genetic analysis of juvenile rheumatoid arthritis: approaches to complex traits. Curr Probl Pediatr Adolesc Health Care. 2006 Mar;36(3):83-90.
23. Kwoh CK, Venglish C, Lynn AH, Whitley DM, Young E, Chakravarti A. Age, sex, and the familial risk of rheumatoid arthritis. Am J Epidemiol. 1996 Jul 1;144 (1):15-24.
24. Bush A, Nicholson AG. Paediatric interstitial lung disease. Eur Respir Mon, 2009, 46, 319–354.
25. Brown KK. Rheumatoid lung disease. Proc Am Thorac Soc. 2007; 4:443- 448.
26. Takatsuki S, Soep JB, Calderbank M, Ivy DD. Pediatr connective tissue disease presenting with signs and symptoms of pulmonary hypertension in children. Cardiol. 2011 August ; 32(6): 828–833.
27. Coren ME, Nicholson AG, Goldstraw P, Rosenthal M, Bush A. Open lung biopsy for diffuse interstitial lung disease in children. Eur Respir J. 1999 Oct;14(4):817-21.
28. Clement A; ERS Task Force. Task force on chronic interstitial lung disease in immunocompetent children. Eur Respir J. 2004 Oct;24(4):686-97.
29. Visner GA, Faro A, Zander DS. Role of transbronchial biopsies in pediatric lung diseases. Chest. 2004 Jul; 126(1):273-80.
30. Smyth R, Carty H, Thomas H, van Zelzen D, Heaf D. Diagnosis of interstitial lung disease by a percutaneous lung biopsy sample. Arch Dis Child. Feb 1994; 70(2): 143–144.
31. Kramer MR, Berkman N, Mintz B, Godfrey S, Saute M, Amir G. The role of open lung biopsy in the management and outcome of patients with diffuse lung disease. Ann Thorac Surg. 1998 Jan;65(1):198-202.
32. Epaud R, Kron C, Flamein F, Nimal D, Nathan N, Corvol H, et al. Azithromycin in interstitial lung disease associated with surfactant metabolism disorders. Available at URL: http://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2010.181.1_MeetingAbstracts.A3993. [retrieved on] 20 October 2014.
33. Haines KA. Juvenile idiopathic arthritis: therapies in the 21st century. Bull NYU Hosp Jt Dis. 2007;65(3):205-11.
34. Tzouvelekis A, Kouliatsis G, Anevlavis S, Bouros D. Serum biomarkers in interstitial lung diseases. Respir Res. 2005 Jul 21;6:78.
35. Fan LL, Kozinetz CA. Factors influencing survival in children with chronic interstitial lung disease. Am J Respir Crit Care Med. 1997 Sep;156(3 Pt 1):939-42.