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Editorial

"Publish or Perish"

That was what Dr. Camilo I. Porciuncula used to say to us when he took over the Editorship of the Philippine Heart Center Journal after being appointed the Assistant Director for Education and Research shortly after Dr. Ludgerio Torres became the Director of the Philippine Heart Center (PHC) and expressed his intention of "reviving" the PHC Journal. And so the story goes with Dr. Jose A. Yulde as he assumed the Editorship of the PHC Journal from Dr. Porciuncula after he succeeded him as Assistant Director for Education and Research. A tradition of excellence in research is now continued with this issue of the PHC Journal.

The Philippine Heart Center or the Heart Center has always been the Center of cardiovascular care in the Philippines. Over the years since 1975 or for the last 30 years, many training centers have risen to meet the demand for cardiovascular training and sophistication in cardiovascular diagnosis and treatment. But the Heart Center has withstood the "competition" and has evolved with the current trends in Cardiovascular Science to become the standard from where other Institutions base and pace their own research and training. This is evident in the clamor for papers for presentation in international and local Meetings

Research has always been a difficult challenge for all of us who are students of Cardiology and its allied disciplines. Often, during our training years, we try to take the easy way out in doing research work and dismissing the completion of a research paper as a mere "requirement" or "formality" for promotion or graduation. It is not a question of a trainee's priority or whether Training goes ahead of Research in preference. In fact, it is from research that we get our best training. And there is really no "easy" way out. The value of research is no better emphasized than by the contents of this issue of the PHC Journal.

The research work presented in this issue of the PHC journal is an excellent compilation of the modest work of the Fellows and Medical Consultants and crosses all inroads of Cardiology and the Allied specialties that make up the services for patient care that only the Heart Center can provide. The Heart Center, therefore, remains foremost in Cardiovascular Research. The PHC Journal will likewise remain the testament to this.

The tradition of excellence continues.

Aristides G. Panlilio, MD
Associate Editor

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Original Article

Absolute Neutrophilia as Predictor for the Development of Early-Onset Congestive Heart Failure in Patients Admitted for Acute Myocardial Infarction

Wilfredo M. Ypil Jr. MD, Ramoncito Tria MD, Santos Jose G. Abad MD.

BACKGROUND: ***The occurrence of congestive heart failure (CHF) during hospitalization for acute myocardial infarction (AMI) is an important factor influencing morbidity and mortality. AMI is frequently associated with leukocytosis. Studies have shown that the cytokines released from neutrophils have negative inotropic effects and hence, contribute to the development of CHF. This study aims to determine if there is an association between absolute neutrophil count (ANC) on admission of patients with AMI and the development of early-onset CHF in such patients.***

DESIGN AND SETTING: ***Retrospective, case-control study at Philippine Heart Center (PHC), tertiary medical center. Patients: A total of 152 patients discharged with a diagnosis of AMI who presented initially as Killip 1 on admission between January 1,1996 to December 31,2000, were included. Main Outcome Measure: Development of CHF within 4 days from hospital admission documented in the medical records as clinical symptoms (progression to Killip 2, 3 or 4) confirmed by chest radiologic and/or echocardiographic findings.***

RESULTS: ***Statistical analyses were performed to examine the relation between the ANC and the development of CHF in the first 4 days after AMI while controlling for baseline characteristics and therapeutic interventions. The mean ANC is 12.3 +/-0.5 X 109/L in the group of patients who developed CHF compared with 7.8 +/-0.3 x 109/L in those who did not. Multivariable analysis revealed a significant correlation with increasing ANC and subsequent development of CHF (adj. OR = 10.8; 95% CI = 5.08-22.97). Other factors found to have a strong association with devel opment of CHF are the presence of diabetes mellitus (adj. OR = 2.48; 95% CI=1.44, 5.38) and use of nitrates (adj. OR = 3.12 95% CI = 1.5-6.47). Subgroup analysis further revealed that ANC is directly correlated with Killip class on day 4 (r = 0.565; p < 0.001).***

CONCLUSIONS: ***High ANC on admission in patients with AMI is associated with the early development of CHF, which may help in the identification of high risk patients who might benefit from more aggressive interventions to prevent or reduce the risk of CHF.***

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Keywords: acute myocardial infarction (AMI), congestive heart failure (CHF), leukocytosis, neutrophilia, absolute neutrophil count

The identification of factors that can be used to predict prognosis of patients with acute myocardial infarction (AMI) has been a challenge since the late 1960's. The occurrence of heart failure during hospitalization for AMI is an important factor influencing short- and long-term morbidity and mortality. Previous studies observed that the incidence of heart failure during AMI either in the intensive care unit or before discharge is 22%.[1] After hospital discharge, heart failure occurs at a rate of 2% per year thereafter up to 10 years.[2] A study by Ali et al observed a bimodal distribution of heart failure after a first AMI with an initial increased occurrence on the first day and again 4 to 7 days after the event.[3]

Acute myocardial infarction is frequently associated with leukocytosis and an elevated peripheral neutrophil count.[4,5] Neutrophils may, in part, mediate the vascular injury with subsequent ischemia, and the neutrophil count could thereby, reflect the intensity of that process. Neutrophils may also occur in response to myocardial necrosis, which is a potent acute phase stimulus that is associated with a local and systemic inflammatory response.[6] Activated leukocytes are postulated to be involved in the rupture of atherosclerotic plaques and to be responsible for the acute coronary syndromes.[7]

In prospective studies from the U.S., France and Japan, total leukocyte count was seen to be positively correlated with future occurrence of AMI, reinfarction, and/or in-hospital death.[8-13]

Surviving patients with AMI are at an increased risk for the occurrence of congestive heart failure (CHF), reinfarction, arrhythmias, and sudden cardiac death.[14-16] However, CHF con-

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tinues to be the prominent clinical problem after AMI, with a poor long-term prognosis, as indicated by the 5-year mortality rate of @ 50% from the time of diagnosis.[17] In the United States, the associated costs are in excess of $40 billion dollars in health care per year.[6]

Accumulating evidence suggests that oxidative stress and the release of proinflammatory mediators/cytokines are known to have negative inotropic effects, such as interleukins (IL-6, IL-2, IL-1b), and tumor necrosis factor a, during myocardial ischemia probably contribute to the development of CHF.[16, 18-19]

Significance and Objectives of the Study

Relatively few studies have examined the relation between leukocytosis (or neutrophilia) and the short-term risk of cardiac events such as CHF after AMI. A recent study by Kawaguchi et al. found a strong association between the band neutrophil count and the presence and severity of coronary atherosclerosis demonstrated at angiography.[20] In a prospective study of patients with chest pain, relative lymphocytopenia and relative neutrophilia were found to be accurate early markers of AMI.[5] The recent study by Kyne et al. demonstrated that the presence of relative neutrophilia on admission to the hospital in patients with AMI may be a useful early indicator of patients at high risk for developing CHF.[6]

With such results, absolute neutrophilia may serve as a simple, inexpensive, non-invasive marker to identify patients who are at high risk for development of CHF and early in-hospital mortality after AMI. Furthermore, if the peripheral neutrophil count truly reflects the myocardial inflammatory response, further interventions that are designed to limit this response could help to reduce morbidity and mortality rates associated with CHF occurring after AMI.

Assuming that the peripheral leukocyte count, particularly the absolute neutrophil count is a marker of the intensity of the peri-infarction myocardial inflammatory response, our objective is to test the hypothesis that there is an association between high absolute neutrophil count on admission and early development of post-infarction CHF.

Methodology

Study design and Selection of Study Population

This is a retrospective, case-control study conducted at Philippine Heart Center, a tertiary hospital. From the hospital records registry, a total of 1053 patients were diagnosed to have acute myocardial infarction (ICD-9-CM Code 410) admitted between January 1, 1996 to December 31, 2000. Only 860 charts (81%) were retrieved and individually evaluated.

A total of 788 patients fulfilled the WHO criteria for the diagnosis of AMI, of which, 340 patients were eliminated either because interventions were already done at a primary or secondary health care unit or time interval from onset of chest pain was more than 12 hours on presentation. Additional 242 patients were further eliminated because they were in Killip Class 2-4 on presentation. Furthermore, 54 patients (39, with documented infection; 8, with chronic renal insufficiency; 3, with gastrointestinal hemorrhage; 2, with documented malignancies; and 2, with no complete blood count determination taken) were eliminated. A final cohort of 152 patients was included in the study.

Data Collection, Outcome Measures and Variable Classification

Based on the patients' records, the following data were obtained: age, sex, location of infarct by ECG, coronary risk profile (hypertension, diabetes mellitus, smoking history), laboratory results (total WBC count, % neutrophils in the differential count, absolute neutrophil count, total CK and CK-MB) and therapeutic regimen used on admission (use of reperfusion strategies such as thrombolysis and PTCA, use of anticoagulants, antiplatelets, beta blockers, nitrates, ACE inhibitors and calcium channel blockers).

Outcome measures include the development of CHF, as described by clinical signs and symptoms with radiologic evidence of pulmonary congestion and/or echocardiographic finding of contractile dysfunction (Ejection fraction <0.40), within 4 days from admission. Four days was chosen as cutoff because after this time, the development of CHF may be influenced by therapeutic intervention and/or other post-infarction complications and therefore, the neutrophil count might be less relevant.[5-8, 13] Furthermore, the 4th day coincides with the later peak of the bimodal distribution of the occurrence of heart failure after an AMI which is reflective of the short and long-term prognosis of these patients.[3]

Age, total CPK, CK-MB values, total WBC count, percentage neutrophil count, and absolute neutrophil counts were recorded as continuous variables. To improve power for analysis across the groups and to adjust for the fact that anterior infarcts are often associated with a worse prognosis and increased risk of development of systolic dysfunction, location of infarct was dichotomized into anterior versus other (inferior, posterior, RV).

The other variables that were categorized: sex (male vs. female); hypertension, diabetes mellitus, smoking history (present vs. absent); use of thrombolytic agents, PTCA, ASA and other antiplatelet agents, heparin, beta blockers, ACE inhibitors, nitrates and calcium channel blockers (use vs. non-use); and the development of CHF within 4 days from admission (present vs, absent). For the purpose of analysis, those who developed CHF were further trichotomized to Killip Class (2, 3 or 4).

Statistical Analysis

The distribution of age, sex, comorbidities, location of infarct, laboratory values and therapeutic interventions were

analyzed by means of standard deviations for continuous variables and proportions for categorical variables. The Student t-test was used for comparison of the mean total WBC counts, percentage neutrophil counts and absolute neutrophil counts of patients who did have postinfarction CHF and those who did not have postinfarction CHF.

We compared other candidate predictors by using Chi-square or Fisher's exact test for binary variables, the Mantel-Haenszel chi-square trend test for multicategory variables and Student t-test for means of continuous variables of patients who had CHF versus those who did not. Correlations between continuous variables were assessed by use of Spearman's correlation. An a level of $p<0.05$ was considered statistically significant.

Absolute neutrophil count and all covariates with a value of $p<0.05$ were entered into a multivariable stepwise logistic regression analysis. This was checked for confounding and effect modification. Adjusted odds ratios were computed using two-by-two table analysis using software by Jerry Keightley and Robert Centor. The 95% confidence intervals were computed using the Sato method.

Results

Baseline Characteristics of Study Cohort

The study cohort was predominantly male (78%) with a mean age of 57 + 12.6 years (range 27 to 94). Majority (62%) had anterior location of infarction. More than half were known hypertensives (58%) and were previous smokers (66%).

More than half of these patients received heparin (95%), aspirin (90%), nitrates (91%) and ACE inhibitors (57%). Only 2 out of 5 patients received reperfusion therapy, either with the use of thrombolytic agents or primary PTCA (Table 1).

Univariate Predictors of CHF

In 74 (49%) patients, CHF developed within the first 4 days of hospital admission, documented as clinical signs and symptoms compatible with the diagnosis of CHF. Of these, 46 (62%) had radiologic evidence of pulmonary congestion and 34 (46%) had echocardiographic findings of systolic dysfunction (EF<0.40)

Out of these 74 patients who developed CHF, 54 (73%) progressed to Killip II, 15 (20%) progressed to Killip III while the remaining 5 (7%) progressed to Killip IV.

The total WBC count, percentage neutrophil and absolute neutrophil count on admission was found to be highly significant predictors of subsequent development of CHF. (Table 2) Subgroup analysis of those who developed CHF further revealed that high absolute neutrophil count is moderately correlated with increasing Killip class on day 4 ($r=0.565$; $p<0.001$). *(Figure 1)*

The other significant positive predictor of CHF is the presence of diabetes mellitus. Patients who received beta-blockers and nitrates at the time of admission were apparently protected against the development of CHF. There was no association between the admission total CPK, CPK-MB and leukocytosis, absolute or relative neutrophilia or between total CPK, CPK-MB values and development of CHF.

Table I. Baseline characteristics of the study cohort

Characteristics (n=152)	**Mean or %**
Age (years)	56.9 + 12.6
Sex (male)	119 (78%)
AMI location (anterior)	95 (62%)
Hypertension	88 (58%)
Diabetes Mellitus	35 (23%)
Smoking history	100 (66%)
Labs on admission: Total WBC count	12.9 + 4.11
Percent neutrophil	0.75 + 0.12
Absolute neutrophil count	9.96 + 4.12
Total CPK	1190.5 + 1331.7
CPK- MB	95.3 + 199.7
Therapeutics: Thrombolytic agents	59 (39%)
PTCA	3 (2%)
Aspirin	137 (90%)
Ticlopidine or clopdogrel	10 (7%)
Heparin	144 (95%)
Nitrates	139 (91%)
Beta blockers	73 (48%)
ACE inhibitors	86 (57%)
Calcium channel blockers	5 (3%)

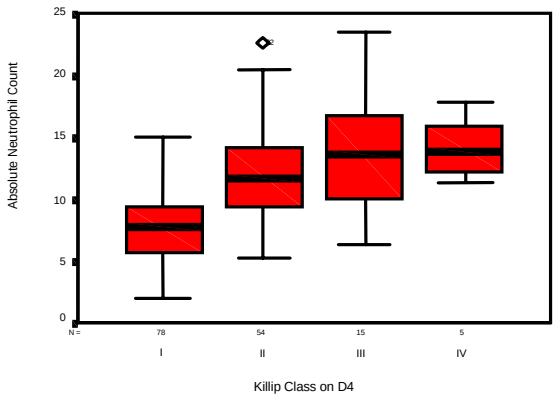

Figure 1. The association of absolute neutrophil count with the development of congestive heart failure categorized further into Killip class on the 4th day post-infarction. (r=0.565; p<0.001)

Multivariable Analysis

The absolute neutrophil count (adjusted OR=10.8; 95% C.I.=5.0826-22.9709) remained significantly associated with subsequent development of CHF even after adjusting for diabetes mellitus and for other predictors such as the use of beta blockers and nitrates. The presence of diabetes mellitus was also associated with development of CHF which persisted after multivariable analysis (adjusted OR=2.4804 95% C.I.=1.1441-5.3774). Patients who received nitrates and/or beta-blockers had a reduced likelihood for the development of CHF. Interaction terms designed to assess whether the effect of absolute neutrophilia was different among those who received beta-blockers and nitrates compared with those who did not receive these agents revealed contrasting results. Significant correlation was noted with the use of nitrates (adjusted OR=3.1169 95% C.I.=1.5013-6.4710) but none was observed with the use of beta-blockers in the final analysis (p=0.0544). (Table 3)

Table II. Variables associated with development of early-onset CHF post-AMI

Characteristics	CHF (N=74)	No (N=78)	CHF P value
Age (years)	58.5 + 1.6	55.4 + 1.3	0.13 NS
Sex (male)	56 (76%)	63 (81%)	0.45 NS
AMI location (anterior)	50 (68%)	45 (58%)	0.28 NS
Hypertension	46 (62%)	42 (54%)	0.38 NS
Diabetes Mellitus	23 (31%)	12 (15%)	0.02*
Smoking history	51 (69%)	49 (63%)	0.53 NS
Admission lab values:			
-Total CK (Mean)	1256.45	1127	0.55 NS
-CPK-MB	110.66	80.73	0.36 NS
-Total WBC count	15.2 + 0.5	10.8 + 0.3	<0.001**
-% Neutrophil	0.8 + 0.01	0.71 + 0.01	<0.001**
-Absolute Neutrophil Count	12.3 + 0.5	7.8 + 0.3	<0.001**
Therapeutics:			
Thrombolytic agents	31 (42%)	28 (42%)	0.55 NS
-PTCA	2 (3%)	1 (36%)	0.61 NS
-Heparin	70 (95%)	74 (95%)	1.00 NS
-ASA	67 (90%)	70 (90%)	0.87 NS
-Ticlopidine, clopdogrel	5 (7%)	5 (6%)	1.00 NS
-Beta blockers	29 (39%)	44 (56%)	0.034*
-ACE inhibitors	41 (55%)	45 (58%)	0.78
-Nitrates	64 (86%)	75 (96%)	0.033*
-Calcium channel blockers	2 (3%)	3 (4%)	1.0 NS

Table III. Variables associated with development of early-onset CHF post-AMI

Variable	Adjusted OR	95% C.I.
Absolute neutrophil count	10.8	5.0826, 22.9709
Diabetes Mellitus	2.48	1.441, 5.3774
Nitrates	3.12	1.5013, 6.471

Discussion

Our study has clearly shown that increasing absolute neutrophil count is strongly associated with early development of CHF in patients with AMI. This significant correlation persisted even after adjustment with covariates such as diabetes mellitus and the use of beta-blockers and nitrates. This result further strengthened previous reports that show prognostic importance of the neutrophil count for coronary events.[5-7, 11, 13, 20, 21]

In a prospective trial by Thomson, et al. of patients admitted to the hospital with chest pain, relative lymphocytopenia and relative neutrophilia were found to be accurate early markers of AMI.[5]

Kawaguchi, et al., found a strong association between the band neutrophil count but not the total leukocyte count and the presence and severity of coronary atherosclerosis demonstrated at angiography.[20]

Studies carried out in small patient samples and one large population-based study have suggested that increasing leukocyte count is associated with increased short and long-term mortality following AMI.[7] Kyne et al. demonstrated that the presence of relative neutrophilia was found to be a useful indicator of patients at high risk for development of systolic dysfunction.[6] The study by Maisel et al. further showed that increased initial leukocyte count during AMI predicts early ventricular fibrillation.[21]

All these previously mentioned studies have utilized both total leukocyte and relative neutrophil counts only. Considering the variability of the total leukocyte count and the arbitrariness of the relative neutrophil count, our study utilized the absolute neutrophil count, which we deem to be more reflective of the actual neutrophil population.

The pathophysiologic basis for the association between neutrophilia and the risk of coronary events including the development of CHF has been studied in several animal models.[22] Neutrophil infiltration into the ischemic myocardium remains an integral component of the post-AMI inflammatory response. Once activated, these neutrophils adhere to the vascular endothelium. By increasing the vascular resistance and impairing dilation of small coronary arterioles, they may aggravate further myocardial ischemia.[23] Neutrophils, moreover, undergo cellular respiratory bursts and release oxygen-derived free radicals, which are toxic to cells, in an antioxidant-deficit milieu.[16] Interactions between infiltrating neutrophils and resident inflammatory cells within the myocardium may occur resulting in the release of lysosomal enzymes and arachidonic acid metabolites, which may increase coronary artery resistance, leading to development of myocardial dysfunction.[24]

Our study, though, cannot possibly determine whether there is a causal relation between neutrophilia and CHF. Neutrophils may not directly contribute to contractile dysfunction but may be a proxy measurement for other mediators of

inflammation that may be directly involved. A growing body of evidence now suggests that proinflammatory cytokines such as interleukin (IL)-6, IL-2, IL-1B, tumor necrosis alpha and low-molecular-weight inflammatory cytokines of the IL-8 family have negative inotropic effects.[16, 25, 26] These cytokines are released during AMI and during reperfusion of the damaged tissue.

Tanaka et al. had demonstrated that heparin can negate the proinflammatory actions of these cytokines.[27] Unfortunately, this was not demonstrated in our study. Several investigators have suggested that reperfusion of ischemic myocardium augments the inflammatory reactions described above and may cause reperfusion arrhythmias and postischemic contractile dysfunction, also known as "myocardial stunning."[28,29] Our study also failed to demonstrate effects of reperfusion therapy, whether use of thrombolytic agents nor primary PTCA.

ACE inhibitors have antioxidant properties in addition to and unrelated to their effect on the renin-angiotensin system.[14,30] Hence, the effect of neutrophilia on the development of CHF may be attenuated by treatment with ACE inhibitors. This was demonstrated in the study by Kyne et al.[6] However, the current study failed to demonstrate evidence of effect modification by these agents.

The early use of beta blockers exert a modestly favorable influence on infarct size and diminished short-term mortality as shown in the first International Study of Infarct Survival Study (ISIS-1).[31] This could be the reason for the trend towards benefit in reducing risk of developing CHF in our study. However, we did not have sufficient statistical power to analyze and formulate generalizations on the effect of the use of such agents.

There is experimental and clinical evidence that intravenous nitroglycerin may reduce infarct size and improve regional myocardial function. It has also been suggested that nitroglycerin may prevent LV remodeling that frequently occurs after a large transmural MI.[32] In addition, the reduction in right and left ventricular preload resulting from peripheral vasodilation, decreases cardiac work and lowers myocardial oxygen requirements.[33] All these hemodynamic effects could have contributed to the protective effect of nitrates from development of CHF demonstrated in our study.

It was previously demonstrated that the myocardial response to acute ischemic stress is different in older animals compared with younger animals.[34] On the basis of these findings and on our knowledge of the observed increase in the incidence of CHF associated with aging, we hypothesized that the association between neutrophilia and CHF may be different in older adults compared with younger individuals. However, we demonstrated no significant difference in between the two groups.

Cigarette smoking was previously shown to be associated with leukocytosis and risk of ischemic events.[9] However, our study had not shown its association with the absolute neutrophil count and risk of developing CHF.

The total CPK and CPK-MB values might reflect myocardial infarct size, however, no correlation with the absolute neutrophil count was noted. Same observation was noted in a previous study done by Recto et al.[35] in the same institution.

The excessive in-hospital mortality in diabetic patients experiencing AMI correlates primarily with an increased incidence of CHF, although increased reinfarction, infarct extension, and recurrent ischemia also contribute.[36] This further strengthened the findings in the study by Ali et al. in which, diabetes mellitus, aside from increased age and tachycardia, is a predictor for occurrence of the delayed phase of heart failure in AMI.[3]

This study has some limitations. It is generalizable only to similar populations in a tertiary referral centers. Selection bias may have occurred because sicker patients are often referred to this hospital. This could explain in part the higher rate of CHF that was observed in this population (49% compared with the 17% to 23% that was reported in other studies).[37, 38]

Another limitation of this study is that the neutrophil count was measured at only one point in time, and this point (although within 12 hours of symptom onset) was not consistent in all patients studied. Serial neutrophil counts, including presymptom onset counts, might be more helpful in identifying high-risk individuals early. A prospective clinical study of patients with chest pain, in whom prior neutrophil counts are available, would address these issues.

Measurements and correlations with other markers of myocardial injury and neutrophil activation such as C-reactive protein, serum neutrophil elastase, or myeloperoxidase could give a more complete picture of the inflammatory process.

Conclusion

Despite all these limitations, this study demonstrated a significant association between absolute neutrophilia in patients admitted for AMI and the subsequent development of CHF within four days, after adjusting for the presence of diabetes mellitus and therapeutic interventions.

The results suggest that absolute neutrophilia may serve as a simple, readily available, inexpensive and noninvasive marker to identify patients at high risk for development of CHF after myocardial infarction. Since neutrophilia reflects extent of myocardial injury and inflammatory process, future interventions that are designed to limit this response could help in reducing morbidity and mortality associated with CHF occurring after AMI.

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Original Article

Profile of Patients with Suspected Neurocardiogenic Syncope Undergoing Head-up Tilt Test: The Philippine Heart Center Experience

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BACKGROUND: ***Head-up tilt test (HUTT) remains a cornerstone in the diagnosis for unexplained syncope since its introduction in 1986. Several factors have been elucidated as possible predictors of a positive tilt test, which include among others, age, sex, and early heart rate rise. Investigations have also been undertaken to observe response to different medications used in the evaluation of syncope during head-up tilt test.***

OBJECTIVE: ***It is the objective of this study to determine the profile of patients with suspected neurocardiogenic syncope undergoing head-up tilt test and the factors that may predict a positive test outcome.***

METHODS AND RESULTS: ***There were 86 patients included in the study. Majority presented with symptoms of syncope and presyncope. Total case findings rate was 37% for all cases, which increased to 74% in patients presenting with a classical prodrome. Age, sex, and ECG did not correlate with a (+) HUTT while the presence of prodrome and early heart rate rise correlated significantly with the outcome. The complication rate was 1%.***

CONCLUSIONS: ***HUTT is a useful tool in suspected neurocardiogenic syncope with 74% case finding rate. The presence of classical prodrome and an early heart rate rise may be a useful guide in predicting a positive outcome for the test.***

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Keywords: hypotension; syncope; neurocardiogenic syncope; tilt test

Syncope is defined as a sudden transient loss of conscious ness and postural tone with spontaneous recovery. The mechanism has been described to be due to a reduction of blood flow to the reticular activating system of the brain, which leads to subsequent loss of consciousness within approximately 10 seconds.[1]

A problem not uncommonly encountered in clinical practice, syncope poses a major concern as it is costly, potentially disabling, can possibly result to injury and may be the only warning before the occurence of sudden cardiac death.[1] The causes of syncope have been classified into four primary types: vascular, cardiac, neurologic/cerebrovascular and metabolic/ miscellaneous. Of particular interest is the reflex-mediated syncope, which consists of increased vagal tone leading to bradycardia, vasodilation, subsequently leading to hypotension and ultimately, presyncope or syncope.

The neurally-mediated hypotension/syncope; also known as neurocardiogenic, vasodepressoer and vasovagal syncope; including carotid sinus syndrome have been recognized as important causes of syncope.[2] This particular type of syncope is described as an abnormality of blood pressure regulation characterized by abrupt onset of hypotension with or without bradycardia usually associated with either reduction of vetricular filling or increased catecholamine secretion. Positive results are subdivided into three types of neurally mediated syncope: cardioinhibitory, vasodepressor and mixed type. Some identified triggers include sight of blood, prolonged standing, pain, warm environment and stressful conditions. In a recent study,[3] evidences pointed to the possibility of syncope being associated with lateralization in the delta frequency of the left side of the brain with the onset of bradycardia and hypotension suggesting the possibile role of the brain with the onset of bradycardia and hypotension suggesting the possible role of the central nervouse system in neurally medicated syncope.[3]

Often, evaluation of syncope is difficult and expensive. Recent experience still showed that a significant number of primary care physicians and even specialists would tend to go for neurologic examinations first (CT scan, MRI) as compared to cardiovascular tests in the evaluation of syncope.[4]

Head-up tilt table testing, introduced in 1986 is an efficient, well-tolerated, and safe tool in the evaluation of patients with unexplained syncope.[5,6] Recent studies have shown 30-45 minutes at an angle of 70 degrees (Westminster protocol). The positive response is the development of syncope or presyncope in association with hypotension and/or bradycardia. The test sensitivity can be increased with fall in specificity by the use of longer duration, steeper tilt angle and provocative agents including isoproterenol, nitroglycerin and edrophonium. The specificity in the absence of provocative agent is estimated at 90%.

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In the Philippine Heart Center, earliest records of head-up tilt test protocol consists of an initial 10-minute observation in supine position with vital signs monitoring every minute for a duration of 45 minutes. The patient is then placed back on a supine position and infused with 1-3 mg/min of isoproterenol, atropine 1 mg or sublingual 5 mg nitrate and the tilt portion repeated for another 15 minutes. Indication to stopping the procedure is the occurence of syncope or presyncope associated with hypotension and/or bradycardia.

Indeed, the head-up tilt test (HUT) has already been considered as the gold standard in the evaluation of syncope. Some characteristics shown to predict a high likehood of positive outcome indicating neurally mediated syncope include: (1) at least two syncopal episodes; (2) no structural heart disease and normal baseline ECG; (3) age <65 years; (4) typical history of neurally mediated syncope, triggering factors plus premonitory signs; and (5) short duration of symptoms and fast recovery without neurologic sequelae. The best predictor however of a positive outcome was noted to be the duration of interval between syncopal episode and baseline HUTT test ($p<0.003$).[7] Trends have shown that among patients undergoing HUTT, age >65 years old appear to have higher incidence of vasodepressor response.[8] Age and sex on the other hand appear to have no effect on the rate of positive test.[9,6] An early heart rate rise (>18 beats /min) had also been implicated as a 100% sensitive marker for a positive response at <15 minutes of tilt with low specificity (61%).[10]

As we currently have no available local data on our patients with suspected neurocardiogenic syncope undergoing head-up tilt test. Additional emphasis will be placed on determining the rate of positive outcome and correlating factors that may possibly predict a positive result of the test.

Objectives

To determine the clinical profile of patients at the Philippine Heart Center with suspected neurocardiogenic syncope undergoing head-up tilt test.

Specific Objectives

1. To describe the presenting symptoms of patients with neurocardiogenic syncope.
2. To determine the overall rate of positive results for the head-up tilt test further subdivided into the positive for baseline tilt and positive after infusion of isoproterenol.
3. To describe the clinical characteristics of patients with positive head-up tilt test.
4. To determine the characteristics of patients that may predict a positive outcome of the test.
5. To determine the complication rate and the complications encountered during the procedure.
6. To determine the rate of response of patients to tilt test using different medications (isoproterenol, atropine and nitroglycerin).

Methods

Research Design

This is a retrospective study.

Study Population

Patients with suspected neurocardiogenic syncope undergoing head-up tilt test (HUTT)

Exclusion Criteria

1. Patients undergoing head-up tilt test who are already on medication with beta-blockers.
2. Patients with significant carotid artery disease.
3. Patients undergoing repeat head-up tilt test after starting treatment with beta-blockers.

Study Setting

Tertiary center (Philippine Heart Center) with facility for head-up tilt test. Time period is from the first time HUTT was done in this center (1996) until present.

Data Collection

All cases with suspected neurocardiogenic syncope referred to the Electrophysiology Section of the Philippine Heart Center who underwent head-up tilt test were identified. The results of the tilt test of these patients were then retrieved and reviewed. Some subjects were excluded according to the stated exclusion criteria. Results of included subjects were reviewed to determine the baseline characteristics including symptomatology, co-morbidity and outcome of the study. The different characteristics were then compared to the outcome of the tilt test to determine possible association between the characteristics and a positive HUTT. A positive head-up tilt test response was defined by syncope or near syncope associated with the following hemodynamic changes: a decrease in systolic blood pressure >60% from baseline values or an absolute value <80 mmHg (vasodepressor response) an/or a decrease in HR >30% from the baseline value or an absolute value <40 beats/min (cardioinhibitory response).[11]

Data Analysis

Data were described as means and standard deviation, frequency and percent distribution. Association of the different factors to the outcome of the tilt test was compared. Using independent t-test and chi-square test. For all statistics, a $p<0.05$ was considered significant.

Results

A total of 91 patients were identified. Two were excluded due to absence of test results while three were repeat tilt on beta-blockers. Eighty-six patients were then included for final

analysis. Ages of patients ranged from nine to 86 years old with a mean age of 47 + 21 years (Table I). There was almost equal sex distribution among included subjects with males comprising 51% of the total study population.

Table I. Distribution of patients according to age

Age Range	Number	Percentage	Cumulative %
No data	15	17.5	17.5
< 18	5	5.8	23.3
18-60	43	5	73.3
> 60	23	26.7	100
Total	86	100	

Majority of the patients (58 or 67.4%) presented with a history of recurrent syncope (Table II) and 38 (44%) presented with the classical prodrome prior to the onset of syncope. A total of 17 (19.8%) patients had existing co-morbidity and all of whom are hypertensive with two having minimal carotid artery disease. Sixty-nine (80.2%) of the patients were without co-morbidity. Among the different provocative agents, isoproterenol was the most frequently used in 63 (73%) patients with one (1%) patient given nitrates before isoproterenol and three (3.5%) patients given atropine. The remaining only underwent baseline tilt.

A total of 32 (37%) patients had a positive head-up tilt test (Table III) with 21 (66%) of cases manifesting with positive result during baseline tilt and an additional 11 (34%) being positive on provocative test. Of the 38 patients who presented with a classical prodrome, 28 (74%) had a positive HUTT. Of these, 19 (50%) had positive HUTT on baseline study with an additional 9 (24%) patients becoming positive on provocative examination.

The other four patients with a positive HUTT did not present with any prodrome. Two became positive on baseline HUTT and the remaining two became positive on provocative testing.

Table II. Distribution of patients according to presenting history

Presenting history	Number	Percent	Cumulative %
Syncope	58	67.4	67.4
Seizure	1	1.2	68.6
Presyncope	7	8.1	76.7
Dizziness	8	9.3	86
Combination of symptoms	6	7	93
Others	6	7	100
Total	86	100	

Table III. Outcome of tilt test

Outcome	Number	Percent
Negative HUTT	54	63
Positive HUTT	32	37
(+) on baseline	(21)	
(+) on provocative	(11)	
Total	86	100

Of the patients with a positive HUTT outcome, majority were classified as mixed type of neurogenic syncope (Table IV). Most patients complained of a combination of dimming of vision and dizziness with note of diaphoresis prior to the onset of symptoms and manifested with either near syncope or frank syncope (19 patients/61%). Of the positive HUTT patients, regain of consciousness was immediate in 31 (97%) of cases with no evidence of disorientation.

Most patients with a positive HUTT presented with simultaneous occurrence of bradycardia and hypotension while others presented with a variety of combination of blood pressure and heart rate changes *(Figure 1)*.

Table IV. Classification of syncope among (+) HUTT patients

Type of Syncope	Number	Percentage
Cardioinhibitory	5	16
Vasodepressor	9	28
Mixed type	18	56
Total	32	100

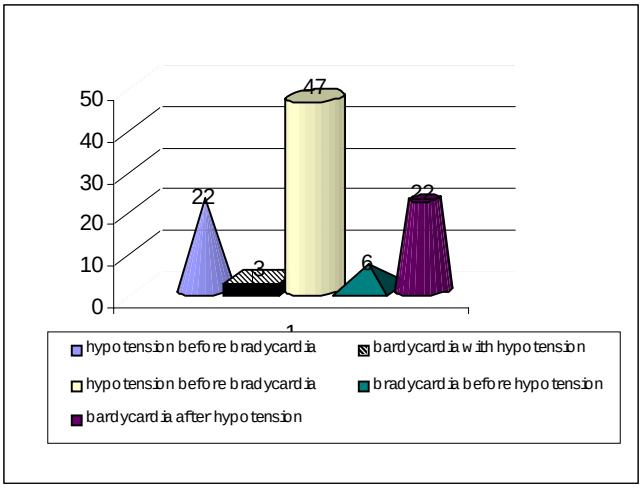

Figure. I. Manifestation of positive HUTT test

Table V. Comparison between patient variables and HUTT outcome

Factor/Variable	Negative HUTT (n=54)	Positive HUTT (n=32)	p-value
Age			0.11
Mean + SD	51 years + 18.89	43 years + 24.28	
Gender			0.889
Male	28 (32%)	16 (19%)	
Female	26 (30%)	16 (19%)	<0.001
Prodrome			<0.001
Present	10 (12%)	28 (32%)	<0.001
Absent	44 (51%)	4 (5%)	
Prodrome (n=86)	(-) baseline tilt	(+) baseline tilt	0.002
Present	19 (22.1%)	19 (22.1%)	
Absent	46 (53.5%)	2 (3.1%)	
Prodrome (n=65)	(-) provocative tilt	(+) provocative tilt	0.072
Present	4 (6.2%)	9 (13.8%)	
Absent	50 (76.9%)	2 (3.1%)	0.412
Early heart rate rise			
Present	10 (12%)	17 (20%)	0.32
Absent	44 (51%)	15 (17%)	
ECG			
Normal	51 (59.3%)	26 (30.2%)	
Abnormal	3 (3.5%)	6 (7%)	
QT interval			
Normal	40 (46%)	27 (31%)	
Abnormal	0 (0%)	1 (1%)	
Carotid sinus massage			
Normal	19 (22%	6 (7%)	
Abnormal	3 (4%)	3 (4%)	

Correlation of the different variables to the outcome of HUTT showed significant correlation between HUTT outcome and occurrence of early heart rate rise. The presence of classical prodrome likewise correlates significantly with a positive HUTT outcome. Age, gender, normal ECG and QT interval did not correlate with HUTT outcome (Table V). The mean age of the different types of neurocardiogenic syncope were as follows: cardioinhibitory (35 + 29.85 years), vasodepressor (44 + 36.79 years) and mixed (31+ 21.62 years) with $p = 0.35$.

Discussion

Data gathered from this investigation showed that in the group of patients that this institution caters to, neurocardiogenic syncope appears to affect both genders nearly equal in contrast to the previous observation in foreign studies that this condition has a predilection to affect females more than males.[8] The mean age of patients is 43 + 24.28 years indicating that it indeed appears to affect the relatively younger age group. On further analysis of the data, there was no significant correlation established between age and sex versus the outcome of HUTT indicating that the outcome of head-up tilt test is independent of the patients age and sex. This collaborates the findings of McGavigan et al and Petersen et al.[8,9]

It has been previously proposed that patients with classical prodrome tend to manifest with positive results more during the baseline tilt test rather than the provocative test.[12] It has likewise been elucidated that more of the patients with a classical prodrome would have a (+) baseline tilt. This study indeed showed that 70% (19 cases) of patients with classical prodrome manifested with positive HUTT outcome during baseline testing, which correlated significantly with a (+) HUTT ($p < 0.001$). Of the remaining patients who were negative on baseline tilt, additional 9 (10.5%) cases became positive on provocative test. Similar to patients with (+) baseline tilt, the presence of classical prodrome correlated significantly with a (+) HUTT on provocative examination. Looking at these data, the total case finding rate of the head-up tilt test has been established at 74%, that is, 28 (+) HUTT cases among 38 patients presenting with a classical prodrome. There was however no difference in the case finding rate between patients without prodrome during the baseline and provocative tests. In this investigation, there was an equal case finding rate between the two phases of the test in patients not presenting with a classical prodrome (two cases of (+) HUTT both in baseline and provocative tests). Correlation analysis further showed a statistically significant correlation between the presence of classical prodrome and the total positive HUTT results ($p < 0.001$) confirming the observation that the presence of classical prodrome increases the likelihood of a positive HUTT result.

The total case finding rate of head-up tilt test as seen in this investigation is 37%, i.e. 32 positive HUTT cases out of 86 patients undergoing head-up tilt test. Of these, 66% (21 cases) were documented during the baseline HUTT with an additional 34% (11 cases) being documented on provocative examination. Development of the symptoms occurred with a mean tilt time of 20-30 minutes with shortest tilt time of four minutes and longest at 43 minutes. As expected, regain of consciousness is immediate in the documented cases (97%) of neurocardiogenic syncope with the exception of one patient who actually developed seizure shortly after syncope and was in post-ictal state for about five minutes after regain of consciousness. This patient had evidence of seizure-like activity on previous electroencephalogram (EEG) manifesting with changes in the delta frequency, which may be in support of earlier findings of possible central nervous system involvement, in neurally mediated syncope.[3] Data however are still inadequate to make a conclusion regarding this proposed mechanism.

Previous evidences showed that patients with neurally mediated syncope more often than not, would have normal electrocardiogram (ECG) and structurally normal hearts, which was further supported by the findings of this investigation. It has likewise been previously proposed that the presence of long QT syndrome may predispose patients to developing neurocardiogenic syncope.[13] In this study, one patient had a prolonged QT interval on baseline ECG and manifested with a positive HUTT. Such finding appears to be compatible the previous observations, however, the number of patients with long QT in this study was clearly inadequate to make this

generalization. Although most patients with a positive HUTT had normal ECG with normal QT interval and structurally normal hearts, none of these factors correlated significantly with a (+) HUTT result.

Of particular interest in the investigation of head-up tilt testing are the attempts to establish possible factors that may predict a positive outcome. One of the variables that have been proposed to predict for a positive outcome is the occurrence of early heart rate increase during HUTT.[14, 15] The early heart rate increase is determined as the maximum difference between the heart rate on the first five minutes of the tilt portion of the test and the heart rate on supine position just before putting the patient on tilt position. Aerts et al.[5] showed that no specific heart rate would predict for a positive outcome. Sumiyashi et al.[10] on the other hand states that an early heart rate rise >18 beats/min is a sensitive marker for a positive response at <15 minutes of tilt with 100% sensitivity and 61% specificity. This study showed that there was indeed a positive correlation between an early heart rate increase and a positive HUTT outcome ($p<0.001$) indicating that this may be a useful predictor of a positive outcome of the test. The mechanism proposed for an early excessive increase in the heart rate during HUTT was possibly a aroreflex-mediated response triggered by the early decrease in systolic blood pressure that was more pronounced in the positive group.[11] As earlier mentioned, there has been no established correlation between age and a positive HUTT. It has been shown however that the vasodeppresor type of syncope appear to have a predilection to affect those who are >65 years old.[8] Although this was not confirmed in this study, it has been observed that patients manifesting with vasodepressor syncope appeared to involve the older subjects with a mean age of 44 + 21.62 years. This is in contrast the cardio-inhibitory type of neurocardiogenic syncope and the mixed type of syncope which appears to affect a younger age group (35 + 29.85 and 31 + 21.62 years, respectively). The differences however in age involvement did not correlate significantly with a positive HUTT result ($p=0.35$).

Majority of the patients (97%) were given isoproterenol as a provocative agent with only three patients receiving atropine, hence, no adequate comparison could be made between these two populations. Only one patient experienced a complication, which was the occurrence of seizure establishing the complication rate at 1%.

Conclusion

Results of this study showed the clinical profile of patients at the Philippine Heart Center with suspected neurocardiogenic syncope referred for head-up tilt testing. Majority of the patients affected was in the relatively young age group with a mean age of 47 + 21 years presenting more often than not with syncope or presyncope.

The overall case finding rate is established at 37%, which increased to 74% in patients presenting with classical prodrome. Age, sex, a normal ECG and normal QT interval did not correlate significantly with the outcome of tilt. It was shown however that the vasodepressor type of syncope appears to affect the older age group. The presence of a classical prodrome and an early heart rate rise on the other hand clearly correlated significantly to a (+) HUTT outcome.

Indeed, the head-up tilt test remains a very useful tool in the evaluation of suspected neurocardiogenic syncope with a very high case finding rate in the presence of symptoms of classical prodrome. Its presence together with an early heart rate increase may be a useful guide in predicting outcome of the test.

Recommendations

The findings of this study established the local baseline data on the profile of patients with suspected neurocardiogenic syncope undergoing head-up tilt test in the Philippine setting. The results appear to be comparable to the findings noted in foreign literature. With these data, the baseline characteristics of the patients have been established, which may be used in determining future studies on head-up tilt test that may be done corollary to these findings.

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Original Article

The Clinical Profile and Outcome of PTCA (with or without stent) in Diabetic and Non-diabetic Patients with Coronary Artery Disease: The Philippine Heart Center Experience

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BACKGROUND: ***Retrospective case-control study conducted at Philippine Heart Center (PHC). This study aims to determine the clinical profile, outcome and survival between diabetic and non-diabetic patients who underwent PTCA.***

METHODS AND RESULTS: ***A total of 128 patients who underwent angioplasty from 1995-2000 were included with 60 diabetic and 68 non-diabetic patients. Males predominated with ages between 58-59 years. Mean duration of Diabetes Mellitus (DM) was eight years. Among the diabetic patients, 63% were smokers, with 32% presenting with hypercholesterolemia and 55% were found to be hypertensive. However, in the non-diabetic group, 8% were obese and 47% were hypertensive. Both the diabetic and non-diabetic groups had predominantly one-vessel involvement. Mean Ejection Fraction (EF) of 57% in diabetic and 59% in non-diabetic group were found in this study. Furthermore, diabetic patients were more likely to be in the New York Heart Association (NYHA) functional class (FC) II on admission, while non-diabetic patients were in the NYHA FC I. Complication rate of 40% was noted in the DM group whereas 24% was found in the non-DM group. The case success rate was 95% in the DM group and 96% in the non-DM group (p=NS). Three patients (5%) in the DM and three cases (4%) in the non-DM group died during hospitalization. Over-all major adverse cardiac events were not different between the two groups (16% vs. 8% p=NS).***

CONCLUSION: ***Long-term and event-free survival rates were not significantly different between the diabetic and non-diabetic patients (81 vs. 89%) up at six years follow-up.***

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Keywords: Angioplasty, Transluminal, percutaneous Coronary; coronary disease; diabetes mellitus

Coronary artery disease (CAD) is the most common cause of death in adults with diabetes mellitus (DM). Percutaneous Transluminal Coronary Angioplasty (PTCA) (with or without stent) is used to revascularize the occluded vessels of these patients to improve their survival. There is an increased incidence of large vessel atherosclerosis and myocardial infarction in patients with DM. Non-invasive procedures such as PTCA are often done to improve the quality of life as well as survival in such patients. Diabetes mellitus is a strong risk factor for the development of CAD, that diabetic patients demonstrate a three-fold increase in atherosclerotic disease, as well as the risk of cardiovascular morbidity and mortality. Medical opinion presently suggests that diabetic patients with coronary artery disease are likely to have diffusely diseased and inoperable vessels.[1,2,3,4] Due to the prevalence of CAD, diabetic patients constitute an important segment, (10-25%)[5] of the population undergoing coronary revascularization procedures; posing a challenge, as the long-term event rates in these patients are known to be higher than in the non-diabetic patients.[6] Hence, the need for a study to demonstrate the outcome of PTCA between diabetics and non-diabetic. Coronary angioplasty is effective in relieving symptoms in patients with single vessels and multivessel coronary disease, even when applied to stenosis with relative high-risk characteristics.[7]

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Research Objectives

The objectives of this study are to determine the clinical profile and outcome of diabetic and non-diabetic patients with CAD following PTCA and to review the factors that will influence the outcome and survival between diabetic and non-diabetic patients who underwent PTCA.

Methodology

This is a retrospective case-control study involving diabetics and non-diabetic patients 30 years old and above who

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had CAD and subsequently underwent PTCA (with or without stent) at the Philippine Heart Center from January 1995 to December 2000. The patients' course were followed up from the time of PTCA up to the time of the study.

The demographic profile of the patients included age, sex, duration of DM (years), smoking history, presence of hypercholesterolemia, coronary artery involvement, obesity, hypertension, ejecyion fraction and New York Heart Association Functional Classification (NYHAFC). Variables for clinical outcome are duration of hospital stay after the PTCA, presence or absence of complications, restenosis, occurence of MI and mortality, and event-free survival rates.

Chart review for data collection and follow-up through telephone contacts with the patients in this study as well as through their attending physicians were made. Patients were asked about the presence of symptoms, hospitalizations subsequent to the index angioplasty, the occurrence of myocardial infarction (MI), and additional angioplasty or coronary surgery. Patients were followed up for up to six years.

Statistical Analysis

Association of different factors with occurrence of DM was determined using t-test, chi-square and Fisher exact probability test. Event-free survival rates were computed using Kaplan-Meier analysis.

Results

Baseline Characteristics

One hundred twenty-eight (128) patients who underwent angioplasty from 1995-2000 were included in this study. Non-diabetic patients (53%) predominated in this study, compared with diabetics (47%). Most of them were males (44 and 64 non-diabetics), whereas females were only 16 and 4, respectively.

Diabetic patients have the disease for a mean duration of eight years, fulfilling any of the following criteria: patients on oral hypoglycemic therapy, insulin therapy, fasting blood sugar (FBS) of 140 mg/dL or GTT 200 mg/dL or more at two hours. Diabetic patients were older, and more likely current smokers. However, the association was not significant. Obesity on the other hand, was found more often in the non-diabetic group but the rate of hypercholesterolemia in excess of 250 mg/dL was higher in diabetic than in non-diabetic group. No significant difference was encountered with respect to the presence of hypertension in both groups. A non-significant trend of concomitant risk factors were seen more in non-diabetic compared with diabetic patients.

One-vessel disease (IVD) was seen more frequently in the diabetic patients (83%) compared to the non-diabetic group (73%) (p = ns). However, two-vessel (2VD) as well as multivessel disease were noted more in non-diabetic patients.

Table I. Diagnostic profile

Category	Diabetic (n=60)	Non-diabetic (n=68)	P value
Age in years	59	58	0.6378
Smoking	38 (63%)	37 (54%)	0.4549
Hypercholesterolemia	19 (32%)	10 (15%)	0.0421
Obesity	0	6 (8%)	0.0289
Hypertension	33 (55%)	32 (47%)	0.52

One-vessel disease (IVD) was seen more frequently in the diabetic patients (83%) compared to the non-diabetic group (73%) (p = ns). However, two-vessel (2VD) as well as multivessel disease were noted more in non-diabetic patients.

Diabetic patients have a lower ejection fraction (EF) compared to the non-diabetic (57 vs. 59%). (See Table II)

Table II. Ejection fraction

EF	Diabetic (n=6)	Non-diabetic (n=34)
< 20	1 (2%)	0
21-30	1 (2%)	3 (4%)
31-40	5 (8%)	2 (3%)
41-50	8 (14%)	11 (16%)
51-60	19 (32%)	20 (29%)
61-70	15 (25%)	24 (35%)

P value = 0.5782

Analysis of patients' functional status revealed a significantly higher number of patients from the non-diabetic group in New York Heart Association Functional Class I (NYHA FC) on admission whereas more diabetics were found in NYHA FC II. Higher NYHA classification is a significant predictor of inferior clinical outcome after PTCA (p=0.000001). *See Figure 1*

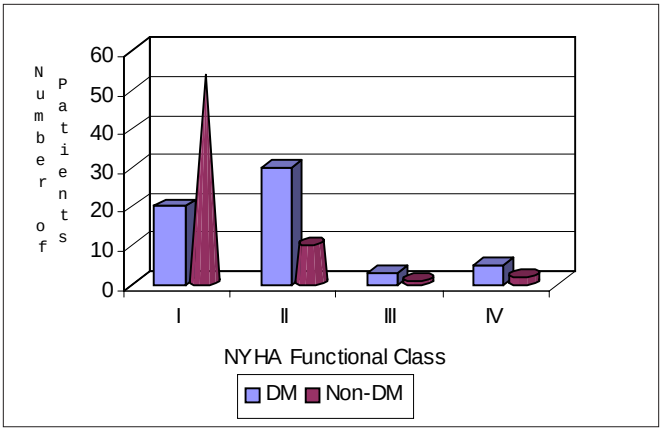

Figure 1. **New York Heart Association Functional Class Status**

Clinically successful procedures was performed in 36 (60%) diabetic patients and 52 (70%) non-diabetic patients (p=ns). The presence of complications such as restenosis, conversion from PTCA to CABG, aborted PTCA due to failure to cross wire, groin complications and periprocedural bleeding as well as death were noted in 24 diabetic compared to 16 in non-diabetic patients. *See Table III*

Table III. Complications

Complications	DM (n=60)	Non-DM (n=68)
Without complications	36 (60%)	52 (70%)
With complication and death	24 (40%)	16 (24%)

In-hospital complication rate didn't differ significantly between the two groups (37 vs. 20%). See Table 4

Table IV. Complications

	DM (n=57)	Non-DM (n=65)
Without complications	36 (63%)	52 (80%)
With complications	21 (37%)	13 (20%)

p value = 0.062

The survival rate between the 2 groups (95 vs. 96%) were comparable and didn't differ significantly. Mortality rate likewise didn't diverge considerably between the diabetic and non-diabetic (5 vs. 4%) patients. *See Table V*

Table V. Early outcome

	DM (n=57)	Non-DM (n=65)
Favorable outcome	57 (95%)	65 (96%)
Death	3 (5%)	3 (4%)

P value = 1.000

Non-diabetic patients (75%) remained for 0-7 days in hospital compared to 45% of the diabetic patients. Furthermore, a significant number of the latter group had longer hospital stay (8 days and above) than the former group. This can be attributed to the complications encountered periprocedurally. *See Table VI*

Table VI. Hospital stay

Number of Days	DM (n=60)	Non-DM (n=67)
0-7	27 (45%)	50 (75%)
14-Aug	19 (32%)	13 (19%)
15-21	8 (13%)	3 (4%)
>21	6 (10%)	1 (1%)

p value =0.001

Mortality rate in both the diabetic and non-diabetic groups during the follow-up period was low. However, more diabetics underwent revascularization from the time of index percutaneous coronary revascularization (PCR) (16 vs 4%; p=ns). Furthermore, event-free survival rates in the diabetics and non-diabetics were high (81 vs. 89%; p=ns). In other authors,[8,9] mortality rate in the comparable time is much higher, being significantly higher in diabetic patients who had undergone revascularization both PTCA and coronary artery bypass graft (CABG).[8,9] *See Table VII*

Table VII. Long term outcome

	DM (n=57)	Non-DM (n=65)	P-value
Mortality	0	1 (2%)	1
Revascularization from index	PCR		
- CABG	9 (16%)	3 (4%)	0.08
- PTCA	0	1 (2%)	
Lost to follow-up	2 (3%)	2 (3%)	1
Event-free survival	56 (81%)	58 (89%)	0.29

Survival function

On follow-up, both the diabetic and non-diabetic groups had a cumulative survival rate of 0.955. There were 6 mortalities (three from the diabetic and three from the non-diabetic group) at some point of the first year of follow-up from the index revascularization and only one mortality thereafter. *See Figure 2*

On the first year of follow up, the non diabetic group had a cumulative survival of .955 which decreased to .940 for the succeeding follow up years. The diabetic group's cumulative survival remained stable at 0.950 throughout the follow up period. *See Figure 3*

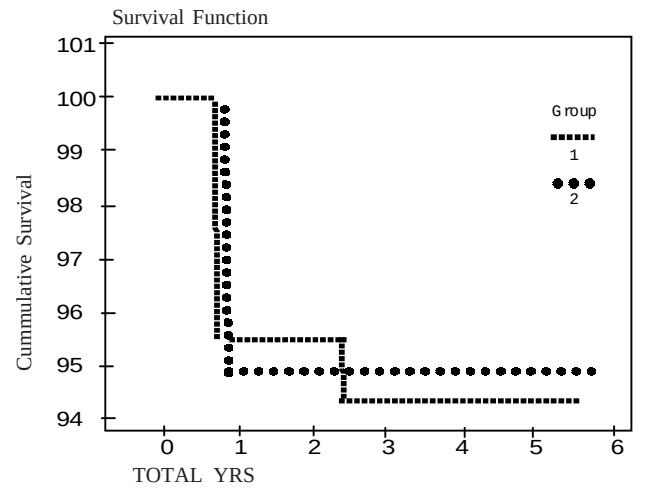

Figure 2. **Hazard function (Kaplan Meier Curve)**

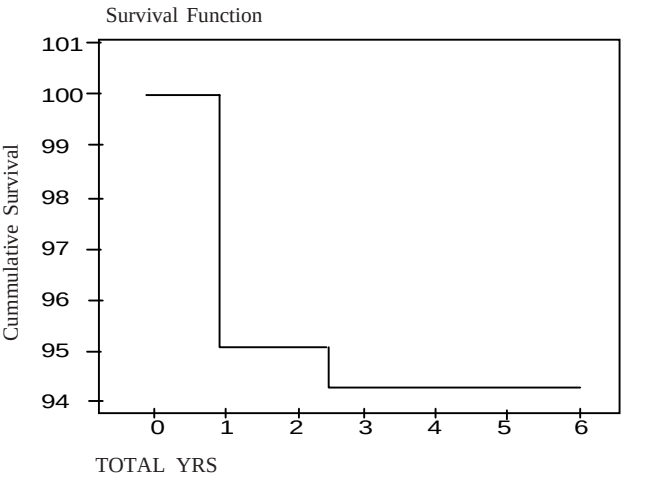

Figure 3. **Survival Function (Kaplan-Mier Curve)**

Discussion

Any coronary revascularization strategy must be evaluated in terms of two treatment goals: to provide a safe and durable treatment of flow-limiting epicardial coronary obstructions and to prevent future morbidity and mortality arising from ongoing atherosclerosis in non-treated coronary segments.

A given target lesion was safely treated, whereby the atherosclerotic segment was converted to a vascular scar virtually incapable of future renarrowing via atherosclerosis. Long-term patency can be practically guaranteed after the six-month vascular repair period was reached without significant narrowing.[2] Thus, PCR has been viewed almost as a "cure" for obstructive coronary disease provided the offending lesion remained patent after six months of follow-up.

Similar to smoking and hypercholesterolemia, diabetes is an independent risk factor that confers cardiovascular death through atherosclerosis and its effect is potentiated by hyperglycemia and lipid abnormalities. In diabetic patients without coronary disease, the risk of death has been shown to be equivalent to that of non-diabetic patients with prior myocardial infarction.

There are conflicting data on safety and efficacy of coronary angioplasty in diabetic patients. Numerous studies did not substantiate meaningful differences in the early outcome between diabetic and non-diabetic patients[10,11,12] but several analysis confirmed higher periprocedural mortality and the incidence of myocardial infarction in diabetic patients.[6]

The effectiveness of PTCA in diabetics with multivessel disease is highly sensitive to severity of atherosclerosis present at initial therapy.[13]

In choosing the best treatment for both diabetic and non-diabetic patients, one must consider the force of atherosclerosis progression that may cause future clinically important coronary narrowings and plaque raptures. The clues that can be used to predict high-probability atherosclerosis progression are not exact and include the extent of the disease, seen at coronary angiography, and the patient's risk factor profile, including the presence of DM.

Results of the BARI trial,[8] RITA-114 and EAST[15] suggest that diabetic patients especially those taking oral hypoglycemic agents with minimally apparent multivessel disease (two-vessel disease) could be considered for PCR.

Presently, it is considerably accepted that given the state-of-the-art technology and availability of stents, diabetes mellitus does not appear to adversely affect the immediate outcome of percutaneous coronary interventions.

Long-term outcome seems to be affected, however. In diabetes, increased blood viscosity, increased synthesis of thromboxane A2, and decreased prostacyclin production are encountered. Levels of fibrinogen, Factors VII, VIII and fibrinopeptide A is elevated in connection with decreased antithrombin III activity.[16]

Due to the endothelial dysfunction, coagulation and fibrinolytic disturbances, platelet aggregation and thrombus formation are enhanced. Kornowski, et al[17] showed that the reason for increased restenosis in diabetes was the exaggerated intimal hyperplasia.

The study identified hypercholesterolemia, obesity, NYHA FC and duration of hospital stay as associated with morbidity and cardiac mortality.

This study also presented the results of diabetic patients who underwent angioplasty. These results were compared with those of non-diabetic patients who underwent PTCA in the same institution during the same period.

Diabetic patients constituted 47% of the population group (53% in the non-diabetic group) with a mean duration of eight years of diabetes mellitus. Hypercholesterolemia was significantly noted in the diabetic group (32% vs. 15% p=0.0421) but the non-diabetics were more often obese. Diabetic patients have a lower NYHA FC status on admission (53% in Class II) compared to the non-diabetics (79% in Class I). Hospital stay among the diabetics was longer (55% stayed eight days and longer) than the former group. Complication rates were noted to be higher in the diabetics compared to the non-diabetic patients (21 vs. 13% p = ns).

Higher re-intervention rate in the present study (16% in the diabetic and 6% in the non-diabetic group) is due to the non-significantly higher restenosis rate and atherosclerosis rate in the diabetic patients. This was corroborated by the results of other studies.[6,9] Furthermore, although Alderman, et al[18] pointed out diabetes mellitus to be a risk factor in atherosclerosis progression within a five-year follow-up period, no significant atheroslerosis progression was noted in the follow-up period of four years in the study of Engelman, et al.[19] Long-term, event- free survival rate was not significantly different between diabetics and non-diabetics (81 vs. 89%) at six years' follow-up. Similarly, Barsness, et al.[20] showed a five year survival among PTCA patients at 76% in the diabetic and 88% in the non-diabetic patients.

Mortality rate in both the diabetic and non-diabetic groups do not differ and remain low. This contrasted from other authors[19,20] who noted significantly higher mortality rates in the diabetic group. However, in the study of Przewlocki, et al.,[21] low mortality was also noted in the diabetic group whose mean age was 53.9 years. In the present study, the mean age was 59 years versus 58 years in the non-diabetic group.

Technologies such as the use of glocoprotein IIb/III a inhibitors and stents[22] brachytherapy[23] as well as aggressive hypoglycemic and hypolipemic therapy[24] may significantly enhance the results of coronary intervention in patients with diabetes mellitus.

Nonetheless, despite the state-of-the-art processes being presented, the effective therapy of coronary artery disease in diabetic patients presents a problem, requiring development of sufficient methods to attenuate the risk in these patients.

Until further evidence is available, all resources should be exhausted to determine treatment strategies for patients with coronary artery disease. Observational databases are important resources in medical decision-making, providing a broad perspective that can enhance randomized trials and provide useful data to patients and physicians.

The present study, suffers from all the attendant disadvantages of a retrospective analysis. Nonetheless, the present study can provide some insight into the differences in prognosis and long-term results between diabetic and non-diabetic patients.

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Original Article

Profile of a High-Risk Subgroup in Acute Inferior Wall Myocardial Infarction: Multi-Center Study

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BACKGROUND: ***The incidence of High-Grade AV block (HGAVB) in inferior wall myocardial infarction (MI) is 16% with a positive correlation on J/R ratio >50%. We would like to validate this statistics as well as the correlation of J/R ratio >50% to HGAVB in the Philippine setting, wherein mortality and duration of hospitalization were considered as endpoints.***

METHODS AND RESULTS: ***All patients admitted at Philippine Heart Center, Veterans Memorial Medical Center, Philippine General Hospital, East Avenue Medical Center, Fort Bonifacio General Hospital, and Jose Reyes Memorial Medical Center from January 1997 to December 2000, who presented with inferior wall MI were entered in the study. Patients with onset of symptoms within 48 hours of admission with anginal chest pains and elevated cardiac markers were included. The demographic profile, Killip class on admission and use of thrombolytics were noted. Pressure highest ST segment elevation on electrocardiograms (ECG's) were classified into pattern 1 (J/R ratio <50%), pattern 2 (J/R ratio >50% in 2 or more leads) and pattern 3 (presence of early Q waves). The incidence of HGAVB, hospital stay and mortality were also assessed. Four hundred and eight patients were included in the study. ECG pattern 1 was seen in 160, pattern 2 in 98, and pattern 3 in 150. HGAVBs were found in 9.4% with pattern 1, 46.9% with pattern 2, and 24.9% with pattern 3. Of 150 the patients who had early Q waves, 37 (24.9%) had HGAVB, 26 (14.3%) out of 182 with J/R ratio <0.5 had HGAVB while 35 (46.7%) out of 75 with J/R ratio >0.5 had HGAVB. Among patients with right ventricular Infarction (RVI) 60% had HGAVB in contrast to those without RVI, 20%. On average, patients with HGAVB were hospitalized for 10.2 days versus 8.3 days for those without.***

CONCLUSION: ***Patients with HGAVB had a higher Killip class and longer hospital stay. Multivariate regression analysis showed that worst Killip (p=0.0019), JR ratio average >50% (p=0.0004), ECG pattern 2 (p=0.000***) and hospital stay (p=0.0441) were independent by associated with HGAVB. Thus, JR ratio average >50%, ECG pattern 2 and RVI were predictors of the development of HGAVB among patients with inferior wall MI.***

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Keywords: myocardial unfarction, heart block

Patients with acute inferior wall myocardial infarction (MI) generally have a better outcome than those with acute anterior wall MI, but some of those with inferior wall MI have an increase risk for complications. For instance, in high-degree (second degree type II and higher) Atrio-ventricular (AV) block developing in inferior wall MI carries a poor prognosis. Although high-degree AV block is usually not permanent, it has been associated with up to 20% in hospital mortality.[1] Early appearance, with the first 24 hours, compared with late appearance of high-degree AV block has been shown to carry higher rates of mortality, left ventricular failure and cardiogenic shock.[2] Thus, the subset of acute inferior wall MI patients with an increased risk for high-degree AV block should be identified early. Inferior wall MI account for 40% to 50% of all acute MI. And patients with acute inferiror wall MI patients with high degree AV block possess a higher mortality risk.[3,4] Referral to a tertiary hospital in patientswith acute inferior wall MI who develop high-degree AV block.[5] Revascularisation may be considered in this subset because mortality is high despite thrombolysis.[6,7] Studies in the local setting to evaluate clinical and electrocardiographic indices that identify acute inferior wall MI patients with increased risk of developing high-degree AV block is needed.

Bassan, et al.[1] who studied 51 patients with inferior wall MI noted that patients with left arterior descending (LAD) coronary artery obsstruction were more likely to develop AV block. Furthermore, patients with inferior MI and LAD coronary artery obstruction have a 6-fold greater chance of developing heart block.

Bilbao, et al. [9] studied 44 patients with posterior inferior wall AMI to determine the anatomic basis of AV block. The results showed lack of correlation between block and lesions of the specialized conducting system. But there was a strong association of block with necrosis of the atrial prenodal myocardium and twenty-nine or 97% with AV block showed necrosis of this area.

Birnbaum, et al.[7] studied 2603 patients with acute

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MI treated with thrombolytic therapy. The patients were classified into two groups - those with and those without distortion of the terminal portion of the QRS complex in two or more consecutive leads, i.e. the emergence of J-point at a level above the lower half of the R wave in leads with qR configuration or disappearance of the S wave in leads with an Rs configuration. They found that an interval of more than two hours from symptom onset to thrombolysis was associated with increased hospital mortality only among patients with QRS distortion, not in those without this ECG finding. Conversely, distortion of the terminal portion of the QRS complex on admission ECG is an independent predictor of hospital mortality, only among those treated with thrombolysis more than two hours after symptom onset. Their study suggest that earlier thrombolysis will improve survival of this subset of patients. This study, however, involved patients who suffered either an anterior or inferior acute MI.

Christian et al.[11] used T-99m sestamibi among 67 patients diagnosed with ST segment elevation acute MI to provide an estimate of infarct size. And he noted that the larger the infarct, the higher was the ST segment elevation.

Birnbaum et al.[7] reported that among patients treated with thrombolytics for inferior wall acute MI, a simple ECG sign of J-point / R-wave ratio >0.5 in more than two inferior wall leads is a reliable predictor for the development of high-degree AV block. Other variables associated independently with high-degree AV block included female gender, Killip class >2, and absence of abnormal Q waves on admission. However, this study, as with the previous one, was limited to patients with acute inferior wall MI who received thrombolytic treatment.

Solodky et al.[8] assessed variables on admission to predict the development of high-degree AV block within the first 24 hours of hospitalisation in 205 patients with acute inferior wall MI. ECG's taken on admission were divided into two patterns: pattern I: J-point/ R-wave <0.5, and pattern 2: J-point/ R-wave >0.5 in at least two inferior leads. They encountered significantly more frequent high-degree AV block in patients with pattern 2 (19%) as compared to patients with pattern 1 (10.2%). By multivariate regression analysis, the variables independently associated with high-degree AV block were initial ECG pattern 2 (odds ratio, OR = 4.47, p = 0.028), age (OR=1.06, p=0.025), and absence of thrombolytic therapy (OR=0.32, p=0.037). There have been no other previous studies that have directly studied variables that might predict high- degree AV block.

Research Objectives

Objectives of this study were:

1. To determine if the following variables contribute to the development on high grade AV block in patients with acute inferior wall MI:
   a. Gender
   b. Age
   c. Hypertension
   d. Diabetes mellitus
   e. Smoking history
   f. Pattern (J-point/ R-wave ratio > 0.5) on highest ST ECG
   g. Presence of pathologic Q waves on admission ECG
   h. Killip class on admission
   i. Thrombolysis
   j. Time to ER from onset of symptoms
   k. Right ventricular infarction (RVI)

2. To determine the prevalence of high degree AV block in ECG pattern 1 and pattern 2

3. To determine the differences in clinical outcome in patients with and without high-degree AV block:
   a. Total in-hospital mortality
   b. Cardiac mortality
   c. Non-cardiac mortality
   d. Killip class >2

Methodology

Study Design

A multi-center retrospective study was used to determine the objectives.

Study Sample

The medical charts of patients admitted at Philippine Heart Center, Veterans Memorial Medical Center, Philippine General Hospital, East Avenue Medical Center, Fort Bonifacio General Hospital, and Jose Reyes Memorial Medical Center from January 1997 to December 2000 were retrospectively reviewed. The diagnosis of inferior wall MI was made based on the following:

(1) Anginal chest pain

(2) Elevated Cardiac enzymes

(3) ST segment elevation in more than two inferior leads.

Patients with the following criteria were excluded:

(1) Negative T wave in more than two inferior leads on admission ECG, as only patients in the acute stages of inferior wall MI were included.

(2) Concomitant acute anterior wall MI.

(3) Intraventricular conduction defect.

(4) Ventricular paced beats (patients with permanent pacemakers).

Identification of Study Variables

For the first objective, the dependent variable is the development of high-degree AV block. The independent variables include:

a. Gender - Male or female

b. Age
c. Hypertension
d. Diabetes mellitus
e. Smoking history
f. Killip class on admission
g. Thrombolysis
h. ECG criteria - The ECG's will be recorded with a 0.1mv sensitivity and a 25 mm/sec paper speed. Single lead ECG monitoring will be done on patients during their stay at the ICU.
h1. Pattern (J-point/R-wave ratio> 0.5) on selected ECG.
h2. Presence of pathologic Q waves on admission ECG.
h3. Presence of ST segment elevation in V3R and V4R.

For the second objective, the patients with the presence or abscence of high-grade AV block. were compared by the following:

a. Total in-hospital mortality - the total number of deaths from cardiac and non-cardiac causes divided by the total number of patients.
b. Cardiac mortality - the number of deaths from cardiac causes divided by the total number of patients.
c. Non-cardiac mortality - the number of deaths from noncardiac causes divided by the total number of patients.
d. Worst Killip class.

Description of Data Collection

All patients admitted from January 1997 to December 2000 were entered in the study. The following variables were noted:

a. Gender-Male or female
b. Age in years
c. Hypertension - presence or absence of hypertension, defined as a systolic pressure >140 mm Hg or a diastolic BP >90mm Hg.
d. Diabetes mellitus (Insulin-requiring or non-insulin requiring) presence or absence of
e. Current smoking - Yes or no
f. Killip class on admission
g. Thrombolysis - Received or not received
h. ECG criteria
h1. Pattern (J-point/R-wave ratio >0.5) on selected ECG
h2. Presence of pathologic Q waves on admission ECG
h3. Presence of ST Segment elevation V3R and V4R

Patients who developed high-degree AV block, or experienced any cardiac or non-cardiac mortality, and the worst Killip class during the hospital stay.

Data Handling

Data were obtained in the data collection form, then tabulated in the necessary tables. All electrocardiograms and rhythm strips were analyzed.

Statistical Analysis

Patients were dichotomised according to whether they experienced high-degree AV block or not. For continuous variables, the mean + SD were computed, and statistical significance between groups were analysed using the two tailed t-test. For dischotomous variables, the absolute and relative frequencies were obtained, and differences analyzed by the chi-square or Fisher's exact test. Multivariate analyses were done. For both models, the dependent variable was the development of high-grade AV block. One model included the following independent variables: gender, age, hypertension, diabetes mellitus, present smoking, Killip class on admission, thrombolysis, time to ER from onset of symptoms, pattern (J-point/R-wave ratio >0.5) on highest ST ECG and presence of pathologic Q waves and Right Ventricular Infarction on ECG. The p values, ODD'S ratios, and 95% confidence intervals were computed. A p-value less than 0.05 was considered statistically significant.

Results

Four hundred and eight patients (n=408) were included in the study. The youngest was 29 years old and the oldest was 92 years old with a mean of 60 years. Eighty out of 330 males had high grade AV block (HGAVB) while 18 only (23%) out of 78 for females. Among the 239 patients with hypertension, 54 (23%) had HGAVB, while in 169 patients without hypertension, 42 (25%) had HGAVB. (Table I)

Thirty three (30%) of diabetic patients had HGAVB while 65 (22%) of the 298 non-diabetics had HGAVB. Sixty two (23%) of the 269 smokers had HGAVB, while 36 (25.9%) of the 130 non-smokers had HGAVB. Time to emergency room data showed the earliest time at 0.3 hours and the latest at 48 hours with a mean duration of 14.8 hours and a median of 6 hours. Admission Killips were recorded and 205, 85, 21 and 37 patients were in Killips Classes I, II, III, and IV, respectively. Fifty seven (21.5%) in Killip I, 25 (30%) in Killip II, 5 (9.5%) in Killip III and 14 (37.8%) in Killip IV had HGAVB.

Eight (20%) of the 40 patients who were given thrombolytics had HGAVB while 85 (21.45%) out of 358 patients without thrombolytics had HGAVB. Electrocardiogram pattern 1 was seen in 160, pattern 2 in 89 and pattern 3 in 149. HGAVBs were found in 10% with pattern 1, 46% with pattern 2, and 24% with pattern 3. Of the 149 patients with early Q waves, 36 (24%) had HGAVB, 36 (14.3%) out of 182 with J/R ratio <0.5 had HGAVB while 35 (46.7%) out of 75 with J/R ratio >0.5 had HGAVB.

On the average, patients with HGAVB were hospitalized for 10.2 days versus 8.3 days for those without. Likewise more patients with HGAVB had Killip class >2 (36 vs. 19%) during hospitalization. Increased cardiac mortality was noted for

patients with HGAVB compared with those without (20 vs. 10%).

Multivariate analysis showed that the only variables to be associated with HGAVB were: presence of RVI ($p<0.001$), highest ST ECG pattern 2 versus pattern 1 ($p<0.001$), JR ratio average >50% ($p=0.004$), worst Killip class >2 ($p=0.00019$), and duration of hospital stay ($p=0.0044$).

Table I. Demographic comparison of patients in acute infarction wall MI in the presence or absence of HBGAV

	HGAVB (-) (n=310)	**HGAVB (+) (n=98)**	**p value**
Gender			
Male	250 (76%)	80 (25%)	NS
Female	60 (77%)	18 (23%)	
Age years(mean)	59.287	60.67	NS
Hypertension			
No	127 (75%)	42 (25%)	NS
Yes	183 (77%)	56 (23%)	
Diabetes mellitus			
No	233 (78%)	65 (22%)	NS
Yes	77 (70%)	33 (30%)	
Smoking Hx			
No	103 (74%)	36 (26%)	NS
Yes	207 (77%)	62 (23%)	
Killip on admission			
1	208 (79%)	57 (22%)	NS
2	60 (70%)	25 (30%)	
3	19 (91%)	2 (10%)	
4	23 (62%)	14 (38%)	

Table II. Clinical and ECG comparison of patients in acute infraction wall MI

	HGAVB (-) (n=310)	**HGAVB (+) (n=98)**	**p value**
J/R Average			
0	113(75%)	37(25%)	<0..0001
<0.5	156(86%)	26(14%)	0.004*
>0.5	40(53%)	35(47%)	
Cardiac Mortality			
No	280(90%)	79(80%)	0.016
Yes	30(10%)	19(20%)	0.4175*
Hospital Stay (mean)	8.376	10.389	0.0042
			0.0441*
Thrombolysis			
No	273(68.6%)	85(21%)	0.718
Yes	32(8%)	8(2%)	NS
Pattern on ECG			
1	144(36%)	16(4%)	
2	48(12%)	41(10%)	<0.0001
3	113(28%)	36(9%)	
RV infarction			
No	293(82%)	72(20%)	<0.0001*
Yes	17(40%)	26(61%)	
Non-cardiac Mortality			
No	302(76%)	93(23%)	NS
Yes	3(0.75%)	0 (0%)	

NS - no significance
HGAVB - high grade atrioventricular block

Discussion

There was no association noted between gender, age, presence or absence of hypertension, diabetes, thrombolytics and smoking history with high degree AV block. The data in this study validated the results of previous studies except for thrombolytic therapy and age. Wherein, other studies showed both parameters correlated with high degree AV block. Age and thombolytic therapy were not predictors of high grade AV block (HGAVB) in this study. Twenty one percent of those without thrombolytic therapy had high grade AV block compared to 20% patients who were given thrombolytics. A decreasing trend of AV block was noted for those with thrombolysis but this was not statistically significant. This suggests that thrombolytic therapy does not alter the progression to high grade AV block of patients with inferior wall MI. Thus, otherrevascularization procedures should be done because thrombolytics is inadequate. The limitation of this study is that only 40 out of 408 patients were given thrombolytics.

A higher incidence of high grade AV block in inferior wall MI was noted in the local setting. Ten percent for pattern 1 and 46% for pattern 2, in the local study, against 10.2% (pattern 1) and 1% (pattern 2) for the foreign literature. Other studies who reported patients with inferior wall MI who underwent thrombolysis were seen within a 24-hr period. Whereas, this study included patients who had no pharmacologic intervention and who had symptoms up to the 48th hour.

This study included patients up to the 48th hour after the onset of symptoms because 101 out of 408 patients were only referred and admitted in our institution after the 12th hour. Thus, a significant percentage of patients with inferior wall MI were seen or referred beyond the window period for which thrombolytic therapy could have been given. This study was unable to do a pre-hospital profile to determine the reasons behind the delay of referral.

There is a significant difference in the incidence of high grade AV Block for patients with pattern 1 compared with pattern 2. This validates previous studies which showed ST elevation to be correlated with incidence of HGAVB and a reflection of the extent of myocardial damage.4,9

A higher percentage (46%) of patients with pattern 2 had HGAVB compared to only 16% in foreign literature. Because highest ST ECG was used in this study instead of admission ECG. This suggests that highest ST ECG is a better predictor of HGAVB than admission ECG.

Thus, serial ECG with ST monitoring (for the first 72 hrs) and J/R ratio determinations should be done to identify patients with pattern 2 ECG. Because pattern 2 ECG is a predictor of HGAVB.

Forty sixty percent of patients (local setting) with pattern 2 progressed to HGAVB which suggest left anterior descending (LAD) artery involvement.1 Furthermore, a multivessel coronary artery disease (left circumflex or right coronary

artery with LAD) was predicted in this subgroup (Inferior wall MI with HGAVB). Thus, early invasive diagnostic or therapeutic procedures should be done in inferior wall MI patients with pattern 2 ECG.

Worst Killip classification was correlated with HGAVB because patients with block, as previously mentioned have, LAD involvement and therefore a larger myocardium at risk which leads to myocardial failure. Further studies should be done to determine the echocardiographic parameters.

The J/R average of >0.5 was correlated with HGAVB. This was studied to assess the use of taking the average of all the inferior leads and set a level at which significant HGAVB arises. Higher incidence of block was noted only at a ratio greater than or equal to fifty percent. This data validates the study by Christian11 correlating ST elevation with extent of myocardial damage.

Patients with HGAVB have prolonged hospital stay because they require a longer time to stabilize and rehabilitate.

Conclusion

Thus, RV infarction, JR ratio average >50% and ECG pattern 2 were predictors of the development of HGAVB among patients with inferior wall MI. And patients with HGAVB have higher Killip class and prolonged hospital stay.

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Original Article

A Comparative Review of Standard Coronary Bypass Grafting under Cardiopulmonary Bypass and Off-Pump Coronary Artery Bypass Grafting in the Management of Multivessel Coronary Artery Disease : Philippine Heart Center Experience

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BACKGROUND: ***There is a worldwide trend in the management of coronary artery disease with off-pump coronary artery bypass grafting without using the cardiopulmonary bypass circuit (CPB). This paper aims to compare the clinical profile and outcome of patients operated for multivessel (more than three) bypass off-pump coronary artery bypass grafting (OPCABG) with those who underwent such procedure by standard coronary artery bypass grafting (CABG) under cardiopulmonary bypass (CPB).***

METHODS AND RESULTS: ***This is a prospective cohort study based on hospital and operating room records of thirty-four (34) consecutive patients who underwent multivessel (more than three) OPCABG at the Philippine Heart Center from January 1, 2001 to August 31, 2001. The control group was composed of 108 patients operated by multivessel standard CABG, who were properly matched and operated within one week of the time that the OPCABG patients were operated. The frequency, mean and standard deviation were calculated for the dependent and independent variables. Comparison between the two groups was analyzed using Chi-square and student's t-test .***

CONCLUSION: ***OPCABG is comparable to standard CABG for the management of coronary artery multivessel (more than three vessel) bypass procedures in terms of improved clinical outcome, incidence of post-op complications and mortality rate and thus, is a safe alternative means of myocardial revascularization. It has the added advantages of diminished operative cost, blood transfusion requirements, and provision for lesser amount of blood components. The operative time, duration of post-operative ventilatory support, recovery room/surgical intensive unit stay and post-operative hospital stay were observed to be shorter in OPCABG compared to standard CABG but are not statistically significant.***

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Keywords: angioplasty, transluminal, percutanelous coronary; cardiopulmonary bypass; coronary artery bypass

Coronary artery disease remains a leading cause of mortality and morbidity in the Philippines.[1] The efficacy of Coronary Artery Bypass Grafting (CABG) in the management of Coronary Artery Disease (CAD) has been proven in several international studies. Coronary artery grafting when compared with medical therapy in the management of coronary artery disease not only improves the quality of life but also prolongs life in selected patients. Interestingly, CABG has remained essentially unchanged for more than 25 years. At present, there is a worldwide trend to revive cardiac revascularization without cardio-pulmonary bypass (CPB) due mainly to its deleterious effects, which brings about a diffuse inflammatory response that affects multiple organ systems.

Kolessov[2] in Russia performed the first left internal mammary artery (LIMA) grafting to the left anterior descending artery (LAD) on the beating heart through an anterior thoracotomy incision for the management of angina pectoris. Goetz and colleagues[3] and Sabiston4 were among the early pioneers of coronary bypass grafting performed on the beating heart. In the early 1990's, two centers in South America, Buffolo[5] and co-workers and Benetti,[6] reported more than 1,000 cases of successful "off-pump" CABG in selected

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patients, basically to one or two vessels on the anterior wall.

With the revival of off-pump coronary artery bypass grafting (OPCABG), there is also a growing trend to introduce innovative instruments and techniques to stabilize the heart while cardiac revascularization is being performed. One of these new instruments is the Medtronic Octopus II Tissue Stabilization System, which was introduced in March 1997 by Spooner and colleagues[7] in the USA. It was also tried and tested by Jansen and colleagues[8] in Utrecht, Netherlands in1995.

On May 1, 1999, OPCABG using this innovative instrument was performed for the first time at the Philippine Heart Center (PHC). Since then, there was an increase in the number of such procedures performed at PHC. The initial experience with this technique was done for one-vessel and two-vessel coronary artery disease with good results.[9] This was due to the fact that the target vessels-left anterior descending artery (LAD) and its branches were accessible anteriorly and using the stabilizer did not bring much hemodynamic compromise as the anastomosis was being accomplished.

Initially there were reservations in the performance of this procedure for multivessel (three-vessel disease) coronary artery disease especially for lesions involving the coronary vessels located posteriorly (i.e. right posterior descending artery-RPDA, right posterolateral-RPL, left circumflex-LCx and obtuse marginal-OM). Anastomosis in these vessels requires displacement of the heart from its pericardial cradle and doing this procedure under beating heart causes hemodynamic problems.

But as surgeons slowly gained experience through training, practice, refinement in techniques and coupled with proper intra-op communication and coordination with the anesthesiologist, the performance of such procedures for multivessel coronary artery disease is slowly gaining acceptance as an alternative to standard coronary artery disease after proper patient selection. At present, more cardiac centers abroad are performing such procedures. Some centers have adopted OPCABG as the initial approach for coronary artery disease and reserve the standard CABG for difficult cases (i.e. poor target vessels which prevent complete revascularization) or perform this procedure initially but convert to standard CABG once hemodynamic problems or graft malfunction are encountered intra-operatively.

Objectives

The purpose of this study is to compare the clinical outcomes namely, mortality, morbidity (post-operative complications), duration of operation, duration of post-operative ventilatory support, duration of recovery room/ surgical intensive care unit (RR/SICU) stay, total post-operative blood loss based on total post-op chest tube output, blood transfusion requirements, total blood component requirements and operative cost of patients with multivessel coronary artery (three or more coronary artery vessel involvement) who underwent OPCABG to that of control subjects who underwent standard CABG under cardiopulmonary bypass.

Methods

This is a prospective cohort study comparing the clinical profiles and outcome of patients with coronary artery disease who underwent multivessel (more than three vessel distal coronary anastomosis) OPCABG and those done under standard CABG at the Philippine Heart Center from January 1, 2001 up to August 31, 2001. The ratio of OPCABG to control group is 1:3. The control group, composed of at least three (3) properly matched patients who underwent multivessel standard CABG, for operated within one week during the time a patient underwent OPCABG. Only patients with multivessel coronary artery bypass grafting (more than three) who were operated on an elective and urgent basis are included.

Emergency operations, re-operations, CABG with other concomitant operations (e.g. carotid endarterectomy) and CABG with surgery for myocardial infarction complications (e.g. ischemic ventricular septal defect, acute mitral regurgitation, and left ventricular aneurysm) were excluded. A data-collecting form was completed per patient. The data included demographic variables, diagnosis (coronary vessels involved and New York heart Association [NYHA] functional class), pre-operative ejection fraction and cardiac events, co-morbid and other risk factors.

Operative data gathered include date and acuity of operation, number of distal anastomosis performed, vessels bypassed, duration of operation, use of intra-aortic balloon, conversion to CABG under CPB for patients who underwent OPCABG with the corresponding reason for conversion and operative cost. Post-operative data include total blood components transfused, total postoperative blood loss measured from the chest tubes output, duration of postoperative ventilatory support (from the end of the operation up to time of extubation), duration of recovery and surgical intensive care unit stay, post-operative hospital stay complications and mortality.

Statistical Analysis

The frequency, mean, and standard deviation were calculated for the independent and dependent variables. Comparison between the two groups was analyzed using Chi-square test and student's t-test.

Surgical Technique

OPCABG PCABG was carried out through a full sternotomy incision under general endotracheal anesthesia. The left internal mammary artery (LIMA) and the saphenous vein grafts (SVG) are harvested and prepared. Three deep pericardial traction stitches using silk 4-0 sutures are applied near the left upper and lower pulmonary veins and to the left of the inferior vena cava, thereby achieving vertical displacement of the heart

apex. With perfectly placed stitches and aggressive traction, the apex of the heart should be elevated to approximately 90 degrees. Opening of both pleural cavities and placing the patient in a gentle right decubitus Trendelenburg position helps provide good presentation of target arteries on the lateral and inferior aspect of the heart.

The Octopus Tissue II (Medtronic, Minneapolis, MN) stabilizer is then attached to the sternal retractor and positioned according to the target vessel to be anastomosed. Prior to anastomosis, ischemic preconditioning is performed whereby the target vessel is temporarily occluded for five minutes by tagging it with a Prolene 4-0 suture proximally and distally and reperfused for another five (5) minutes. During this period, the heart and the patient's hemodynamic status are observed. Any untoward events such as hemodynamic instability, ST segment elevation and arrhythmia may be enough reasons to convert the procedure to CPB-assisted.

If there is no untoward event, the heart is immobilized by mechanical and medical methods. Medical reduction of heart rate and myocardial contractility are achieved by giving a short-acting beta-blocker esmolol with a dose of -1 mg/kg bodyweight (BW). Esmolol has a duration of action of 10 -15 minutes. The heart rate should be maintained equal or less than 60 beats per minute. The blood pressure should be maintained at a range of 100-110 systolic and this may be achieved by giving Nitroglycerine drip (25 mg NTG/250 cc D5W=0.1 mg/cc) given at 1-4 mg to titrate the BP to the desired level. Nicardipine drip (0.1-5 mg/kg) may also be used.

Mechanical stabilization is achieved with the aid of the Octopus II tissue stabilizer. Stabilization is accomplished by suction domes underneath two parallel paddles, which are attached by tubings to a suction apparatus. The ideal suction should be able to generate a pressure of negative 400 mm Hg to fix the target site.[8] The suction paddles are applied on both sides of the target vessel. The suctioning effect lifts up the heart rather than push it against the pericardium and this prevents hemodynamic problems. When applied on the anterior surface, the suspended anterior wall did not impede left ventricular diastolic filling.[7]

The coronary arteries are opened longitudinally and anastomosis is performed using prolene 7-0 continuous running suture. For a relatively dry field, the target coronary vessel is temporarily snared with a Prolene 4-0 suture or metal clips. Additional technique to ensure a relatively bloodless field is the use of the heart lung machine generated filtered blower (HLMG Fil-blo, PHC).

The proximal aorto-SVG anastomosis is accomplished under partial occlusion using continuous running Prolene 6-0 suture. During aortic partial cross clamping, there may be transient increase in blood pressure and this may be controlled by deliberate hypotension by giving either NTG, nicardipine or esmolol. Upon release of the aortic cross clamp, the patient is given sodium bicarbonate (1mg/kg BW) and calcium gluconate. The patient is then started on inotropic supports and NTG as the need arises. Intra-operative problems are dealt with accordingly. Premature ventricular contractions are treated with lidocaine bolus given at 1mg/kg BW or as a drip at 1-4 mg/hour. For ST wave elevations, bolus doses of either glyceryl trinitrate or isosorbide dinitrate is given. Hypotension brought about by cardiac manipulation may be treated with Trendelenburg maneuver (redistribution of blood volume), fluid supplementation o inotropic drug support.

After the anastomoses are accomplished, doppler flow studies of the grafts are done and once the patient is hemodynamically stable, a French 36 chest tube is inserted and the sternum is closed. The chest tubes are later attached to a thoracic (Emerson) pump at the recovery room and maintained at a pressure of negative 20 cm water. The chest tubes are removed within 24-48 hours when the output is negligible.

Standard CABG is performed using a median sternotomy for access. Heparin is administered prior to cannulation at a dose of 300-400 units/kg. The goal of adequate heparinization is to maintain an activated clotting time (ACT) of 480 seconds. In all cases, the ascending aorta is cannulated for arterial return and the right atrium is cannulated using a single two-stage venous cannula for venous drainage. These cannulae are connected to the cardiopulmonary bypass (CPB) machine for circulatory support.

The CPB circuit contains a membrane oxygenator and a centrifugal pump. Coronary revascularization with CPB is performed under moderate hypothermia (32-340C). Myocardial preservation is achieved by delivery of hyperkalemic cold cardioplegic blood solution through the aortic root antegradely and through the coronary sinus at the right atrium retrogradely. After achieving global myocardial arrest, the anastomoses are accomplished. Intermittent cardioplegia is given retrogradely every 15-30 minutes. After the procedure, the patient is rewarmed to 350C before weaning the patient from CPB.

Results

There were thirty-four (34) consecutive patients who underwent multivessel OPCABG at Philippine Heart Center from January 1, 2001 up to August 31, 2001. The control group consisted of one hundred eight (108) patients operated on by standard CABG during the same period. (Ratio of 3.2 patients operated by standard CABG per patient operated by OPCABG). Three (3) patients in the OPCABG group were converted to standard CABG under cardiopulmonary bypass with a conversion rate of 8.82%.

The reasons for conversion were bradycardia and hypotension in two patients while the other patient presented with arrhythmia (premature ventricular contractions). The first two patients underwent LIMA to LAD anastomosis under OPCABG but when the anastomosis was being performed for the posteriorly located vessels, the patients went into

hemodynamic instability thus the immediate conversion to standard CABG under cardiopulmonary bypass. The third patient was undergoing anastomosis for the LIMA to LAD but was converted to standard CABG due to premature ventricular contractions. The comparison of patient profiles is shown in Table I.

Table I. Demographic Profiles

CHARACTERISTICS	STANDARD CABG (n=108)	OFF-PUMP CABG (n=34)	P-VALUE
AGE (years): RANGE	34-81	39--80	
MEAN+SD	59.47 + 10.11	57.7 + 10.16	0.39
SEX: Male	84 (80.77 %)	30 (88.24%)	
Female	20 (19.23 %)	4 (11.76 %)	0.46
Patient Category: Service (Dd)	11 (10.58%)	7 (20.59%)	
Private (A)	93 (89.42%)	27 (79.41%)	1.48
Functional Class Mean	2.39	2.26	0.23
Ejection Fraction(Mean)	64.02 + 24.09	65.0 + 23.86	0.71
History of Myocardial Infarction	52 (50%)	19 (55.88%)	0.69
Pre-operative Cardiac Events	74 (71.15%)	23 (67.64%)	0.56
Presence of Co-morbid Factors	26 (76.47%)	95 (91.36%)	0.64

Table II . Pre-Operative Cardiac Events

Cardiac Event	Standard CABG (n=108)	PCABG (n=34)	Total
Chronic Stable Angina	36	11	47
Unstable Angina	37	11	48
Congestive Heart Failure	0	1	1
Arrhythmia	1	0	1
None	30	11	41
Total	104	34	138

Table III. Co-Morbid Factors

Co-Morbid Factors:	Standard CABG (n=108)	PCABG (n=34)	Total
Diabetes Mellitus	39	10	49
Hypertension	65	19	84
Smoker	43	9	52
Bronchial Asthma	4	0	4
Chronic	2	1	3
Pulmonary Tuberculosis	0	1	1
Chronic Renal Insufficiency	3	0	3
End Stage Renal Disease	1	0	1
Diabetes Mellitus Nephropathy	1	0	1
Cerebrovascular Disease	5	0	5
Abdominal Aortic Aneurysm	1	0	1
Thoracic Aortic Aneurysm	2	0	2
Complete Heart Block	1	0	1
Chronic Venous Insufficiency	1	0	1
Dyslipidemia	0	2	2
None	9	7	16

The two groups were comparable with regards to patient profile and clinical characteristics. There were more males than females and more private patients than service patients in both groups. The pre-operative cardiac events and co-morbid factors for the two groups are presented in Tables II and III, respectively.

The target vessels or coronary arteries that were grafted for each group is shown in Table IV.

The perioperative data are shown in Table V. There were more elective operations in each group. There were more grafts anastomosed (vessels bypassed) in the standard group than in the OPCABG group which was significant. More intra-aortic balloon was inserted pre-operatively in the standard group and this may be attributed to the fact that there were more patients with left main coronary artery involvement with left ventricular dysfunction in this group.

Although the mean duration of operation, ventilatory support duration, recovery/surgical ICU stay and post-operative hospital stay was relatively shorter for the OPCABG group, it was not statistically significant. A statistical significance is noted regarding post operative blood loss, blood transfusion requirements and operative costs between the two groups. It was lesser for the OPCABG group.

The clinical outcome of the two groups as shown in Table VI was comparable. The number of patients with improved status, mortality rate and the incidence of immediate post-operative complications like peri-operative myocardial infarction and re-operation for post-operative bleeding were not statistically significant for the two groups.

The post-operative complication per organ system is shown in Table VII. Although there were more complications noted in the standard CABG group, it was not statistically significant.

The number of blood components used per group is presented in Table VIII. Except for the requirement for fresh whole blood and cryoprecipitate which was comparable for the two groups, there were more units of fresh frozen plasma and packed RBC and platelet concentrate consumed among patients who underwent standard CABG than OPCABG.

Table IV. Target Vessels

Coronary Arteries	**Standard CABG (n=108)**	**OPCABG (n=34)**
Left Anterior Descending	102 (26.98%)	34 (29.31%)
Ramus	4 (1.06%)	1 (0.86%)
Diagonal	71 (18.78%)	14 (12.07)
Right Coronary	24 (6.35%)	9 (7.76%)
Right Posterior Descending	56 (14.85%)	21 (18.10%)
Right Posterolateral	14 (3.70%)	2 (1.72%)
Left Circumflex	46 (12.17 %)	21 (18.10%)
Obtuse Marginal	60 (15.87%)	14 (12.07%)
Left Posterior Descending	1 (0.26 %)	0
Total	378	116

Table V. Perioperative Data

Parameters	**Standard CABG (n=108)**	**OPCABG (n=34)**	**P- value**
Acuity:			
Elective	103 (99%)	33 (97.06%)	
Urgent	1 (1%)	1 (2.94%)	0.43
Mean Number of Grafts Anastomosed	3.64 + 0.56	3.42 + .609	0.02
Mean Duration of Operation (Minutes)	334.67 + 78.96	320 + 86.74	0.37
Use Of Intra-Aortic Balloon Pump (Pre-Op)	13 (12.5%)	2 (5.89%)	0.36
Blood Transfusion:			
Yes	102 (98.08%)	26 (76.74%)	<0.01
No	2 (1.92%)	8 (23.53%)	0
Mean Total Post-Operative Blood Loss (Cc.)	490.35 + 488.18	338.09 + 266.137	0.032
Mean Ventilatory Support Duration (Minutes)	975.30 + 1303.55	664.31 + 545.65	0.05
Mean Duration of Rr/Sicu Stay (Days)	4.5 + 2.36	3.76 + 1.18	0.22
Mean Post-Op Hospital Stay (Days)	9.49 + 4.67	7.65 + 2.47	0.056
Mean Operative Cost	135,732.36 +	81,451.65 +	
(Philippine Pesos)	87,014.44	14,289.98	<0.01

Table VI. Clinical outcome

Parameters	**Standard CABG (n=108)**	**OPCABG (n=34)**	**P-Value**
Improved	101 (97.12 %)	34 (100%)	1
Died	3 (2.88 %)	0	1
Complications	19 (17.59 %)	4 (11.76%)	0.54
Perioperative Myocardial Infarction	0	0	1
Reoperation For Postoperative Bleeding	4 (3.85%)	1 (2.94%)	1.0

Table VII. Post-Operative Complications

Complications	**Standard CABG (n=108)**	**OPCABG (n=34)**	**Total**
Pulmonary:			
Atelectasis	1	0	1
Pulmonary Congestion	1	1	2
Pneumonia	2	1	3
Pleural Effusion	4	0	4
Neurologic:			
Hypoxic Encephalopathy	1	0	1
Seizures	1	0	1
Delirium	1	0	1
Stroke	2	0	2
Gastrointestinal:			
Acute Gastritis	1	1	2
Acute Pancreatitis	1	0	1
Wound Infection:			
Sternal Dehiscence	1	0	1
Sternal Infection	0	1	1
Acute Renal Failure	2	0	2
Total	19 (17.59%)	4 (11.76%)	23

Table VIII . Blood Components Transfused

Blood Component (Mean Units + Sd)	**Standard CABG (n=108)**	**OPCABG (n=34)**	**P-Value**
Fresh Whole Blood	1.34 + 1.75	1.12 + 1.32	0.98
Fresh Frozen Plasma	3.05 + 2.99	0.32 + 94	<0.01
Packed RBC	2.35 + 1.79	1.38 + 2.18	<0.001
Platelet Concentrate	4.48 + 3.94	0.53 + 1.26	<0.001
Cryoprecipitate	0.23 + 1.05	0	1.0

Discussion

With the revival of beating heart or off-pump coronary artery bypass grafting, there has been a worldwide resurgence in interest to do coronary revascularization without cardiopulmonary bypass even for multivessel involvement. OPCABG has been offered as an alternative to standard CABG. Several clinical studies show that off-pump CABG is safe and effective in selected cases.[10-15] At the Philippine Heart Center, initial experience with OPCABG was performed for single and anterior cardiac vessels but as surgeons gained experience, more multivessel cardiac anastomoses were performed. As expected, there were conversions from OPCABG to standard CABG. The conversion rate in this study is about 8.82%. Most of these patients were service patients. In the study of Hart et al.[15] their conversion rate was between 2-6%. According to these authors, the decision to proceed to off-pump CABG was an intraoperative decision after evaluation of the coronary anatomy and the patient's tolerance to cardiac displacement.[15] Ideal indications for OPCABG include no calcified coronary arteries, no intramuscular arteries, target vessels not less than 1.5 millimeter and severe left ventricular hypertrophy is contraindicated due to difficulty of displacement of the heart.[16]

In the study of Soltoski et al,[17] their conversion rate was about 25% and they have classified the reasons of conversion as follows: Class I-Surgeon considered complete revascularization impossible by off-pump; Class II-converted due hemodynamic instability during the procedure and Class III-graft malfunction determined by the flow measurements or clinical evidence. The conversions in this study were mostly Class II.

In this study, the patient population studied were matched except for the vessel grafted. There were more anastomosis performed in the standard CABG. This has been the observation in other studies.[18] Many cardiac surgeons still feel comfortable doing multivessel CABG especially for more than three-vessel anastomosis under CPB.

With regards to the peri-operative data, it was noted that there was a shorter operative time in OPCABG but it was not significant. The shorter operative time is expected in OPCABG due to elimination of cardiopulmonary resuscitation, rewarming and termination of cardiopulmonary bypass which may save about 45-60 minutes.[16] In this study, one factor that may have an effect on the length of operative time is the learning curve of the surgeon since this is relatively a new technique and takes quite sometime and practice to master.

Most international studies point to shorter ventilatory support duration, recovery room and surgical ICU and postoperative hospital stay in the OPCABG group.[10,13,14,21] The shorter ventilatory support time was due mainly to the absence of cardiopulmonary bypass which may bring about diffuse inflammatory response which may affect the lungs and cause neutrophil and complement activation, surfactant degradation, increased capillary permeability, interstitial edema, decreased pulmonary compliance and atelectasis.[10] Although this was noted in this study, the shorter ventilatory support time was not significant. The longer post-operative hospital stay for most patients who underwent standard CABG has also been attributed to the use of cardiopulmonary bypass in these patients with concomitant systemic inflammatory side effects.

There were three important significant findings in this study. The operative cost, post-operative blood loss, blood transfusion requirements and blood components used were relatively lesser in the OPCABG group than the standard CABG. With the absence of cardiopulmonary bypass, a lower cost is expected since materials (i.e.heart-lung machine, cannulae, tubings, membrane oxygenator, priming solutions, blood components, etc.) for this procedure are not used. Blood contact with the artificial surface of the CPB circuit brings about a diffuse inflammatory response with release of cytokines and activation of complement system as well as destruction of RBC, platelets and consumption of coagulation factors. This is one reason why blood cells and coagulation factors are deranged with an expected higher requirement for blood transfusion. In this study, about 76% of OPCABG patients had blood transfusion compared to almost all patients in standard CABG. The number of patients who required blood transfusion in OPCABG was also low as noted in the studies of Puskas (50%),10 Hart (13.6-14.5%).[14] Ascione noted that less than 5% of patients who underwent OPCABG required fresh frozen plasma and platelet transfusion compared to 30% and 25% respectively in the standard CABG group.[20] The mortality and morbidity rate for OPCABG is within acceptable limits and is comparable to standard CABG. The mortality rate in the study of Cartier[12] was 1.3% while that of Hart[15] was 1.0%. The incidence of reoperation for bleeding in this study was 2.94% while that of Hart[15]was 1.2% (0.6-1.0%). Although there were more systemic complications in OPCABG than standard CABG, (Table VII) it was not significant.

Off-pump coronary artery bypass grafting (OPCABG) is a safe alternative in the management of properly selected patients with multiple coronary vessel involvement including those with lesions located in the posterior wall of the heart (circumflex, obtuse marginal and right posterior descending and right posterolateral coronary arteries). The clinical outcome, morbidity and mortality rates are comparable to standard CABG. The blood transfusion requirements and operative costs were lesser than standard CABG.

Although it was noted in this study that patients operated had shorter operative time, duration of ventilatory support, RR/SICU stay, post-operative hospital stay and lesser post-operative blood loss, it was not statistically significant. OPCABG may be done safely in properly selected patients by competent cardiac surgeons. The surgeon should not hesitate to convert to standard CABG when intra-operative morphologic evaluation of target vessels and hemodynamic events warrant doing

the myocardial revascularization safely under a globally arrested heart under CPB assisted CABG.

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Original Article

Six-Minute Walk Distance of Filipino High School Students

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BACKGROUND: *Timed walk test has enjoyed widespread clinical application because of their convenience of administration, their close similarity in daily activity than tests of maximal exercise capacity and lack of need for sophisticated equipment. It has been suggested that six-Minute Walk Test (6-MWT) provide a useful alternative method for assessing exercise tolerance and oxyhemoglobin desaturation in chronically ill children awaiting heart-lung or lung transplantation. It has commonly been employed as an outcome measure for cardiac and pulmonary rehabilitation program. While there are available data for adults from which adult patients with cardiopulmonary disease can be compared with, reference values for healthy pediatrics are not yet available. The objective of this study is to determine reference values for six-Minute Walk Distance (6-MWD) among Filipino children, to investigate the influence of demographic and anthropometric parameters on 6-MWT in children, and to determine the relationship between physical activity and 6-MWD in Filipino children.*

METHODS AND RESULTS: *All students aged 12-18 years old from Carlos P. Romulo High School were included in the study. Those who were not given parental consent and those with any medical disorder particularly history of asthma and other pulmonary disease, exertional chest pain or syncope, heart disease, neuromuscular disease, FEV1 or FVC < 80% of predicted on spirometry were excluded. There were 125 students included in the study.*

CONCLUSION: *The mean 6-MWD by Filipino high school students (12 -18 years old) was 490.77 + 53.66 meters. From this study, the only variable that was statistically significant was gender. The best 6-MWD by boys was greater than girls by an average of 32 meters. This study did not show any significant correlation between 6-MWD and age, height, BMI and pulmonary function tests. The 6-MWD in this study was not related to the daily activities nor to the subject's smoking habits.*

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Keywords: oxyhemoglobins; walking; exercise test

Exercise testing has the potential of providing important information for gauging the impact of many childhood and adolescent disorders. The progressive exercise testing on a cycle ergometer or treadmill remains the cornerstone of most exercise testing in childhood and adults. However, it is becoming increasingly apparent that peak or maximal exercise test is not representative of pattern of physical activity actually encountered in the lives of children. Children are engaged in very short bursts of high intensity physical activity interspersed with varying intervals of low and moderate intensity. Sustained heavy exercise from which the peak / maximum oxygen uptake during traditional exercise testing is measured, rarely occurs in children. Other viable alternatives to traditional adult-modeled maximal test are available for children.

Cooper propose that brief constant work rate exercise protocols (lasting several minutes of less) serve as an initial screening test.

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Timed-walk tests have enjoyed widespread clinical aplication because of their convenience of administration, their close similarity to daily activity than tests of maximal exercise capacity and lack of need for sophisticated equipment. Walk test, provides an estimate of functional capacity and has been shown to predict morbidity and mortality.

It has been suggested that 6-Minute Walk Test (6MWT) may provide a useful alternative method for assessing exercise tolerance and oxyhemoglobin desaturation in chronically ill children awaiting heart-lung or lung transplantation.

Previous studies have shown walk distances to correlate significantly with some measures of resting pulmonary function with aerobic fitness (as measured by peak oxygen uptake) and with minute ventilation during exercise testing. It has commonly been employed as an outcome measure for cardiac and pulmonary rehabilitation program.

At Philippine Heart Center Pediatric Pulmonary Program, 6-minute walk test is one of the parameters utilized as an outcome measurements.

Reference values have been published among healthy adults. Gibbus, et al.[1] have shown the Best 6-Minute Walking Distance (6-MWD) in 79 healthy subjects (22-79 years old)

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ranging from 474-1,040 meters (average 698 + 96 m). In Troosters et al.6 50 subjects (50-85 years old) have showed an average 6-MWD to be 631+ 93 meters (383 - 820 meters). From the Guinness Book of Records, 40th edition, typical 6-MWD for a competent marathon runner is 1,500 meters and for a person walking along a street it is 700 meters.

These are available data for adults from which adult patients with cardiopulmonary disease can be compared with. Reference values for healthy pediatrics are not yet available.

Objectives

1. To determine reference values for 6-MWD among Filipino children.
2. To investigate the influence of demographic and anthropometric parameters on 6-MWT in children.
3. To determine the relationship between physical activity and 6-MWD in Filipino children.

Methods

All students aged 12-18 years from Carlos P. Romulo High School were included in the study. Parental consent forms were given to determine inclusions. Those who were not given consent and those with any medical disorder particularly history of asthma and other pulmonary disease, exertional chest pain or syncope, heart disease, neuromuscular disease, FEV_1 or FVC < 80% of predicted on spirometry were excluded.

The age, sex, standing height in centimeters and weight in kilograms self-reported habitual activity or any form of habitual exercise and smoking history were taken and recorded. For the purposes of this study, the subjects' physical activity was classified as ACTIVE if very active in both house and school and engage in regular sports activity 2-3 times a week; MODERATELY active if active both in house and school but no regular sports activity and SEDENTARY if not very mobile in both house and school and no regular sports activity.

Spirometry was performed using a microloop to determine forced vital capacity (FVC) and expired volume in one sec. (FEV_1).

Functional Exercise Test

A 6-minute walk test was performed twice with a 30-minute interval rest. Subjects were asked to walk at their own pace along a 35 meter long gymnasium. Subjects were asked to walk from end to end covering as much ground as they could during the allotted time without running. Encouragement was standardized every minute. Subjects were given feedback on time progression and were encouraged to keep on walking. During the test, oxygen saturation and heart rate were measured by transcutaneous pulse oximetry. The percentage maximum heart rate (maximum heart rate based on Nelson Textbook of Pediatrics, 15th edition) was calculated and recorded.

The protocol stated that the testing was to be interrupted if threatening symptoms appeared. The subjects were told they could rest if they were too exhausted to continue the test. No test, however was interrupted. The distance covered in six minutes was recovered. The test was repeated with equal encouragement and the best of two tests was used for further analysis.

Analysis

Data was reported as group means + standard deviation. The greatest distance covered in six minutes by each subject was identified from the two 6-MWD trials performed (best 6-MWD) and then used as the primary outcome variable in the analysis. Statistical equation done to determine associations of 6-MWD to the different variables were t-test, analysis of variance and correlation analysis. Regression analysis was determined to compute for the predicted values for 6-MWD. A p-value of equal or less 0.05 was considred significant.

Results

Two hundred (200) students were screened. Seventy-five (75) students were excluded from the study because of low FVC and or FEV_1 (73 students) and history of asthma (2 students). There were 125 students included in the study.

Patient characteristics are summarized in Table I. There were 72 (57%) boys and 54 (43%) girls. The age of the subjects ranges from 12-18 years (mean 14.06 + 1.78). The mean height, weight and BMI were 154.18 + 10.87, 43.91 + 10.49, and 18.29 + 2.89, respectively. The pulmonary function was all within normal limits for all subjects (FEV_1=100.0 4 + 11.35% predicted and FVC 89.67 + 9.37). During the best 6-MWD, patients reached 101.15 + 14.02 % of their maximal predicted heart rate. Oxygen saturation remained unaltered throughout both tests (mean of 97.13 + 1.48%). The mean best 6-MWD was 490.77 + 53.66. There were 24 students (19.2%) who are smoking (minimum of one stick per week for a year and a maximum of 2.5 pack years). Six (4.8%) students are classified as active. Most of them are engaged in basketball and one plays badminton 2-3 times a week. One hundred nineteen (95.2%) students are moderately active.

Table II shows the mean walking distances of the first and second tests are 465+56.06 and 474+55.4 meters (p=0.081). Fifty-two (42% of students had the best 6-MWD at first trial and 73 (58%) of students had the best 6-MWD at the second trial.

Table III shows the mean best 6-MWD for boys and girls which was statistically significant.

Table IV shows no significant correlation between 6-MWD and the various patient variables such as age, height, weight, BMI and pulmonary function tests (FEV_1 and FVC).

Tables V and VI show the 6-MWD was not related to the

classification of daily activity nor to the subject's smoking habits.

Table I. Characteristics of study subjects

Total number of subjects	125 students
SEX (no./%)	
Male	72 (57)
Female	54 (43)
Age (yrs) (mean+SD)	14.06 + 1.78
Height (cms) (mean+SD)	154.18 + 10.87
Weight (kgs) (mean+SD)	43.91 + 10.49
BMI (kg/m2)	18.29 + 2.89
FEV1 (% predicted)	100.04 + 11.35
FVC (% predicted)	89.67 + 9.37
% max. heart rate at Best 6-MWD	101.15 + 14.02
O2 sat. at best 6-MWD (%)	97.13 + 1.48
Best 6-MWD (meters) mean+SD	490.77 + 53.66
With smoking history (no/%)	24 (19)
Level of activity (no/%) moderately active	6 (48)
	119 (95.2)

Table II. Mean First and second 6-MWD in meters among high school students

AGE (yrs)	BOYS	GIRLS	p-value
12	468.22 + 34.69	482.39 + 41.08	
13	521.31 + 78.36	483.55 + 50.87	
14	508.04 + 60.9	483.48 + 39.97	
15	479.56 + 18.39	480.5 + 18.66	
16	509.5 + 37.68	431 + 35.37	
17	466.84 + 27.51	——	
18	499.56 + 71.54	475.33 + 36.17	
Mean + SD	**500 + 58.71**	**478.58 + 43.79**	**0.026**

Table III. Best 6-MWD in meters as a function of age among high school students

AGE (yrs)	FIRST 6MWD	SECOND 6MWD	p-value
12	460.98 + 11.07	461.40 + 9.62	0.968
13	471.48 + 10.44	483.87 + 11.03	0.287
14	486.32 + 12.99	479.97 + 12.06	0.574
15	466.61 + 7.95	466.54 + 7.02	0.995
16	442.73 + 11.98	472.42 + 15.24	0.116
17	444.96 + 11.70	461.39 + 8.72	0.181
18	451.98 + 25.30	481.90 + 21.92	0.128
Mean + SD	**465 + 56.06**	**474 + 55.4**	**0.08**

Table IV. Univariate Correlation Cofficient between the 6--MWD and patient variables

	Age (yrs)	Height (cms)	Weight (kgs)	BMI (kg/m2)	FEV1	FVC
6-MWD	-0.09	0.08	-0.01	-0.08	0.09	0.09
p-value	0.33	0.35	0.9	0.38	0.31	0.33

Table V. Best 6-MWD in meters as a function of the presence or abscence of smoking history

(Mean + SD) Smoking History	Best 6 MWD	p-value
With	486 + 48.70	
Without	491.75 + 54.95	0.68 NS

Table VI. Best 6-MWD in meters as a function of daily activity

(Mean+SD)	Best 6 MWD	p-value
Active	467.27 + 46.76	
Moderately active	491.95 + 53.88	0.273 NS

Table VII. Reference equations for 6-MWD in Filipino children

BOYS: 6-MWD= 584.37 - 5.703 (age in years)

GIRLS: 6-MWD= 540.22 - 4.597 (age in years)

Alternate equations
using height: 6-MWD= 427.54 + 0.414 (height in cms)
using BMI: 6-MWD= 518.10 - 1.46 (BMI)

Discussion

The present study was able to determine 6-MWD among Filipino high school students (12-18 years old) ranging from 366-676 meters. On average, the 6-MWD was 490.767 + 53.66 meters.

This study did not show any significant correlation between 6-MWD and age, height, BMI and pulmonary function tests as against the study done by Gibbons et al.[1] He has shown a significant inverse relationship between best 6-MWD and age and BMI and a significant direct relationship between best 6-MWD and height.

In the present study, best 6-MWD was found to be significantly different between boys and girls (p value= 0.026) which was comparable to the study of Gibbons et al. among 88 healthy adults. In their study, they had shown that age, gender accounted for 41% of the between subject variance in best 6-MWD in the healthy adults. Likewise Troosters et al.[6] showed 6-MWD among males to be 84 meters greater than females.

Guyatt et al.[8] have shown that multi-test repetition provides test familiarity ("the learning effect") significantly influence intra-individual variability in 6-MWD. Nixon et al.3 cited that at least three walks are needed to minimize intra-individual variability in 6-MWD. However, in this present study the 6-MWD of first and second trials were not statistically

significant (p value=0.081) and this is because encouragement was equally given in both tests. The present findings were in agreement with Guyatt et al. who showed that when encouragement was unaltered, the 6-MWD did not improve significantly after the second walking test. Hence, they have cited the use of only one practice walk in well motivated subject was believed to be valid.

As in the study of Troosters, the 6-MWD in this study was not related to the daily activities not to the subject's smoking habits.

Conclusion

The mean 6-MWD by this Filipino high school student (12-18 years old) was 490.77 + 53.66 meters. From this study, the only variable that was statistically significant was the gender. The best 6-MWD by boys was greater than girls by an average of 32 meters. This study also showed best 6-MWD was not related to the subject's daily activity.

Recommendation

A larger study population to represent the population characteristics is recommended.

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Original Article

An Analysis of Maximum Oxygen Consumption Determination in Filipino Schoolchildren

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BACKGROUND: *The Multistage Fitness Test (MFT), a 20-meter shuttle run test adopted from Leger and Lambert and introduced by the National Coaching Foundation, is a simple means to determine maximum oxygen consumption ($V0_2$ max). The MFT requires the subject to exercise maximally in accordance to the loading pattern of a maximum oxygen consumption testing. This study was conducted to: (1) obtain baseline data on V02max in a group of Filipino schoolchildren using the Multistage Fitness Test and; (2) to determine the correlation of V02max to respiratory symptoms, respiratory diseases, physical activity and FEV_1 among Filipino schoolchildren.*

METHODS AND RESULTS: *Four hundred nine high school students aged 12-16 years participated in the study. There was no significant difference in the mean age between the sexes. However, boys were on average 3.8 kg. heavier and 4 cm. taller than girls. Boys had significantly higher VO_2 max (32 ± 2.87 vs. 28. 85±2.11 ml/kg/min, p<0.001) and FEV_1 (2.61±0.50 vs. 2.18±0.31L, p<0.001) than girls. On the other hand, girls reported a significantly higher prevalence of chronic cough (10.9 vs. 4.1%, p=0.020) and a higher proportion of physical inactivity (53.4 vs. 37.4%, p=0.002) than boys. Because the number of adolescents who reported positive for respiratory symptoms and/or diseases was small, boys and girls were combined in the analysis. No significant differences in VO_2max nor FEV_1 were observed in children with respiratory symptoms/diseases compared to those without. Physical inactivity, as an independent factor, was significantly associated with decreased VO2max (p<0.001). However, no significant correlation was noted between VO_2max and FEV_1 (r=0.253).*

CONCLUSION: *The maximum oxygen consumption (VO2max) among Filipino schoolchildren was lower compared with those of their Caucasian counterparts. This was attributed to the differences in height, weight and physical activity.*

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Keywords: exercise test; $V0_2$max, FEV_1, $V0_2$max

Maximum oxygen consumption (VO_2max) is a useful measure of cardiorespiratory capacity. It reflects the ability of the cardiorespiratory system to deliver oxygen from the air to the working muscles. Thus, a person with a high VO_2max is regarded as having good "aerobic fitness" or "cardiorespiratory fitness".[1] The most accurate determination of maximum oxygen consumption is obtained by measuring it directly in the laboratory where patient is made to exercise either on a treadmill or bicycle ergometer. As work rate increases (speed and grade on a treadmill or resistance and tempo on a bicycle ergometer), the rate of oxygen uptake (VO_2) also increases, until it plateaus. This maximal rate of oxygen uptake is the maximum oxygen consumption (VO_2max) and represents a physiologic limit. VO_2max is measured by analysis of the patient's expired gases via a mouthpiece attached to the gas analyzer and is expressed in ml/kg/min or liters/min.[2] However, since testing large numbers of people in the laboratory is not easy and requires high level of expertise and equipment, many attempts have been made to predict maximum oxygen consumption from simple field tests.[3]

In 1982, Leger and Lambert introduced the concept of a progressive shuttle run test for the prediction of maximum oxygen consumption.[4] They compared the VO_2max values obtained from three methods: the directly measured VO_2max (an inclined walking treadmill test), the retroextrapolated VO_2max (maximum O_2 consumption assessed by establishing O_2 recovery curved following maximum multistage test) and the VO_2max predicted from the maximal speed achieved during the 20-meter shuttle run test using the appropriate regression equation. Results showed that the 20 meter shuttle run test yielded results similar to a conventional inclined treadmill test and from the retroextrapolated VO_2max. Following this publication, the test was adopted by the Council for Europe as part of its range of cardiorespiratory and motor fitness tests for assessing the physical development of schoolchildren.[5]

In 1986, a validation study was done by van Mechelen, et al[6] where eighty-two subjects (41 boys and 41 girls) aged 12-14 years performed the 20-meter shuttle run test and the 6-minute endurance run and had their $V0_2$max or more days

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directly measured during maximal treadmill running. They noted a higher correlation between $V0_2$max and the 20-MST (r=0.76) than the 6-minute endurance run (r=0.53). Thus, the 20-MST was considered to be a more suitable tool for the evaluation of maximal aerobic power.

In 1988, the National Coaching Foundation, in partnership with Loughborough University introduced the Multistage Fitness test (MFT), a 20-meter shuttle run test adopted from Leger and Lambert as a simple means to determine VO_2max.[5] The subjects were required to exercise maximally by the end of the test, similar to the loading pattern of a VO_2max test. Results of subsequent validation studies had shown that this test was reliable. The values were highly correlated with the measured VO_2max, with correlation coefficients ranging from 0.8-0.9 in adults 1, and 0.8 in children.[7]

Since then the MFT has been used to determine the cardiopulmonary fitness in large numbers of children in European and North American countries. In Hong Kong Wong, et al.[3] published the first and only study in Asia among 8-12 years old schoolchildren. They showed that the mean VO_2max values obtained from the test were relatively low in Hong Kong Chinese schoolchildren com- pared with the Caucasians. They attributed this to racial differences and a lower level of physical activity among their study population. They likewise showed that a reduced $V0_2$max was significantly associated with respiratory diseases and habitual physical inactivity.

This research study was undertaken to obtain baseline local data for VO_2max in Filipino schoolchildren using the MFT, without the use of sophisticated equipment and the required expertise.

Research Objectives:

(1) To provide baseline data on VO_2max in a group of Filipino schoolchildren using the Multistage Fitness Test from ages 12-16 years.

(2) To determine the correlation of VO_2max to respi- ratory symptoms, respiratory diseases, physical activity, and FEV_1 among Filipino schoolchildren.

Research Hypothesis:

The Multistage Fitness Test (MFT) is a useful method to evaluate cardiorespiratory fitness in children. The mean VO_2max values obtained from the tests is lower among Filipino adolescents compared with their Caucasian counterparts. The reduced VO_2max is significantly correlated with respiratory symptoms, respiratory diseases, and habitual physical inactivity and FEV_1.

Methodology

Study Design

An experimental study.

Study Sample

All high school students of the Iloilo National High School were invited to participate. A consent from the parent/ guardian was obtained prior to inclusion in the study. The parents/guardian were also requested to answer a questionnaire. The student was then asked to perform lung function test followed by the Multistage Fitness test (MFT).

Inclusion Criteria

1. High school students in the selected school.
2. Able to follow instructions in doing spirometric studies and MFT.
3. With written informed consent and a parent-completed questionnaire.

Exclusion Criteria

1. Inability to perform the prescribed testing procedures.
2. Those afflicted with any injury or illness that would contraindicate participation in the Multistage Fitness Test.

Study Setting and Time Period

Iloilo National High School, Iloilo City from January- February 2002.

Identification of Study Variables

The parameters evaluated in this study included anthropometric measurements (weight and height), spirometric studies specifically FEV_1 , presence or absence of respiratory symptoms or diseases, level physical activity and the VO_2max.

Detailed Description of Data Collection

A written approval was obtained from the school principal prior to the conduct of the study. Questionnaires together with the consent forms were distributed to the parents of each student a week before the tests were performed. Consent for lung function and exercise tolerance tests were given by parents for their children to participate in each of the tests.

Questionnaire

The questionnaire included a history of children's respiratory symptoms in the previous year, respiratory diseases that occurred from birth to the time of the survey, and habitual physical activities. Both parents (when possible) were asked to complete their questionnaires jointly at home.

Health outcome variable was considered positive when "yes" is given to one or more of the following questions 3 :

1. Chronic cough: did the child cough on most days (4 per week) for as much as 3 months of the year, in the previous year?
2. Chronic sputum: did the child bring up phlegm on most days (4 or more days per week) for as much as 3 months of the year, in the previous year?
3. Wheezing: did this child ever sound wheezy or whistling apart from colds.

4. Did the child ever had asthma and or bronchitis diagnosed by a doctor?

Definition of Habitual Physical Activity

Depending on the frequency and duration of organized sports and vigorous free play, habitual physical activity was categorized as active and inactive. Active children were defined as those who actively participated in sports and or vigorous free play at least 3x a week for at least 30 minutes each time. Inactive children were those who did not fulfill the preceeding criteria.

Lung Function Test

Spirometry was performed using a portable spirometer (Microloop 2 Spirometer #3874 by Micromedical Company, Ltd. England). Three spirometric trials were done and the best FEV1 result from the 3 trials was recorded.

Multistage Fitness Test

All participants came in their complete PE uniforms as requested. The MFT was conducted in a partially shaded open field within the school campus. The field surface was dry and nonslippery. Twenty-meter tracks were measured on the ground and each end was marked by flaglets. One participant was assigned to a track. In this test, subjects were asked to carry out a series of shuttle runs between the two markers at an exact distance of 20-meters. The running pace is set by audio signals (bleep sounds) emitted at set intervals from a recorded compact disc. (The Multi- stage Fitness Test-The National Coaching Foundation).

The following instructions were given to the partici- pants. The test begins with a five second countdown to the start. Thereafter, single bleeps are emitted at regular intervals. The subjects should aim to be at the opposite end by the time the first bleep sounds. They should then continue running at this speed, being at one end or the other each time there is a bleep.

The participants should always place one foot either on or behind the 20-meter mark at the end of each shuttle. If the participants arrive at the marker before the bleep sounds, they should turn around and wait for the bleep, then resume running and adjust their speed.

After each minute, the time interval between bleeps will decrease, so that the running speed will need to be increased. The first running speed is referred to as level 1; the second speed as level 2 and so on. Each level last approximately 1 minute. The end of each shuttle is denoted by a single bleep;the end of each level is denoted by a triple bleep and by the taped voice message. The frequency of sound signals is increased at a rate correspon- ding to an increase in running speed of 0.5 km hr-1 each minute from a starting speed of 8.5 km hr -1. Thus the timing begins very slowly but becomes progressively faster each minute, so that it becomes increasingly difficult to maintain the set pace.

The MFT was performed in groups of 5 students who were instructed to run at the pace of the audio signal and to give their maximum effort when performing the test and therefore attempt to reach as high a level as possible before stopping. The runner stops when he or she can no longer maintain the running speed or is withdrawn from the test when he or she was no longer complying with the test regulations. Two verbal warnings are given if they fail to reach the line before the audio signal and are then with- drawn from the test after a third failure.

The number of shuttles completed at the highest level attained was then recorded. VO2max was derived from the level (maximal speed) and the number of shuttles achieved during the multistage test based on the table provided by Brewer et al, of Loughborough University.[5] There were observers assigned to each participant to help the author take note of the level and the number of shuttles into the level at which each participant withdraws from the test.

Description of Data Handling

Data were described as mean standard deviation, or frequency and percent distribution. Baseline anthropo- metric data, exercise levels, VO_2max, FEV_1, and the prevalence of respiratory symptoms and diseases were compared between boys and girls using two-tailed t-tests and Chi- square tests.

The VO_2max and FEV_1 of children with reported respiratory illnesses (symptoms and/or diseases) and those without were compared by analysis of covariance, adjusted for age, gender, height, and weight. Association of FEV_1 with VO_2max was determined using Pearson correlation analysis. P value < 0.05 were considered statistically significant.

Results

A total of 946 high school students were invited to participate, of which 529 (56%) responded with parent- completed questionnaire. Of those who responded, 522 students were allowed by their parents to participate in the research study. Subsequently, 462 students were able to participate in the multistage fitness test. Sixty students did not participate because of various reasons (39 were absent, 7 were involved with other activities, 10 were not feeling well, 4 had dysmenorrhea). Data from 409 students were subsequently entered into the study and analyzed (53 participants were not able to reached level 4 of the MFT, which is the minimum level where a corresponding predicted VO_2max value is assigned. Level below this correlates poorly with the VO_2max).

Table I presented the anthropometric characteristics, performance data of the MFT, the VO_2max and FEV_1 among 409 adolescents. There was no significant difference in the meanage between the sexes. However, boys were on average 3.8 kg heavier and 4 cm. taller than girls. Boys had significantly

higher mean values of VO_2max (32 + 2.87 vs. 28.85 + 2.11 ml/kg/min) and FEV_1 (2.61 + 0.50 vs. 2.18 + 0.31 L) than girls.

Table I. Anthropometric, performance and FEV_1 data of Filipino schoolchildren

	Boys (n=171) Mean + SD	Girls (n=238) Mean SD	p-value
Age (years)	14.39 + 1.24	14.31 + 1.10	0.508
Height(cm)	157.90 + 7.10	153.90 + 5.30	< 0.001
Weight(kg)	48.20 + 11.50	44.40 + 7.30	<0.001
Exercise level	5.30 + 0.95	4.40 + 0.64	<0.001
VO_2max (ml/kg/min)	32.00 + 2.87	28.85 + 2.11	<0.001
FEV_1(L)	2.61 + 0.50	2.18 + 0.31	<0.001

The age specific values for height and weight are shown in Figure 1-A and 1-B, respectively. In general, mean height and weight for boys increase with age. Similar observation was also noted in girls.

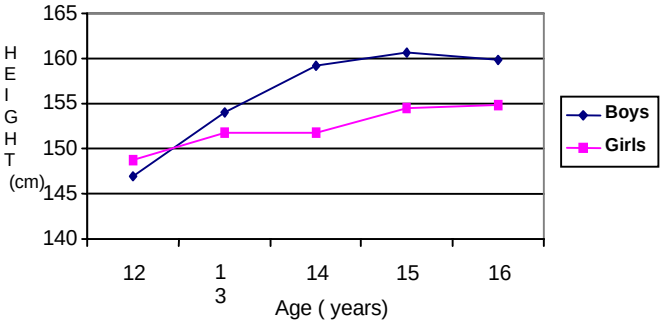

***Figure 1-A.* Age specific valuse for height**

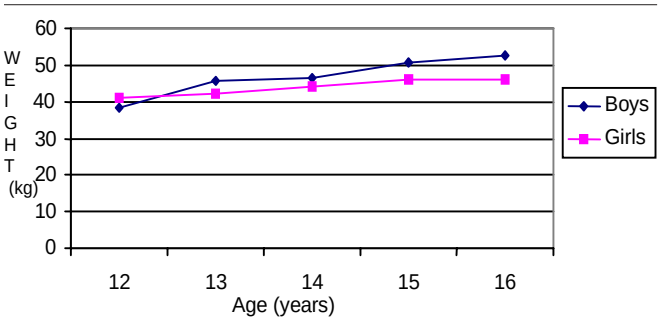

***Figure 1-B.* Age specific values for weight**

Figure 2 presents the prevalence of reported respiratory symptoms, diseases and physical inactivity. Girls reported a significantly higher frequency of chronic cough (10.9 vs. 4.1%, p=0.020) than boys. Likewise, a significantly higher proportion of girls was physically inactive (53.4 vs. 37.4%, p=0.002).

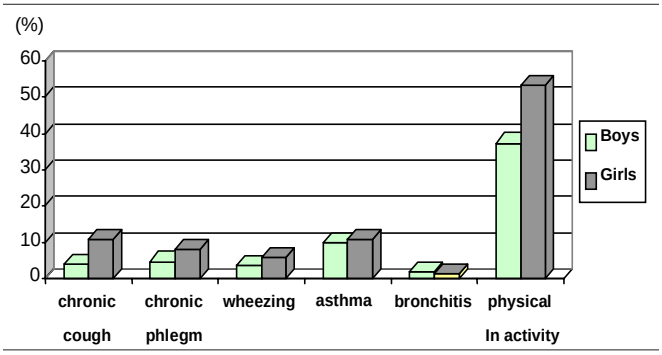

***Figure 2.* Prevalence of reported respiratory symptoms, disease and habitual physical inactivity**

Table II shows a comparison of the values of VO_2max and FEV_1 between adolescents with at least one respiratory symptom (either chronic cough or phlegm or wheezing), disease (either asthma or bronchitis), and those without. As the number of adolescents who reported positive for respiratory symptoms and/or diseases was small, boys and girls were combined in the analysis. No significant differences in either VO_2max or FEV_1 were observed between the children with respiratory symptoms or diseases and those without. Presence of one symptom or at least one disease did not affect the VO_2max and FEV_1 values.

Table III shows the comparison of mean VO_2max and levels of physical activity. The mean VO_2max was significantly decreased among physically inactive school children in both sexes.

Table II. VO_2max and FEV_1 in relation to respiratory symptoms and diseases in schoolchildren

Mean+SD	VO_2max (ml/kg/min)	FEV_1 (L)
At least one symptom		
Yes (n=45)	29.61 + 3.19	2.35 + 0.50
No (n=364)	30.24 + 2.87	2.36 + 0.44
p- value	0.170 NS	0.813 NS
At least one disease		
Yes (n=49)	30.36 + 3.49	2.36 + 0.47
No (n=360)	30.14 + 3.49	2.36 + 0.45
p- value	0.629 NS	0.932 NS

Table III. Mean VO_2max in relation to physical activity

	Active (VO_2max)	Inactive (VO_2max)	p-value
Boys	32.76 + 2.71	30.74 + 2.68	<0.001
Girls	29.18 + 2.24	28.56 + 1.95	0.02
Both sexes	30.94 + 3.06	29.29 + 2.45	<0.001

Figure 3 shows the correlation of the VO_2max with FEV_1. There was no significant correlation between VO_2max values and FEV_1 (r=0.253).

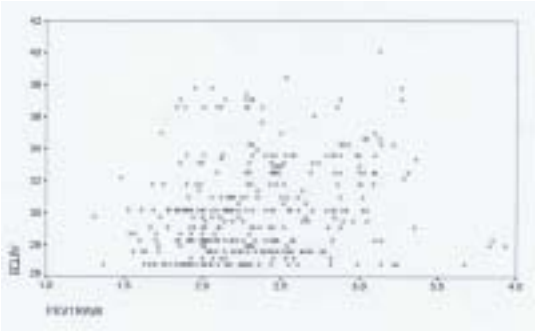

Figure 3. **Correlation of VO_2max and FEV_1**

Discussion

This study showed the VO_2max in a group of Filipino schoolchildren aged 12-16 years, using the Multistage Fitness Test (MFT). VO_2max reflects the maximum capacity of the cardiorespiratory system for oxygen uptake during exercise. The MFT has been shown to be highly correlated to VO_2max measured in the laboratory. The simplicity of the MFT and its applicability to a large population render it a suitable tool for epidemiologic studies.

The mean VO_2max in our subjects using the MFT was 32 + 2.87 ml/kg/min for boys and 28.85 + 2.11 ml/kg/min for girls aged 12-16 years. The mean height and VO_2max in boys were significantly higher than girls. The significant difference of VO_2max between boys and girls is closely related to the differences in height, mainly due to discrepancy in leg length, leg muscle mass and cardiac output, [3] and physical inactivity.

Studies on the validity of the MFT to predict the VO_2max have been done among children of different ages and races. The study by Wong C[3] reported that the mean values of VO_2max among Hong Kong Chinese school children was 30.3 + 5.2 ml/kg/min for boys and 28.6 + 3.6 ml/kg/min for girls aged 8-12 years. Our VO_2max values were higher than those of Hong Kong Chinese schoolchildren. However, it is difficult to compare the two groups because of the differences in age range. The study by van Mechelen et al[6] showed that in 82 Caucasian children (41 boys and 41 girls) aged 12-14 years, the VO2max was 41-43 ml/kg/min for boys and 34-36 ml/kg/min for girls. Another study by Mahoney[7] showed that the VO_2max values for boys were 47.4 ml/kg/min and 31.3 ml/kg/min for girls aged 12 years. The 103 subjects in this study consisted of a multiracial UK population composed of Indian, Afro-Carribean and mixed races. Based on these studies, the VO_2max values using the MFT was lower among Asian (Hong Kong Chinese and Filipino) children when compared with Caucasian and non-Caucasian children living in the United Kingdom. Several factors could possibly explain the differences in the VO_2max values obtained.

The MFT does require well-motivated subjects with some knowledge of pace judgement and an understanding of the test requirements. In our study, the participants were instructed to give their maximum effort when performing the test and should attempt to reach the highest level possible before stopping.

Differences in height among different races could be a possible explanation for the differences in the VO_2max obtained from the MFT. We compared our 12 year old subjects with the multiracial (non-Caucasian) UK population of the same age 7. It was noted that their subjects were taller (152.5 vs. 148 cm for boys and 153.8 vs. 149 cm for girls) than our study population. Cooper, et al.[8] in 1984 also stated that VO2max obtained using breath-by-breath analysis highly correlated with increasing height, in their study of 109 children of mixed races.

Another factor that explained the difference in VO_2max was physical inactivity. A study comparing 9-11 year old well-trained swimmers with untrained children of similar age, height and body mass, showed that the former had a significantly higher VO_2 max.[9] Relatively high VO_2max values had been obtained in children involved in exercise training.10 A significant correlation between physical inactivity and lower VO_2max was shown in our study. Our subjects did not have any regular exercise training before the MFT was performed. In fact, 37.4% and 53.4% of the boys and girls respectively, were physically inactive. In contrast, among the 12-year old multiracial UK population, 42% of the subjects played organized sports, 20% completed housework and 10% had part-time jobs.[7] Also, it is well-known that Caucasian children are in general physically more active than their Asian counterparts.[11] A small study of 16 moderately active Japanese 12-year olds reported a VO_2max of 41.2 ml/kg/min, a much higher value than that obtained in our 12-year old subjects.[12] However, the sample size in their study was too small for any meaningful inference.

In our study, no significant association was found between

reporting of respiratory symptoms, (chronic cough and chronic phlegm) VO_2max and FEV_1. There was also no association between the reporting of at least one disease (asthma or bronchitis), VO_2max and FEV_1. This is in contrast with the findings of Wong et al.[3] who reported a small but significant association between respiratory diseases and VO_2max. Children with asthma or bronchitis had a significantly lower VO_2max compared to those without. Their finding however, is not consistent with other studies that reported normal exercise capacity and aerobic fitness in adolescents with mild to moderate asthma.[13] Our findings showed that there was no significant correlation between VO_2max and FEV_1. This is consistent with the study of Ludwick, et al.[14] which showed that abnormalities in cardiopulmonary endurance did not correlate with historical features commonly used to define severe asthma or degree of airways obstruction. Likewise, similar observation was reported by Wong et al.[13] Ludwick, et al.[14] showed that VO_2max can be markedly increased by appropriate training of children. Their study consisted of 65 children with severe asthma, whose cardiopulmonary fitness improved after bicycle ergometry training. Physical exercise is beneficial for both healthy children and children with respiratory diseases.[3]

Conclusion

In conclusion, we have shown that the MFT is a useful method to evaluate cardiorespiratory fitness in Filipino schoolchildren. The mean VO_2max values were 32 + 2.87 ml/kg/min for boys and 28.85 + 2.11 ml/kg/min for girls aged 12-16 years. No significant association was found between VO_2max, FEV_1, respiratory symptoms, and respiratory diseases. However, there was a significant association between physical inactivity and VO_2max.

Another study with a bigger population and under range of groups is recommended to further validate the results of the study.

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Original Article

Continuous Positive Airway Pressure (CPAP) Among Patients with Cardiogenic Pulmonary Edema: Philippine Heart Center Experience

Christina A. Uy MD, Aileen V. Guzman MD, Ma. Encarnita B. Limpin MD, Teresita S. De Guia MD

BACKGROUND: ***Severe cardiogenic pulmonary edema is a frequent cause of respiratory failure especially in the Philippine Heart Center. Many patients with this condition require endotracheal intubation and mechanical ventilation. The authors investigated whether continuous positive airway pressure (CPAP) could reduce the need for endotracheal intubation, reduce the number of complications, and shorten ICU and hospital stay. They also investigated factors that could predict successful outcome among patients subjected to CPAP.***

METHODS: ***Thirty-one patients with cardiogenic pulmonary edema were randomly assigned to two groups: those receiving CPAP and those who underwent intubation. Improvement in oxygenation 30 minutes and 2 hours after initiation of mechanical ventilation (PaO2 / FiO2 and SaO2), duration of mechanical ventilation, length of ICU stay and length of hospital stay between the two groups were compared. Likewise, the Simplified Acute Physiologic Score II (SAPS), age, smoking history, tolerance to CPAP and co-morbidities were compared between the non-invasive group requiring endotracheal intubation and those who did not.***

RESULTS: ***CPAP was able to reduce the need for endotracheal intubation in 47% of patients. The noninvasive group had a shorter duration of mechanical ventilation (46.28 ± 17.56 vs. 156 ± 159 hours; p=0.01) and ICU stay (3.0 ± 2.5 vs. 9.6 ± 4.9 days; p=0.03) compared to the invasive mechanical ventilation group. The SAPS II, co-morbidities, age, blood gas parameters were not significantly different between the failed and successful CPAP groups. Improvement in oxygenation and tolerance to CPAP were the main factors noted to predict successful outcome of non-invasive mechanical ventilation. The numbers of complications were not statistically significant between the invasive and non-invasive mechanical ventilation groups (p = 0.16).***

CONCLUSION: ***CPAP reduced the need for endotracheal intubation by 47%. Furthermore, a shorter duration of mechanical ventilation use and ICU stay among these patients were noted. The major factors for CPAP success were improvement in oxygen saturation and tolerance to the procedure.***

Phil Heart Center J 2002;9:41-47

Keywords: Respiration, artificial; pulmonary edema; tracheal disease; ventilation, mechanical

Tracheal intubation and mechanical ventilation can successfully provide support and allow the survival of many patients suffering from acute respiratory failure. However, nasotracheal or orotracheal intubation or tracheostomy may by themselves, be a source of added morbidity, and severe complications have been described with the use of these techniques. Furthermore, the endotracheal tube itself, may increase work of breathing and subsequently prolo ng the duration of weaning from the respirator by inducing respiratory muscle fatigue. Recently, a non-invasive positive-pressure ventilation technique using facial or nasal mask without tracheal intubation has been described. It is safe and effective in improving gas exchange in selected patients with varying types of respiratory failure. In patients with acute respiratory failure, the therapy slightly decreases the rate of intubation and improves survival but the effect was not statistically significant.

In another study done by Meduri, et al,[1] they showed that Continuous Positive Airway Pressure (CPAP) was as effective as conventional ventilation in improving gas exchange and is associated with shorter stay in the intensive care unit. One of the common conditions where its use has been widely studied is hypoxemic respiratory failure secondary to cardiogenic pulmonary edema.[1]

As a cardiac referral center, various cardiac conditions are admitted to the intensive care units daily. Acute Coronary Syndrome and Rheumatic Heart Diseases are the two most common cardiac conditions encountered. Majorities of these patients present with pulmonary edema often resulting to acute hypoxemic respiratory failure and subsequent endotracheal

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intubation. Several prospective controlled studies done have proven that noninvasive ventilation such as CPAP had resulted to reduced need for endotracheal intubation in these patients. A review of the different studies (Pang et al, 1998)[2] on the use of CPAP in patients with cardiogenic pulmonary edema suggests that there is a modest amount of favorable evidence to support its use, due to the decrease in the need for intubation and a trend toward a decrease in mortality. The authors further add that the greatest benefit may be obtained in those patients with severe ventilatory failure.[2] In a local case-control study by Dimacutac, et al. (1995)[3] involving 6 patients, they have shown that CPAP may be an option that can be utilized in patients with cardiogenic pulmonary edema. There has been no similar study done locally so far.

With the paucity of data regarding the use of noninvasive positive airway pressure in patients with cardiogenic pulmonary edema, this study was undertaken.

Objectives

The main objective of this study is to determine the efficacy of noninvasive Continuous Positive Airway Pressure (CPAP) via nasal mask in improving oxygenation of patients with acute hypoxemic respiratory failure secondary to cardiogenic causes in conjunction with aggressive medical therapy and who require mechanical ventilation.

Specifically, this study would like to determine its efficacy in terms of improvement in gas exchange, frequency of complications, duration of mechanical ventilation, duration of stay at the ICU, and length of hospital stay as compared to conventional mechanical ventilation by endotracheal intubation.

Furthermore, this study aims to determine the predictors for successful outcome in these patients who received continuous positive airway pressure.

Methodology

This is a randomized controlled trial involving patients aged 19 years old and above admitted at the Philippine Heart Center (Emergency and Intensive Care Units) from January to September 2002 with acute hypoxemic respiratory failure secondary to cardiogenic pulmonary edema. The following were the inclusion criteria

1. Patients with known cardiac diseases (e.g. Coronary Artery Disease, Valvular Heart Disease, etc)
2. Acute respiratory distress (RR>25/min, active contraction of the accessory muscles of respiration or paradoxical abdominal motion) that continue to deteriorate despite aggressive medical management (diuretics, oxygenation, inotropics, etc).
3. Ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2: FiO_2) of less than 300 while breathing through face mask.
4. Hemodynamically stable (SBP = / > 90 mm Hg, HR <100/min, absence of cyanosis).

Patients with any of the following were excluded in the study:

1. Those requiring emergency intubation for cardiopulmonary resuscitation, respiratory arrest, severe hemodynamic instability or encephalopathy.
2. Respiratory failure caused by neurologic disease, status asthmaticus, or chronic obstructive pulmonary disease (COPD)
3. Those with two or more new organ failures (e.g. Simultaneous presence of renal and cardiovascular failure)
4. Those patients who underwent tracheostomy or recent oral, esophageal, or gastric surgery (< 6 months)
5. Patients with Glasgow coma scale < 13 or who were unable to expectorate or clear secretions
6. Those with facial deformity (e.g. Micrognathia, etc)

Patients who met the inclusion criteria were assigned into two groups by blocked randomization. Group 1 comprised the noninvasive (CPAP) group and Group II were patients placed on mechanical ventilation. Appropriate standard medical management was given to both groups as deemed necessary. Written informed consent was obtained from each patient. Data collected included age, sex, co-morbidities, Simplified Acute Physiologic Score (SAPS II), causes of respiratory failure and smoking history.

Invasive Mechanical Ventilation

Patients randomized to the invasive mechanical ventilation (MV) group were intubated using cuffed endotracheal tubes with internal diameter ranging from 7.5-8.0 cm. Sedation with diazepam 5 mg IV was given. No paralyzing drug was administered. Mechanical ventilators used were Puritan Bennett 7200 and Newport Breeze. The initial ventilatory setting was assist/control with an FiO_2 of 100%, tidal volume calculated at 6-8 ml/kg, RR of 14-18 breaths per minute, and initial Positive end-expiratory pressure (PEEP) of 8 cm H_2O. The patients' heads were elevated at 45 degrees. Depending on the arterial blood gas results, the PEEP was increased at an increment of 2-3 cm H_2O up to 20 cm H_2O until an adequate oxygenation (PaO_2 > 60 mm Hg; O_2Sat > 90%: or P/F ratio>300) was obtained. When adequate oxygenation was maintained and patients' condition stabilized, the FiO_2 was gradually decreased by decrements of 10% until 40% or less was reached. With oxygen still maintained at an acceptable level, PEEP was slowly reduced at decrements of 2-3 cm H_2O up to 5 cm H_2O. Weaning using T-piece was started when weaning parameters were fulfilled. Extubation was done after 2 hour weaning was tolerated (with RR<30/min and PaO_2 > 75 mm Hg).

Noninvasive ventilation: continuous positive airway pressure (CPAP).

Patients randomized to Non-invasive ventilation were hooked to CPAP (Good Nite machine) using nasal mask. After the mask had been secured, the initial positive pressure applied was 6 cm H_2O at 10 L/min. The head of the bed was elevated at 45 degrees angle. For patients with nasogastric tubes, a seal connector was used to minimize leakage. The positive pressure was increased at an increment of 2-3 cm H_2O (maximum of 20 cm H_2O) until adequate oxygenation was achieved. The FiO_2 was then gradually decreased until 6 L/min is attained and positive pressure to 5 cm H_2O maintaining adequate oxygenation. At that level, CPAP was discontinued and patient shifted to nasal cannula.

CPAP was considered failed when patient was subsequently intubated. Criteria for switching to conventional (invasive) mechanical ventilation were:

1. Failure to maintain a PaO_2 above 60 mm Hg with an FiO_2 of 0.6 or less
2. Development of conditions necessitating endotracheal intubation to protect airways (coma or seizure disorders) or to manage copious tracheal secretions
3. Hemodynamic or electrocardiographic instability
4. Inability on the part of the patient to tolerate face mask because of discomfort.

Monitoring of Oxygenation

Both groups were hooked to pulse oximeter to provide continuous monitoring of patient's oxygen saturation (SaO_2) with SaO_2 maintained > 90%. Arterial blood gases were taken at: (1) baseline prior to intubation, (2) 30 minutes after the initial set up of mechanical ventilation; (2) 30 minutes after each adjustment of MV or CPAP; (4) 2 hours after study entry; (4) during weaning; and (5) when oxygen dasaturation was noted on pulse oximetry. Based on the arterial blood gas (ABG) results, the ventilator set up was adjusted accordingly. Standard management for acid-base imbalance was given.

Endpoints and Definitions

The primary endpoints were oxygenation (PaO_2, O_2 saturation, PaO_2/ FiO_2 ratio) and the need for invasive mechanical ventilation. Improvement in gas exchange is defined as the ability to increase the PaO_2:FiO_2 ratio to >/= 200 or an increase in the ratio of >100 from baseline. This evaluation was done within 1 hour after initiation of either invasive or non-invasive mechanical ventilation (initial improvement) and over time (sustained improvement). Sustained improvement in gas exchange is defined as the ability to maintain the abovementioned improvement in PaO_2:FiO_2 ratio until mechanical ventilation is discontinued. Acceptable oxygenation is defined as PaO_2> 60 mm Hg or SaO_2> 90%.

The secondary end-points include survival, frequency of complications, duration of mechanical ventilation, the duration of stay at the intensive care unit (ICU) and the length of hospital stay.

The SAPS II was calculated 24 hours after admission to the emergency room or ICU. The score takes into account the following variables: age, heart rate, systolic blood pressure, body temperature, urinary output, white blood cell, Glasgow coma score, serum potassium, sodium, bicarbonate, urea nitrogen concentration. A range of 0 to 4 was assigned to each variable (possible score: 0 to 56). Higher score indicates higher risk for death.

Statistical Analysis

Univariate analysis comparing the two groups (CPAP vs. Mechanical Ventilator; CPAP success vs. CPAP Failure) was done using the Chi square and Fisher Exact Test for nominal data and t-test for continuous data.

Results

Between January to September 2002, a total of 415 patients were admitted to the intensive care units (ICU). Of the 415 patients admitted, 263 had hypoxemic respiratory failure. Only 47 patients met the inclusion criteria, of which, 31 gave their written informed consent and were enrolled into the study. Fifteen (15) were randomized to the noninvasive mechanical ventilation group (NIV) and sixteen (16) to the invasive ventilation group (IMV).

The baseline demographic and clinical characteristics of the two groups were comparable as shown in Table I with the exception of mean body temperature which was noted to be higher in the mechanical ventilation group ($p<0.04$) but is still within the normal range.

Eight (8) of the 15 patients in the noninvasive group (53%) were eventually intubated within the first 30 minutes after initiation of CPAP. Five (67.5%) of these patients were unable to tolerate the said procedure while 3 patients (37.5%) developed hypotension (BP<90/60 mm Hg).

The initial mean change in PaO_2:FiO_2 ratios between successful invasive and CPAP groups were comparable (Figure 1). All seven (7) patients in the successful NIV group showed an increase in their P:F ratio from baseline to 30 minutes after initiation of CPAP (mean increase of 56.2) but only 2(28.57%) showed significant improvement in gas exchange (an increase of 100 or more from their baseline P:F ratio). Two hours after initiation of CPAP, 5 patients (71.43%) were able to achieve sustained improvement in gas exchange (P:F ratio). In the invasive mechanical ventilation group, 14 (87.5%) patients showed an increase in their P:F ratio within 30 minutes of mechanical ventilation (mean increase of 96.79) but only 8 (50%) had significant improvement in gas exchange. Two hours after invasive mechanical ventilation, 15 (93.75%) patients were able to sustain improvement in their P:F ratio. The

difference in the number of patients achieving improved gas exchange (30 minutes and two hours after mechanical ventilation) between the two groups is not statistically significant (p=0.40 and 0.21 respectively).

Table I. Baseline demographic and clinical characteristics of the two groups

VARIABLES	Noninvasive Ventilation Group (n=15)	Invasive Ventillation Group (n=16)
Age (yrs) (Mean + SD)	66.60 + 11.47	63.40 + 16.47
Male : Female Ratio	5:01	5:03
SAPS II		
Heart Rate (beats/ min)	34.20 + 7.91	32.81 + 8.13
Systolic Blood Pressure	96.20 + 12.32	100.06 + 22.80
(mm Hg)	129.27 + 17.99	124.06 + 28.31
Temperature (0C)	36.48 + 0.37	36.91 + 0.43
Urine output (L/ 24H)	2.16 + 1.38	1.59 + 0.84
Hematocrit	0.41 + 0.05	0.38 + 0.07
WBC count	10.50 + 2.80	11.33 + 5.50
Serum Creatinine (umol/L)	0.14 + 0.56	0.21 + 0.15
Serum Potassium (mmol/L)	4.12 + 0.50	4.49 + 1.12
Serum Bicarbonate	23.47 + 8.22	21.56 + 3.52
pH	7.37 + 0.09	7.34 + 0.12
PaCO2 (mmHg)	41.64 + 11.02	45.50 + 14.00
P:F ratio	100.46 + 52.99	119.26 + 54.43
		10 (62.50%)
No. of smokers (Ex- or current)	10 (66.67%)	
Causes of ARF	1	0
Pneumonia	15	15
Cardiogenic Pulm	1	0
Edema	8	6
Post-op. RF	1	0
COMORBIDITIES	2	0
Diabetes milletus	1	0
Pneumonia	2	0
Bronchial Asthma	6	4
Hypertension	1	0
Bronchiectasis	1	0
Nephropathy	6	7

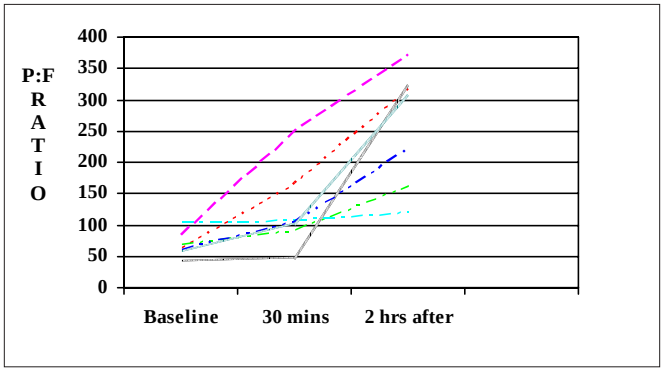

Figure 1. **P:F ratios at baseline, 30 minutes and 2 hours after among patient with successful CPAP (Initial and sustained improvement in gas exchange)**

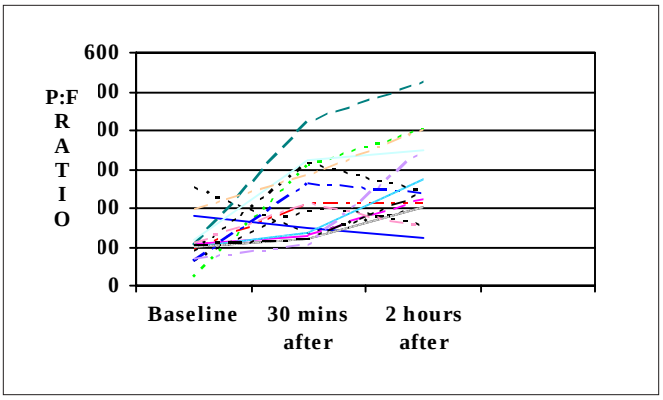

Figure 2. **P:F ratios at baseline, 30 minutes and 2 hours after among patients on Invasive Mechanical Ventilation (Initial and sustained improvement in gas exchange)**

Overall, 24 patients (eigth patients from the NIV group with failed CPAP and 16 patients from the conventional mechanical ventilation group), underwent endotracheal intubation. One patient in the invasive mechanical ventilation group died of hypovolemic shock due to ruptured abdominal aortic aneurysm within six hours after intubation and one patient was discharged (against medical advice) before treatment was completed. The duration of mechanical ventilation (Figure 2) in noninvasive group with successful CPAP was shorter compared to failed CPAP and invasive mechanical ventilation groups (46 + 17 vs. 148 + 151 vs. 156 + 159 hours; p = 0.02 and 0.01, respectively).

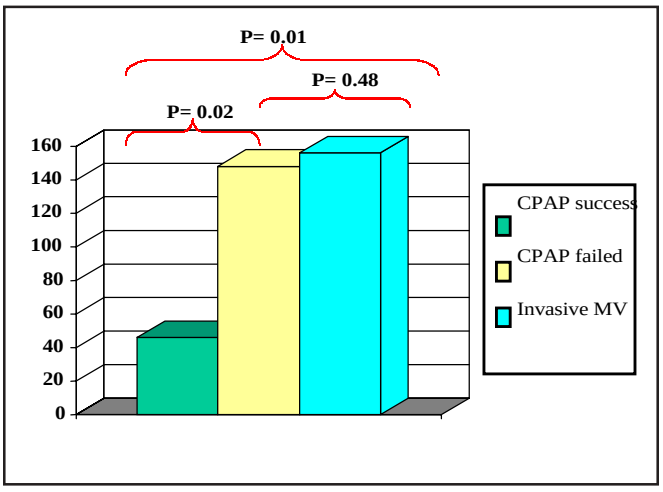

Figure 3. **Duration of mechanical ventillation (Hrs) in successful and failed CPAP and invasive mechanical ventilation groups**

Figure 3 showed that the length of ICU stay was significantly shorter in the successful CPAP group compared to both failed CPAP and invasive mechanical ventilation groups (3.0 + 2.5 vs. 8.0 + 4.9 vs. 9.6 + 4.9 days, respectively; p = 0.03). However, no statistical difference was noted in the length of ICU stay of failed CPAP to that of invasive mechanical ventilation (8.0 + 4.9 days vs. 9.6 + 4.9 days; p=0.48). The mean duration of hospitalization was lower among patients with successful CPAP compared to the patient with failed CPAP and conventional ventilation groups (9 + 4.9 vs. 22 + 18 days vs. 24 + 21 days; p=0.11 and 0.31, respectively).

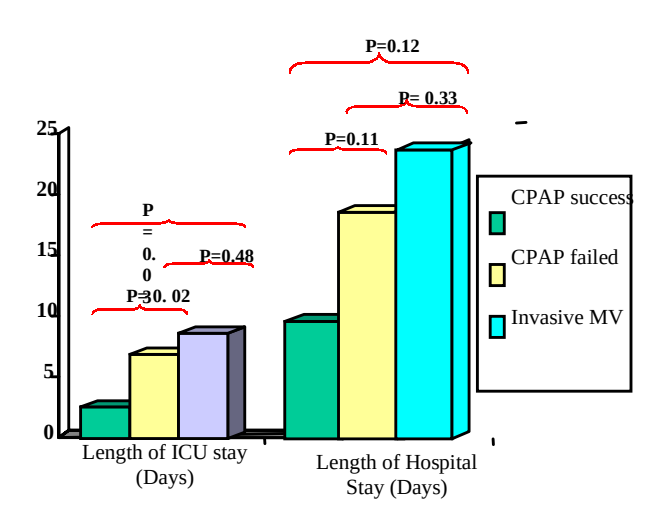

Figure 4. **The Length of ICU and Hospital Stay in successful and failed CPAP and Invasive MV groups.**

Table II. Comparison of factors that may predict outcome of non invasive positive airway pressure

VARIABLES	SUCCESSfUL CPAP n=7	FAILED CPAP n=8	P value
Age (yrs)	64.29	68.62	0.48
SAPS II	34 + 5	35 + 10	0.83
Tolerability			
Yes	7	3	0.026*
No	0	5	
SaO2(% sat)			
Mean change	4.58	-8.8	0.002**
Systolic BP (mm Hg)			
Mean change	-9.66	-10.16	0.952
Diastolic BP (mm Hg)			
Mean change	-8.75	10.75	0.863

* significant using Chi square
** significant in Chi square and Fisher exact test
* - not significant; P>0.05 compared with CPAP success

Table II showed the factors that may predict outcome of non invasive positive airway pressure. Mean age (64 + 10 years vs. 68 + 12; p=0.48), SAPS II (34 + 5 vs. 35 + 10; p=0.83), mean change (Baseline and 30 minutes after) in systolic blood pressure (-9.66 vs. -10.16 mm Hg ; p=0.952) and diastolic blood pressure (-8.75 vs. + 10.75 mm Hg: p=0.863) were comparable between the successful and failed CPAP. On the other hand, the mean change in oxygen saturation (SaO2) from baseline to 30 minutes after initiation of CPAP was noted to be significantly different between the successful and failed CPAP. The successful CPAP group attained an increase in SaO2 of 4.58% whereas failed CPAP had further reduction in oxygen saturation by 8.80% from baseline (p=0.952). Likewise, the number of patients who were able to tolerate the said procedure was also statistically significant between the two groups (p=0.026) with all patients in the successful CPAP and only 3 patients in the failed CPAP group able to tolerate the strategy.

The complications noted in each study group were shown in Table III. There were more patients in the invasive mechanical ventilator group who had complications compared to those in the successful CPAP group but this was not statistically significant (68% vs. 28%: p=0.17). The most common complication noted in any of the ventilatory strategy groups was pneumonia: 2 (28.5%) in the successful CPAP; 6 (75.0%) in failed CPAP; and in the invasive mechanical ventilation, 10 (62.5%).

Table III. Comparison of factors that may predict outcome of non invasive positive airway pressure

VARIABLES	Noninvasive Ventillation Group (n=15)		
	Success (n=7)	Failure (n=8)	P value
Patients with complications -# (%)	2(28.6%)	6(75.0%)*	
Patients w/ complications causing death at ICU	0	0	
COMPLICATIONS			
Cardiogenic shock	0	0	0
Sepsis	0	0	1(6.25%)
Renal Failure	0	0	1(6.25%)
Phlebitis	0	0	1(6.25%)
Arrythmia	0	0	1(6.25%)
Pneumonia	2(28.5%)	6(75.0%)	1(6.25%)
Sinusitis	0	0	0
Pulmonary embolism	0	0	1(6.25%)
Cerebrovascular Accidents	0	0	1(6.25%)
Massive blood loss	0	0	1(6.25%)

* - not significant compared with CPAP success

Discussion

In this study, noninvasive ventilation using Continuous Positive Airway Pressure (CPAP) had reduced the need forendotracheal intubation to 47% in patients with cardiogenic pulmonary edema. This result is similar to the study done by Meduri, et al.[1] where seven of the 32 patients receiving CPAP had cardiogenic pulmonary edema as the underlying cause. CPAP was successful in 4 (57%) of these patients. The success rate of CPAP was higher in a study done by Lin, et al.[4] (1995) where among the 50 patients with cardiogenic pulmonary edema receiving CPAP, 41 (82%) successfully avoided endotracheal intubation. Other studies reported varying success rate from 60% in 30 patients (Carlucci, et al. 2001) 5 to 100% in 19 patients (Bersten et al, 1991). [6]

Success in CPAP has been associated with several variables. Meduri, et al.[1] reported a significantly lower age group (47 vs. 67 years) and SAPS II (12 vs. 16) among patients with successful CPAP compared to those who failed. Likewise, Carlucci et al5 also noted SAPS II to be a significant variable for successful noninvasive mechanical ventilation by CPAP. In our study, however, the age and SAPS II of successful and failed CPAP were not statistically significant. The reason for this could be the homogeneity of the study population involving patients developing acute hypoxemic respiratory failure secondary to cardiogenic pulmonary edema. Age range was likewise limited ranging from 5th to 6th decade.

Other variables that were cited by Carlucci and coworkers[5] include encephalopathy score, pH at admission, clinical toleration of noninvasive ventilation (NIV) and the presence of air leaks. Both high severity score and presence of air leaks have been shown to predict failure in other similar studies. In this study, air leaks did not occur in any of the patients studied.

This study showed that both initial and sustained improvements in gas exchange did not differ significantly between successful non-invasive and invasive mechanical ventilation groups. This points to the fact that non-invasive mechanical ventilation will provide the same improvement in gas exchange similar to invasive mechanical ventilation. This result somehow differs from the result of Meduri and co-workers that reported a higher initial and sustained improvement in gas exchange among the noninvasive ventilation group.

A multiple regression analysis for prediction of NIV failure found that severity score, SAPS II and poor toleration of NIV were independent risk factors for secondary intubation. It added that severely ill patients with higher SAPS II are poor candidates for noninvasive ventilation.[5] In another study, Soo Hoo, et al.[7] reported that there was a more rapid decrease in $PaCO_2$ in patients where NPPV was successful whereas Meduri, et al.[8] reported that $PaCO_2$ increased when NPPV failed and decreased when NPPV was successful. Furthermore, Poponick, et al.[9] reported that an improvement in $PaCO_2$ and pH 30 min after initiation of NPPV predicted success. Among the variables considered as predictors, only oxygen saturation change (baseline and 30 minutes after) and tolerability were found to be significant between successful and failed CPAP groups. Among patients in whom CPAP failed, all of them were intubated within 30 minutes from initiation of CPAP. This supports the report of Hess, et al. (2001)[10] that the initial response to Non-invasive Positive Pressure Ventilation (NPPV) may predict success or failure. In this report, he cited the study of Brochard, et al.[11] showing that most patients who failed NPPV were intubated within the first 12 hours of therapy.

This study, furthermore, showed a significantly shorter duration of mechanical ventilation use (46 vs. 156 hr; p=0.02) and intensive care unit (ICU) stay (3 vs. 9.6 days; p=0.02) among patients receiving noninvasive ventilation compared to the invasive mechanical ventilation group. Meduri, et al.[1] cited several factors that may have been involved in shortening the duration of mechanical ventilation: avoidance of sedation, elimination of extra work of breathing imposed by endotracheal tube, the lower rate of ventilator-associated pneumonia and earlier removal from mechanical ventilation.

Likewise, these could also probably explain the lower frequency of complications among the successful CPAP group (2 vs. 11 patients) although this was not statistically significant (p=0.16). Meduri, et al.[1] also reported a lower rate of serious complications, particularly related to intubation (pneumonia and sinusitis) among the noninvasive group. He emphasized that endotracheal intubation is the single most important predisposing factor for ventilator-associated pneumonia. This group also had shorter duration of mechanical ventilation and ICU stay. In addition, he noted that there were more patients with respiratory acidosis in the invasive ventilation group and this may have affected the duration of mechanical ventilation and outcome of this group. However, this was not noted in our study. The same findings were reported by Carlucci et al,[5] wherein the duration of ventilation and the length of ICU stay were shorter in NIV group. Both studies reported a lower mortality rate among the noninvasive group.

The study did not look into the mortality outcome since there was only one mortality in the invasive mechanical ventilation group and none in the noninvasive group. Another concern raised by some authors of similar studies is the impact of CPAP on the cardiac condition of the patients. Pang et al2 reported that the potential for harm exists if CPAP leads to greater myocardial demand in the setting of an acute myocardial infarction. An increase in myocardial demand could occur if the work of breathing is greater in patients treated with CPAP than those intubated and sedated. He further added that this increase in demand could cause more severe and extensive ischemia resulting to malignant dysrrhythmias, cardiac arrest, and / or death. In survivors, more extensive myocardial damage may result in worse left ventricular function and long term disability. Only one of the three trials that this group reviewed addressed the potential for harm. In our study,

myocardial infarction or other cardiac complications mentioned above were not noted. While there is currently no evidence that CPAP causes harm in patients with cardiogenic pulmonary edema, the evidence available is insufficient to exclude this concern.

Conclusions

On the basis of the preliminary results, noninvasive mechanical ventilation with the use of Continuous PositiveAirway Pressure (CPAP) can achieve improvement in oxygenation without the need for endotracheal intubation in 47% of patients with hypoxemic respiratory failure secondary to cardiogenic pulmonary edema. Furthermore, the duration of mechanical ventilation and length of ICU stay was significantly shortened thereby reducing hospital costs. Improvement in oxygen saturation

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Serum Uric Acid Levels among Patients woth Chronic Obstructive Pulmonary Diseases

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BACKGROUND. Elevated serum uric acid levels were observed in clinical conditions associated with hypoxia such as heart failure, primary pulmonary hypertension and congenital heart disease but no such observation was reported among COPD patients. Therefore, we aimed to determine whether serum uric acid levels correlate with hypoxemia and COPD severity in stable and exacerbating COPD patients.

METHODS. Included are 110 diagnosed COPD patients based on spirometry, grouped into stable COPD, and in acute exacerbation. Simultaneous blood extractions for serum uric acid and ABG's were determined with the patient in a steady state and in upright position. Independent t-test was employed to determine the association between serum uric acid levels with blood gas variables, age and sex. The correlation between serum uric acid levels with COPD severity was explored using ANOVA.

RESULTS. There was a highly significant correlation between hypoxemia and serum uric acid levels in both stable and exacerbating COPD patients (p <0.000 and 0.004 respectively). There was no significant correlation of age and sex with that of uric acid levels (p value > 0.05). The relation of COPD severity and serum uric acid levels showed that the higher the serum uric acid level, the more severe the COPD is among subjects in the stable COPD group (p <0.000). However, the same does not apply among the subjects in acute exacerbation (p 0.070).

CONCLUSION. There is a strong correlation between hypoxemia and the severity of COPD with serum uric acid level among stable COPD patients. Thus, elevated serum uric acid levels may serve as a noninvasive indicator for the severity of COPD and hypoxemia in non-exacerbating COPD patients.

Phil Heart Center J 2002;9:48-55

Keywords: Obstructive pulmonary disease, chronic; serum uric acid

Chronic Obstructive Pulmonary Disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.[1]

COPD is a major cause of chronic morbidity and mortality throughout the world. COPD is currently the fourth leading cause of death in the world and further increases in the prevalence and mortality of the disease can be predicted in the coming decades.

The late stages of COPD are characterized by a marked decline in pulmonary function and a decrease in reversibility of obstruction following administration of inhaled bronchodilator. As lung function declines, the alveolar-arterial gradient for oxygen increases, primarily because of an increase in abnormal ventilation-perfusion relationships. Hypoxemia, pulmonary hypertension and cor pulmonale develop.[2]

Serum uric acid (UA), the final product of purine degradation has been shown to be increased in hypoxic states such as chronic heart failure, cyanotic congenital heart disease and obstructive pulmonary disease.[3] Because tissue ischemia and hypoxia deplete adenosine triphosphate (ATP) and promote degradation of adenosine nucleotides to inosine, hypoxanthine, xanthine and UA, increased serum UA levels may reflect impaired oxidative metabolism in such diseases. Interestingly, serum UA levels have recently been shown to have strong independent association with long-term mortality of patients with chronic heart failure[4] but not with COPD patients hence this study.

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Review of Related Literature

Hyperuricemia may be defined as a plasma (or serum) urate concentration greater than 420 umol/L (7 mg/dl). This definition is based on physicochemical, epidemiologic and disease-related criteria. Physicochemically, hyperuricemia is the concentration of urate in the blood that exceeds the solubility limits of monosodium urate in plasma, 415 umol/L (6.8 mg/dl). In epidemiologic studies, hyperuricemia is defined as the mean plus 2 standard deviations of values determined from a randomly selected healthy population.

When measured in unselected individuals, 95% have serum urate concentrations below 420 umol/L (7 mg/dl). Finally, hyperuricemia can be defined in relation to the risk of disease. The risk of developing gout or urolithiasis increases with urate levels greater than 420 umol/L (7 mg/dl) and escalates in proportion to the degree of elevation.[5]

It is useful to classify hyperuricemia in relation to the underlying physiology, whether the hyperuricemia results from increased production, decreased excretion or a combination of the two.

Accelerated purine nucleotide degradation cause hyperuricemia. Nucleic acids released from cells are hydrolyzed by the sequential activities of nucleases and phosphodiesterases, forming nucleoside monophosphates, and then are degraded to nucleosides, bases and urate. Hyperuricemia can result from excessive degradation of skeletal muscle ATP after strenuous physical exercise or status epilepticus and in glycogen storage diseases types 111, V and V11. The hyperuricemia of myocardial infarction, smoke inhalation and acute respiratory failure also may be related to accelerated breakdown of ATP. Most of literature reviewed revealed an association of increased serum uric acid levels with chronic heart failure, primary pulmonary hypertension and congenital heart disease. Related literature reviewed was on the association of urinary uric acid: creatinine ratio in sleep associated hypoxemia.

Hasday and Grum[6] measured overnight changes in urinary uric acid: creatinine ratio in 17 patients with documented sleep associated hypoxemia, 13 control patients who remained normoxemic during polysomnography and 14 normal volunteers. The urinary uric acid: creatinine ratio increased overnight in patients with sleep associated hypoxemia, whereas it decreased in the control subjects with negative sleep studies and in the normal volunteers.

The above study was validated by Braghiroli[7] et al in 1993. They selected 10 normal volunteers, 29 COPD patients and 49 subjects with obstructive sleep apnea (OSA). The patients underwent standard polysomnography, which was repeated in 14 subjects with nasal continuous positive airway pressure (CPAP), and were subdivided into 2 groups: Group D included desaturating subjects who spent at least 1 hour at oxygen saturation <90% and 15 minutes below 85%, and Group ND were non-desaturating subjects. The overnight change in the uric acid: creatinine ratio was negative in normal subjects and ND groups. In both COPD and OSA Group D, the ratio was usually positive despite 4 of 15 false negative results in COPD and 8 of 20 in OSA. CPAP effective treatment induced a marked reduction in change in urinary uric acid: creatinine ratio, leading to a negative value. They concluded that the change in uric acid: creatinine ratio seems to be a promising index of significant nocturnal tissue hypoxia with good specificity but poor sensitivity (about 30% false negative), which might be useful for the long-term follow-up of outpatients on nasal CPAP with a positive ratio at baseline.

Changes in oxygen tension such as those associated with hypoxic ischemia or hyperoxia may potentially modulate purine nucleotide turnover and production of associated catabolites. Elsayed[8] et al used an isolated perfused rat lung preparation to evaluate the effect of oxygen tension on pulmonary uric acid production. Three oxygen concentrations (21% normoxia; 95% hyperoxia; 0% hypoxia) were utilized for both pulmonary ventilation and equilibration of recirculating perfusate. All gas mixtures contained 5% carbon dioxide and were balanced with nitrogen. After a 10-minute equilibration period, uric acid levels were measured at 0 and 60 minutes in lung perfusate and at 60 minutes in lung tissue. After 60 minutes of ventilation/perfusion, they observed significant uric acid accumulation in both lung tissue (25-60%) and perfusate (8-10 fold) for all 3 oxygen regimen. However, hypoxia produced substantially greater net uric acid concentration than either normoxia or hyperoxia.

Elevated serum uric acid concentration has been observed in clinical conditions associated with hypoxia such as chronic heart failure[9], primary pulmonary hypertension[10] and congenital heart disease[11].

Research Objectives

General: To determine the association of serum uric acid levels to the severity of COPD and blood gas variables among COPD patients.

Specific:

1. To correlate the relationship of serum uric levels with COPD severity and blood gas variables among stable COPD patients.
2. To determine the relationship of serum uric acid levels with COPD severity and blood gas variables among COPD patients in exacerbation.

Research Hypothesis

High serum uric acid level is related to the severity of COPD, low PaO_2, and low SaO2.

Definition of Terms

1. COPD - a disease state characterized by airflow limitation that is not fully reversible.
2. Serum uric acid - the final product of purine degradation
3. COPD severity - classified as mild, moderate or severe. Mild COPD is characterized by mild airflow limitation (FEV1/FVC <70% but FEV_1 >80% predicted) and usually but not always, by chronic cough and sputum production. Moderate COPD is characterized by worsening airflow limitation (30% <FEV_1 <80% predicted) and usually the progression of symptoms with shortness of breath typically developing on exertion. Severe COPD is characterized by severe airflow limitation (FEV_1 <30% predicted) or the presence of respiratory failure or clinical signs of right heart failure.

4. Normal uric acid group - a group of individuals, whether male or female, who belong to the normal serum uric acid level (0.21-0.51 mmol/l).
5. High uric acid group - a group of individuals, whether male or female, who belong to the upper serum uric acid level (>0.51 mmol/l).
6. Arterial blood gas - blood extracted directly from an artery for determination of pH, $PaCO_2$, PaO_2, HCO_3 and SaO_2.
7. Hypoxemia - calculated by the PaO_2 and FiO_2 ratio and the result should be less than 400 to say that the person is hypoxemic.
8. Stable COPD - characterized by no episodes of increasing dyspnea, no increase in sputum production or no change in the color of the sputum
9. COPD in exacerbation - characterized by increasing episodes of shortness of breath, increase in the amount of sputum production or with change in the color of the sputum.

Methodology

A. Study Design

This is a prospective, cross-sectional study of the relationship of serum uric acid among COPD patients.

B. Study Sample

All patients diagnosed to have COPD: stable, in acute exacerbation or in
respiratory failure, in the OPD or in the wards will be included in the study. COPD is diagnosed if patients have symptoms of cough, sputum production or dyspnea and/or a history of exposure to risk factors with a postbronchodilator FEV1 <80% of the predicted value in combination with an FEV1/FVC <70%.

Patients with any of the following are excluded in the study: presence of renal failure (serum creatinine >1.5 mg/dl), those who are taking drugs which could decrease serum uric acid excretion such as salicylates, diuretics, alcohol, levodopa, ethambutol, PZA, nicotinic acid and cyclosporine, and those with coronary risk factors, which might influence serum uric acid levels such as hypertension, hyperlipidemia and diabetes mellitus.

An informed consent will be obtained from all of the subjects.

C. Study Setting and Period

This is a 12-month study period to be conducted at the Philippine Heart Center. All patients diagnosed to have COPD from January 1, 2002 to December 31, 2002 will be included in the study. They will undergo serum uric acid level determination as well as ABG determination.

D. Sample Size and Basis for the Calculation

With the uric acid abnormality rate of 95% and the total width of confidence interval (@ = 0.05), the following is the calculated sample size:

%	n
5	292
10	73
15	32
20	18

E. Identification of Study Variables

A. Independent variable - serum uric acid level
B. Dependent variable - COPD
C. Confounding variables - COPD severity, ABG (PaO_2 and SaO_2)

F. Detailed Description of Data Collection

After obtaining results of spirometry, these patients are classified according to severity whether they are mild, moderate (stage llA or llB) or severe COPD patient. Venous blood will then be drawn after an overnight fast for measurement of serum UA levels. Serum uric acid levels were determined by a 2-step sequential enzymatic reaction measured by spectrophotometry (uricase-peroxidase method). Because of sex difference in serum uric acid levels, different median values for men and women were used to separate the high uric acid group from the low uric acid group.

Simultaneous with venous blood extraction for serum uric acid, an arterial blood gas (ABG) will be determined with the patient in a steady state and in upright position. ABG analysis is determined thru an ABL 600 machine.

Statistical Analysis

Independent t-test was employed to determine the association between serum uric acid levels with blood gas variables, age and sex. The correlation between serum uric acid levels with COPD severity was explored using ANOVA.

Results

112 COPD patients were recruited for the study, however, 2 patients declined to sign the consent thus were excluded. The patients were then categorized to stable group or in exacerbation group. These groups of patients were further subdivided according to their serum uric acid levels whether normal or high.

Among the stable COPD patients, the mean age with

normal serum uric acid was 67.28 years while the mean age with high uric acid was 68.52 years. Concerning COPD patients in exacerbation, the mean age with normal serum uric acid was 66.9 years while those with high uric acid were 69.81 years. (Table 1)

Table 1. Characteristics of COPD Patients (Stable or in Exacerbation) in Relation to Serum Uric Acid Levels as to Age and Sex

Variable	STABLE COPD PATIENTS					COPD IN EXACERBATION				
Age (yrs)	Normal Uric Acid Mean	SD	High Uric Acid Mean	SD	P value	Normal Uric Acid Mean	SD	High Uric Acid Mean	SD	P value
	67.28	9.34	68.52	8.06	0.588	66.9	10.02	69.81	8.14	0.348
Sex	N	%	N	%		N	%	N	%	
Male	37	95	24	96		10	100	35	97	
Female	2	5	1	4		0	0	1	3	
Both Sexes	39	100	25	100	1	10	100	36	100	0.348

Among males, 37 patients (95%) had normal uric acid while 24 patients (96%) had high uric acid whereas among females, 2 patients (5%) belong to the normal uric acid group while 1 patient (4%) belonged to high uric acid group among stable COPD patients.

With regards to COPD patients in exacerbation, 1 male patient (100%) had normal uric acid while 35 patients (97%) had high uric acid; however, only 1 female patient (3%) belonged to the high uric acid group as shown in Table 1.

Using the t-test as a statistical tool, there was no significant correlation between the 2 COPD groups (stable and in exacerbation) with either normal or high uric acid levels about age (p value of 0.588 and 0.348 respectively). As to sex, there was also no significant correlation between the 2 COPD groups with either normal or high uric acid levels (p value of 1.000 and 0.348 respectively) using the chi-square test.

As to COPD severity distribution, 64 were stable COPD patients, majority of whom belonged to the moderate stage 11-A COPD with 34 patients (53.13%). Forty-six COPD patients were in exacerbation, majority of whom belonged to moderate stage 11-B COPD with 19 patients (41.30%) as seen in Table 2.

Table 2. Distribution of Patients of the 2 COPD Groups as to Severity

COPD Severity	Stable COPD Patients n = 64	%	COPD in Exacerbation n = 46	%
Mild	5	7.81	2	4.35
Moderate 11-A	34	53.13	14	30.43
Moderate 11-B	22	34.38	19	41.3
Severe	3	4.69	11	23.91

Partial pressure of oxygen (PaO_2) among stable COPD patients showed decreasing results from a high of 83.40 mmHg to a low of 58.33 mmHg among the different categories of COPD (mild, moderate 11-A, moderate 11-B and severe COPD). In the analysis of variance, there was significant correlation between PaO_2 and COPD severity among stable COPD patients (p value 0.000). (Table 3)

Table 3. Comparison of the 2 COPD Groups as to PaO_2 and COPD Severity

COPD Severity	STABLE COPD PATIENTS PaO2 Mean	SD	COPD IN EXACERBATION PaO2 Mean	SD
Mild	83.4	11.63	78	5.66
Moderate 11-A	81.68	11.36	67.5	9.27
Moderate 11-B	65.59	7.67	65	11.84
Severe	58.33	1.53	61.36	8.8
P value	0.000***		0.131 NS	
COPD Severity	**SaO2 Mean**	**SD**	**SaO2 Mean**	**SD**
Mild	96.16	1.12	95.15	1.06
Moderate 11-A	95.15	2.1	91.73	5.68
Moderate 11-B	89.99	7.02	91.72	2.5
Severe	91.3	1.13	92.16	3.04
P value	0.000***			0.155 NS

PaO_2 among COPD patients in exacerbation also showed decreasing results from a high of 78.00 mmHg to a low of 61.36 mmHg among the different categories of COPD. However using ANOVA as a statistical tool, there was no significant correlation between PaO_2 and COPD severity among COPD patients in exacerbation (p value 0.131).

Oxygen saturation (SaO_2) among stable COPD patients also showed decreasing results from a high of 96.16% to a low of 91.30% among the different COPD severities. There was a highly significant correlation with regards to SaO2 and COPD severity among stable COPD patients (p value 0.000).

SaO_2 among COPD patients in exacerbation likewise showed decreasing results among the different COPD severities. However, when tested using ANOVA, there was no significant correlation between SaO_2 and COPD severity among COPD patients in exacerbation (p value 0.155) as shown in Table 3.

Blood gas variables, namely PaO_2 and SaO_2, were analyzed in relation to the serum uric acid level (Table 4). Using the independent t-test, there was significant correlation between hypoxemia and elevated serum uric acid level (p value 0.000) among stable COPD patients. The more hypoxemic the patient is, the higher will be his uric acid. Inversely, the more normoxemic the patient is, the lower is his uric acid level.

Table 4. Correlation of Serum Uric Acid Levels with Oxygenation in COPD Patients who are Stable and Exacerbating

Variables	Stable COPD					COPD in Exacerbation				
	Normal Uric Acid		High Uric Acid			Normal Uric Acid		High Uric Acid		
Oxygenation	Mean	SD	Mean	SD	P value	Mean	SD	Mean	SD	P value
PaO2	83.85	8.79	61.68	3.35	0.000***	73.7	11.28	63.17	9.25	0.004 **
SaO2	95.82	1.24	89.3	6.1	0.000***	95.43	1.37	91.02	3.7	0.001 **

Figures 1 and 2 represent the relationship between oxygenation and uric acid levels whereby it is noted that in stable COPD patients, the higher the uric acid level, the lower is the PaO2 and SaO2. This observation does not apply among COPD patients in exacerbation where there is no such trend noted.

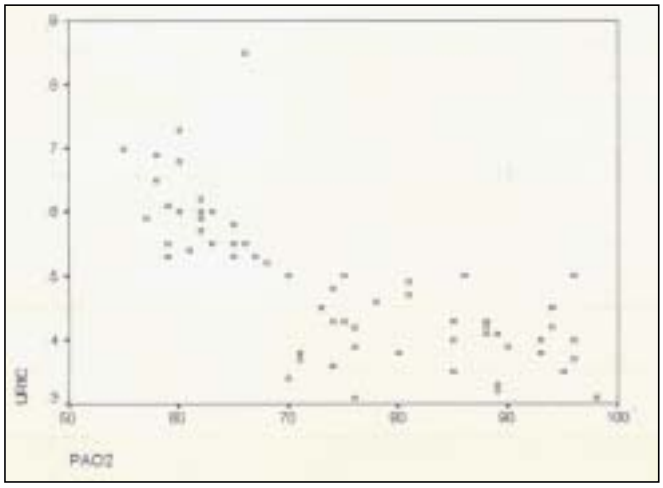

Figure 1. Correlation between individual serum uric acid values and PaO2 depicted for all patients with stable COPD

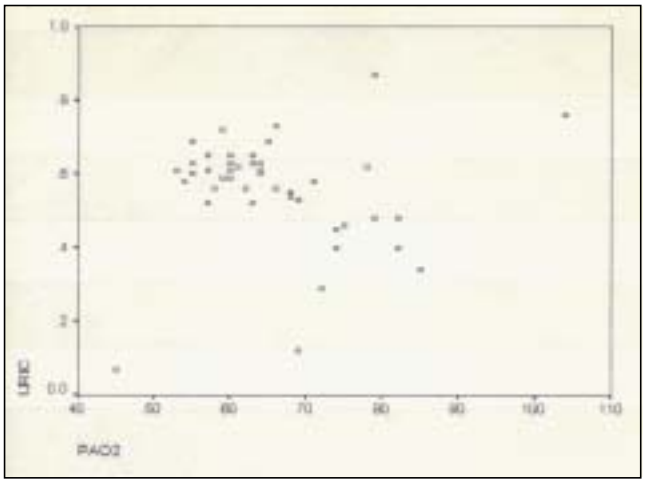

Figure 2. Correlation between individual serum uric acid values and PaO2 depicted for all patients with COPD in exacerbation

This observation was also noted among COPD patients in exacerbation where there was significant correlation between hypoxemia and elevated serum uric acid level (p value of 0.004).

The correlation of the severity of COPD among the 2 COPD groups with that of serum uric acid is shown in Table 5.

Table 5. Correlation of Serum Uric Acid Levels with COPD Severity in Patients who are Stable and Exacerbating

Variable Stable COPD Quantitative Uric Acid Level (mmol/L)			COPD in Exacerbation Quantitative Uric Acid Level (mmol/L)	
COPD Severity	Mean	SD	Mean	SD
Mild	0.38	0.044	0.425	0.035
IIA	0.433	0.081	0.504	0.099
IIB	0.566	0.103	0.619	0.068
Severe	0.657	0.07	0.565	0.245
P value	0.000***		0.070 NS	

Serum uric acid among stable COPD patients showed increasing results ranging from a low of 0.380 mmol/L to a high of 0.657 mmol/L among the different COPD severities. Using ANOVA as a statistical tool, the higher the serum uric level, the more severe is the COPD with a p value of 0.000 which is highly significant among stable COPD patients.

Among COPD patients in exacerbation, serum uric acid levels also showed increasing results from a low of 0.425 mmol/L to a high of 0.565 mmol/L among the different COPD severities. When tested using ANOVA, there was no significant correlation between serum uric acid and COPD severity among COPD patients in exacerbation (p value 0.070).

A Bonferroni test was used to compare the different stages of COPD severity with serum uric acid levels. There was significant differences between: mild and moderate stage 11-B (p value 0.000), mild and severe (p value 0.000), moderate 11-A and 11-B (p value 0.000), moderate 11-A and severe (p value 0.000) among stable COPD patients. However, there were no significant differences between: mild and moderate stage 11-A (p value 1.000), moderate 11-B and severe (p value 0.586) among stable COPD patients.

Among COPD patients in exacerbation, there was no significant differences between the different stages of COPD severity with serum uric acid levels: mild and moderate 11-A (p value 1.000), mild and moderate stage 11-B (p value 0.401), mild and severe (p value 1.000), moderate stage 11-A and 11-B (p value 0.141), moderate stage 11-A and severe (p value 1.000), and moderate 11-B and severe (p value 1.000).

Discussion

COPD refers to a constellation of clinical and pathologic findings, that individually or in combination, produce chronic airflow obstruction, disability and sometimes death. It is characterized by chronic inflammation throughout the airways, parenchyma and pulmonary vasculature. Pathological changes in the lungs lead to corresponding physiological changes characteristic of the disease.

In advanced COPD, peripheral airways obstruction, and pulmonary vascular abnormalities reduce the lung's capacity for gas exchange thereby producing hypoxemia.

Hypoxemia is one of the numerous factors that might influence serum uric acid levels and have to be considered when discussing these observations. The other common conditions known to be associated with elevated serum uric acid levels such as renal failure, drugs which could decrease serum uric acid excretion (salicylates, ethambutol, pyrazinamide, nicotinic acid, etc.) and coronary risk factors which might influence serum uric acid levels were not present in our patient. Thus the observation in this study suggests that elevated serum uric acid is a result of COPD per se.

An intensive literature search was done utilizing the internet using PubMed and Cochrane as well as case series, reviews, and this search did not yield any published literature on the relationship of serum uric acid level with hypoxemia and COPD severity. The only published articles that were noted were those of primary pulmonary hypertension, Eisenmenger syndrome and chronic heart failure. A study conducted by Hardy[6] and Braghiroli[7] correlating uric acid and severity of hypoxia in patients with COPD and obstructive sleep apnea made use of urinary uric acid:creatinine ratio as an index of significant nocturnal tissue hypoxia.

In the present study, we demonstrated that serum uric acid levels had a significant correlation with hypoxemia as well as with the severity of COPD among stable COPD patients. Ross and colleagues have shown that hyperuricemia in cyanotic congenital heart disease is attributable to enhanced urate reabsorption secondary to abnormal intrarenal hemodynamics. An increase in lactate in hypoxic states has also been shown to inhibit tubular uric acid secretion.[12] The reduced excretion of uric acid because of impaired intrarenal dynamics contribute to hyperuricemia, however, those patients with renal failure were already excluded at the start of the study. This observation may be applied in COPD patients where hypoxemia is a part.

Alternatively, overproduction of uric acid could be responsible for increased serum uric acid in these patients. Earlier studies have shown that tissue ischemia deplete ATP and activate the purine nucleotide degradation pathway to uric acid, resulting in urate overproduction in the heart, lungs, liver and skeletal muscle.[8,13,14,15] In fact, production of uric acid has been shown to increase in proportion to the severity of hypoxia

in patients with COPD and obstructive sleep apnea as reported by Hardy and Braghiroli respectively. Hypoxia leads to accumulation of the precursors of uric acid (hypoxanthine and xanthine)[16] and activation of xanthine oxidase/dehydrogenase. Although the liver is the principal source of uric acid, the endothelium also contributes to its production. Accordingly, elevated serum uric acid would be expected to reflect the metabolic effects of hypoxia on the microvasculature. It is possible that tissue hypoxia will induce overproduction of uric acid in a variety of organs in patients with COPD.

Earlier studies have shown that an increase in serum uric acid levels is related to hypertension, hyperlipidemia and diabetes mellitus.[17] In this study, those patients with hypertension, hyperlipidemia and diabetes mellitus were excluded outright at the start of this study so as not to allow these conditions to affect the actual serum uric acid levels of the patients included. However, multivariate analysis demonstrated that serum uric acid levels did not independently correlate with hypertension, hyperlipidemia and diabetes mellitus among patients with primary pulmonary hypertension and Eisenmenger syndrome.

Drugs such as salicylates, levodopa, ethambutol, pyrazinamide, nicotinic acid and cyclosporine can influence serum uric acid levels. Diuretic therapy is also known to affect serum uric acid metabolism.[18] Previous reports showed that there was no independent correlation between serum uric acid and diuretic treatment in patients with primary pulmonary hypertension[10] and Eisenmenger syndrome.[9]

This study demonstrated that elevated serum uric acid levels correlated with COPD severity among stable COPD patients, however, no significant correlation were shown between serum uric acid level and COPD severity among COPD patients in exacerbation. Therefore, the more severe the COPD is the more elevated would be the serum uric acid levels. This is particularly true since hypoxia is usually present at the end of the spectrum of COPD severity. No significant correlation was noted between serum uric acid levels and COPD severity among COPD patients in exacerbation since this group of patient's exhibit only transient hypoxemia. During the episodes of hypoxemia, there was a greater fall in PaO2. This can be caused by a change in variation of ventilation-perfusion ratios between different alveoli. The classic theory of gas exchange depends upon steady-state conditions and such conditions do not apply during transient episodes of hypoxemia as can be found among COPD patients in exacerbation. A follow-up on these patients should be done to correlate serum uric acid levels with morbidity and mortality as shown in previous study by Nagaya et al correlating serum uric acid levels with the severity and mortality of primary pulmonary hypertension. An echocardiogram is useful in determining the degree of pulmonary hypertension and hypoxemia which may be related to mortality. Moreover, future studies should be done on the effect of long term oxygen therapy on serum uric acid levels among COPD patients.

Thus serum uric acid is an important tool in correlating the degree of hypoxemia as well as the severity of COPD among non-exacerbating patients. It can be measured routinely, is simple to perform and relatively inexpensive. It may also serve as a noninvasive indicator for the severity of COPD.

Conclusion

There is a strong correlation between serum uric acid and hypoxemia as well as to the severity of COPD among stable COPD patients. This association suggests that in COPD, serum uric acid concentrations reflect an impairment of oxidative metabolism. Elevated serum uric acid levels may serve as a noninvasive indicator for the severity of COPD among non-exacerbating COPD patients.

Recommendations

The following recommendations are made:

1. Further studies should be undertaken on the effect of long-term oxygen therapy on serum uric acid levels among stable COPD patients.
2. Further studies should be done on the correlation of serum uric acid on the outcome of COPD patients (morbidity/ mortality).
3. An echocardiogram should be done to determine the degree of pulmonary hypertension and hypoxemia.

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Case Report

A Case of Total Anomalous Systemic Venous Connection to the Left Atrium

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This is a case of a 15-year old, female, from Novaliches, Quezon City, who came in because of cyanosis upon crying at two months old (Figure 1). Consulted with a private physician who referred the patient to Philippine Heart Center, however, the parents did not comply not until 4 months of age when the nailbeds were cyanotic. Patient was then worked-up and cardiac catheterization was done at seven months old and was found out to have anomalous systemic venous return to the left atrium (Figure 2). She was scheduled for operation of the anomalous systemic venous return but a day before the OR schedule, the patient acquired varicella infection and was sent home. She was then lost to follow-up. From then on, there was no note of frequent respiratory tract infection, nor any hospitalization (Figure 3). There were no episodes of "blue spells" but had exercise intolerance as the patient grew older. Until at 11 years old, she complained of easy fatigability with hypercyanosis, muscle cramps and shortness of breath when doing strenuous activities which were becoming more frequent thus sought consult at Philippine Heart Center at 14 years old and subsequently admitted (Figure 4).

Figure 1. Pt at 4 mos.

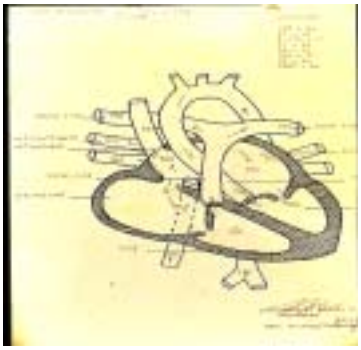

Figure 2. Cath Result at 7 mos.

Figure 3

Figure 4

On physical examination, patient was conscious, coherent, ambulatory, and not in respiratory distress with a weight of 39kg (p25), Height: 152 cm (p75). She had suffused palpebral conjunctivae, with cyanotic lips, clear breath sounds. Cardiovascular findings showed a dynamic precordium, apex beat at 5th intercostals space left midclavicular line, (-) thrill, (-) heave, S1 normal, S2 single with normal P2, (-) murmur. Nailbeds were clubbed and cyanotic.

Repeat work up was done on admission. The chest x-ray was normal (Figure 5). The ECG was otherwise normal except for the leftward P axis (-) 75 (Figure 6). Echocardiogram showed a suspicious drainage of systemic veins to the left atrium (Figures 7,8). The initial cardiac cath which was done on the 3rd hospital day, showed a persistent left superior vena cava (SVC) and a suspicious membrane at the right atrium (RA) was noted probably a cortriatriatum dexter was entertained versus an anomalous drainage of systemic veins to the left atrium (Figure 9). Transesophageal echocardiography was done to investigate the RA and it showed that the RA was small, their was no membrane thus cor tritriatum dexter was ruled out (Figure 10). Contrast echo were then done to delineate well the drainage of the systemic veins. Using an agitated saline solution 15-20 ml was injected into the vein of the right hand showing the microbubbles which were first seen at the left atrium then shunted into the right atrium thru the atrial septal defect (ASD) (Figure 11). Another injection done at the vein of the left hand and the solution drains into the left atrium but the entrance of the drainage is different from that of the right right hand, hence a possible persistent left SVC was considered. Lastly, injection of saline solution at the right foot which also showed the drainage of microbubbles into the

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left atrium first then to the RA. These strengthened the impression of Anomalous drainage of systemic veins to the left atrium (LA).

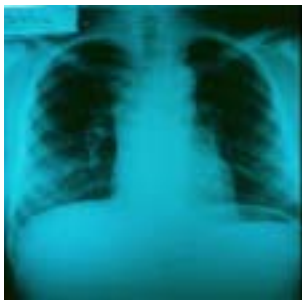


Figure 5. CXR

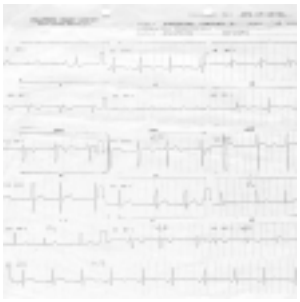


Figure 6. ECG

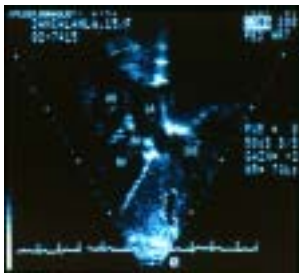


Figure 7. 2Decho- Subcostal View

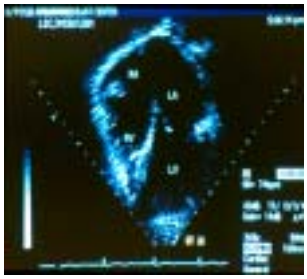


Figure 8. 2D echo- Apical View

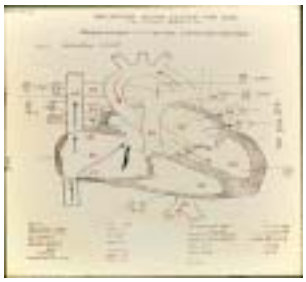


Figure 9. Initial Cath Result

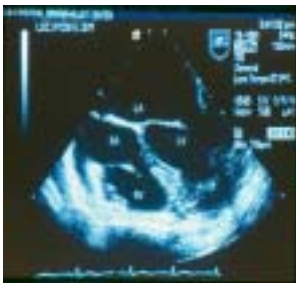


Figure 10. TEE

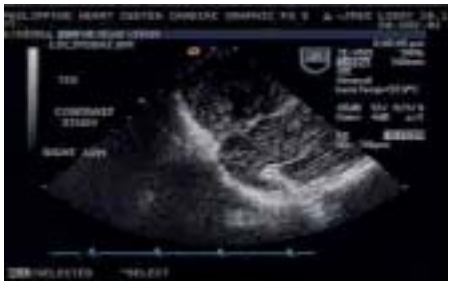


Figure 11. TEE with contrast study

On the 9th hospital day, repeat cardiac catheterization and digital subtraction angiography (DSA) were done to further define the precise location or drainage of the systemic veins. This was done with simultaneous transeophageal echocardiography. During cardiac catheterization, the intravenous catheter was manipulated from the right femoral vein into the inferior vena cava which then enters into the left atrium instead of right atrium. This was confirmed by simultaneous transesophageal echo in which the tip of the intravenous catheter was found at the LA instead of RA (Figure 12). The intravenous catheter was further manipulated and entered into a persistent left SVC. Injection of dye into the brachial vein of the left arm was done which opacified a persistent left SVC draining into the coronary sinus then into the LA which further opacifies the ascending aorta (Figures 13,14). A guide wire was manipulated at the right brachial vein thru the IV site and with the simultaneous transesophageal echocardiography, it showed that the tip of the catheter was found out in the LA instead of the RA. This catheter was manipulated further below into the hepatic vein which had a separate entry as that of the inferior vena cava. Injection of dye was also done at the right arm showed a right SVC which opacifies the LA and further opacifies the aorta (Figures 15,16). No innominate vein noted. The IVC catheter was manipulated and entered into a sinus venosus ASD. Injection of dye at this area opacifies the small RA then into the small RV then into the main pulmonary artery and its branches which were of good sizes (Figure 17). Therefore, repeat cardiac cath with DSA and simultaneous Transesophageal Echocardiography confirm the diagnosis of Total Anomalous Systemic Venous Return (IVC, Right and Left SVC, hepatic vein) into the left atrium as shown in schematic diagram on Figure 18.

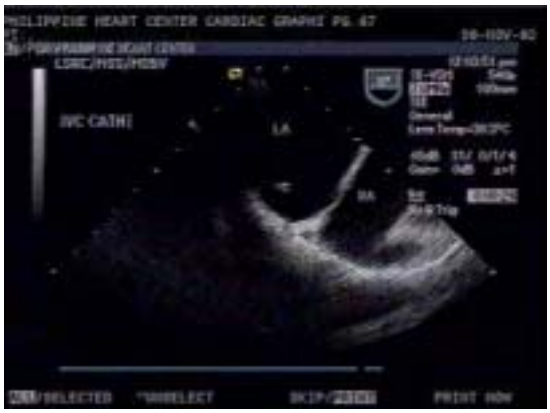


Figure 12. Simultaneous Transesophageal ECHO and Cath

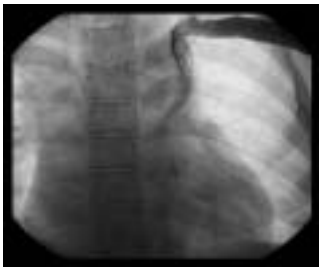


Fig. 13. Angio. Left SVC drains aorta

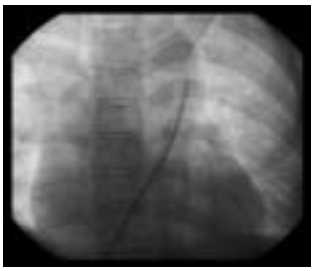


Fig. 14. L SVC to LA then to LA opacifies

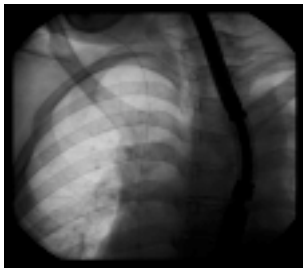


Fig.15 Wire guide at the

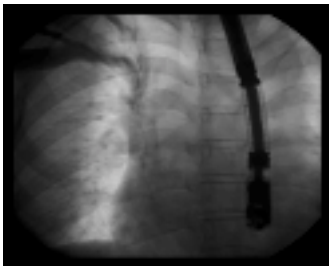


Fig.16 R SVC drains to RSVC LA

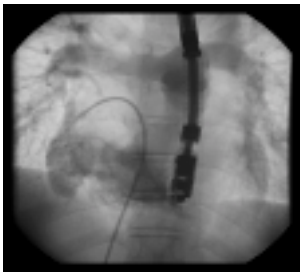


Fig.17. Dye injected at Venosus

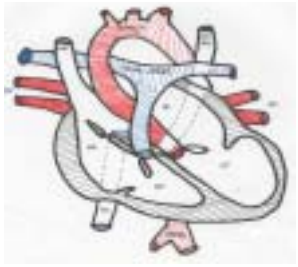


Fig. 18 Schematic Diagram- ASD cath result

She underwent Bilateral Bidirectional Glenn Shunt (Fig.19) with the interatrial septum enlarged and converted into a common atrium, and then atrial baffle using a pericardial patch was used to divert IVC and hepatic veins to the right atrium (Fig.21).

Post-operatively, there was marked improvement of O^2 saturation from pre-op of 80% to 98% post-op. She was extubated after 24 hours and transferred to PICU. On the 5th post-op day repeat CXR showed haziness at the right lower lung field probably due to pleural effusion. Post-op 2D echo showed minimal to moderate pericardial effusion. An ESR was taken showed an elevated ESR. Post pericardiotomy syndrome was entertained; hence, the patient was started on aspirin. On the 8th post-op day, there was progression of pleural effusion such that CTT was inserted. Serosanguinous fluid was drained. Augmentin was started. On the 16th post-op day, there was complete resolution of the pleural and pericardial effusion. She was then discharged on the 20th post-op day improved.

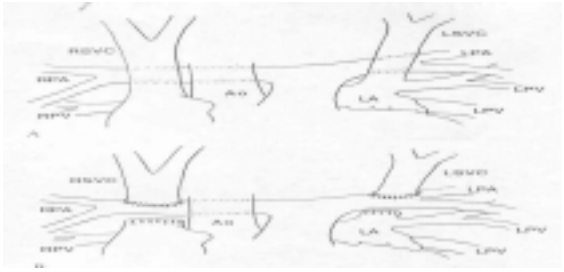


Fig 19. Bilateral Bidirectional Glenn Shunt (Modified from McElhinney D. Bidirectional Cavopulmonary Shunt in Patients with Anomalies of Systemic and Pulmonary Venous Drainage. Ann Thorac Surg 1997;63:1676-84) [1]

On the 15th hospital day, the patient underwent surgery with the following intra-op findings (Figure 20).

- bilateral SVC of good size, no innominate vein in between
- Right SVC drains to the left atrium with sinus venosus ASD adjacent to it
- left SVC drains into the coronary sinus and then into the LA
- IVC drains to the LA with separate hepatic vein which also drains into the LA
- small patent foramen ovale
- small RA and right ventricle
- good size main pulmonary artery, as well as right and left pulmonary artery
- all 4 pulmonary veins drain to LA

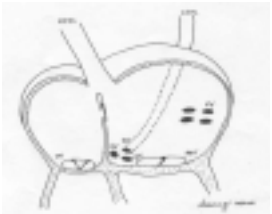


Fig. 20. *Schematic Diagram (Intra-op Findings)*

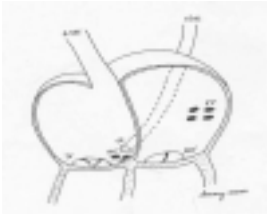


Fig. 21. *Schematic Diagram (Post-op Findings)*

Presently patient is doing well who had regular follow-up at the PHC-OPD department. She is now a fourth year high school student with good scholastic performance (Fig. 22).

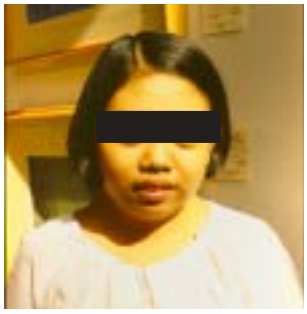


Fig. 22. Patient post-operatively

Discussion

Presenting a case of a 15 y/o female who had cyanosis and clubbing. There was no history of hypoxic spells or squatting. No signs of congestive heart failure. Only exercise intolerance noted during strenuous activities. Physical examination revealed a well-developed child, weight 39kg (25 percentile) and height 152 cm (75 percentile). Cardiovascular findings revealed a dynamic precordium with normal S1 with single S2 and no murmur appreciated. Peripheral O2 saturation was 80%. Hemoglobin was 17.9g/L and hematocrit was 56%. Chest roentgenogram showed normal findings and electrocardiogram was otherwise normal except for the leftward P axis (-75).

Differential Diagnosis

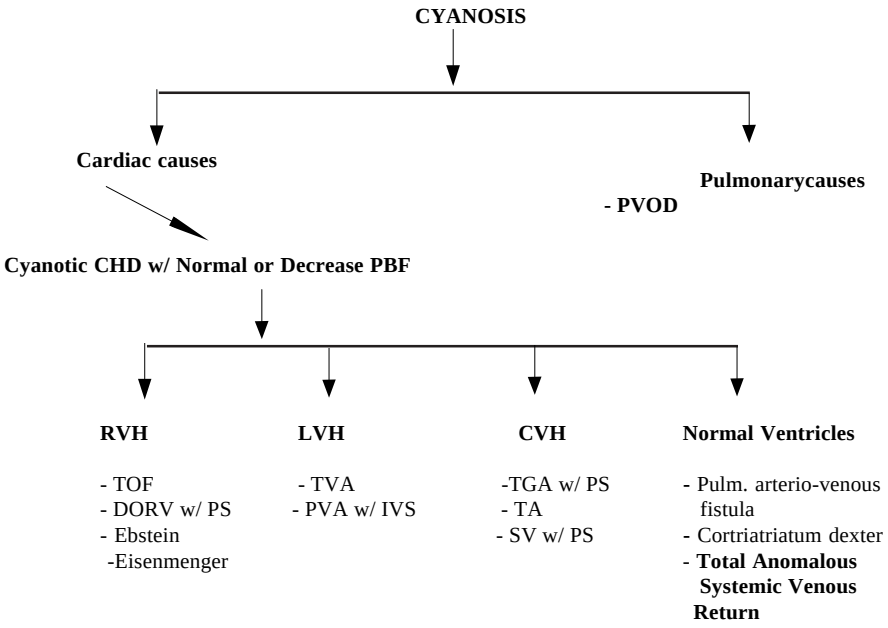
Given these data now we should rule out pulmonary causes of cyanosis like pulmonary vascular obstructive disease in which they may also present as dyspnea or fatigue on exertion with cyanotic and clubbed nailbeds. This may also present as normal heart size on CXR unless CHF supervenes. However, PVOD patient will present a characteristic loud P2 with ejection click, a PR or TR murmur with signs of right-sided heart failure with RAD RAE and RVH on ECG which is not found in our patient thus PVOD is ruled out. For the cardiac causes of cyanosis we will be focusing on cyanotic type of CHD with normal or decrease pulmonary blood flow. Like TOF or DORV with PS were also be one of the considerations with history of cyanosis and normal heart size but it is ruled out since their was no history of spells nor squatting and on PE their was no SEM at the LUSB which is characteristic findings of TOF due to the PS murmur and it showed RVH in CXR and ECG which is not found in this patient thus this is ruled out. Other cyanotic CHDs would be TVA or PVA with IVS but this is ruled out since these would present as enlarge heart due to RAE and LVH which contradicts to the findings of the patent. TGA with PS could be one of the, considerations with the history of cyanosis and single S2 on PE but this is ruled out since this would present as biventricular hypertrophy on ECG and CXR and the 2D echo did not present as such. So another close differential diagnosis will be those cyanotic heart disease with normal heart size which would include pulmonary arterio-venous fistula, cortriatriatum dexter and anomalous drainage of systemic veins to left atrium.

In pulmonary arterio-venous fistula, the desaturated systemic blood from the pulmonary arteries reaches the pulmonary veins, bypassing the lung tissue and resulting in systemic arterial desaturation and cyanosis. The PBF and pressure remain unchanged, and there is no volume overload to the heart thus the chest x-ray films and ECG would show a normal heart size which are found in our patient. However, a faint systolic or continuous murmur may be audible in 50% of patients with pulmonary arterio-venous fistula which was absent in our patient. It is only by angiography which is the definitive method for locating pulmonary AV fistula in which we can rule this out. The angiography of our patient did not show any pulmonary AV fistula, thus this was ruled out.

Another consideration is cortiratriatum dexter, a rare congenital anomaly associated with complex right heart abnormalities, characterized by a membrane that divides the right atrium into two chambers. This would present as exertional fatigue, cyanosis, clubbed and cyanotic nailbeds which were present in our patient, however the S2 is usually split and a systolic murmur is usually heard at LUSB which is not a finding in our patient. This can be ruled out only by transesophageal echocardiography. This is ruled out in our patient because the TEE showed otherwise- **TOTAL ANOMALOUS SYSTEMIC VENOUS RETURN TO LEFT ATRIUM.**

Before discussing the anomalous systemic venous return per se and their clinical significance. The embryology of the systemic venous system will be briefly reviewed

Fig. 23. Differential Diagnosis:



EMBRYOLOGY

Normal venous development is a process of progressive appearance of a series of paired venous structures, development of anastomotic channels between them and the eventual selective regression of certain segments.

Development of Systemic Venous System

The atria are located dorsally and the ventricular chambers are ventrally located. The sinus venosus lie dorsal to the atria. The sinus venosus has right and left sinus horns and empties into atrial segment of the tube. Three major venous channels drains into the sinus venosus at this stage: the omphalomesenteric (vitelline) veins, the umbilical veins, and the common cardinal veins. Each common cardinal vein is formed by the union of the anterior and posterior cardinal veins which drain the cephalic and caudal regions of the embryo respectively.

At the beginning of the 4th week [2] of embryonic life (Fig. 24), the left sinus horn and the transverse portion of the sinus venosus will make a rightward shift and become separated from the left side of the atrium. There is now preferential flow to the right sided structures. There then follows gradual regression of the left umbilical and vitelline veins and the right umbilical vein. The right and left anterior cardinal vein connects an anastomosing vein called the brachiocephalic or innominate vein (Fig.25). The development of innominate vein is usually followed by the involution of the left SVC which becomes the ligament of marshall.

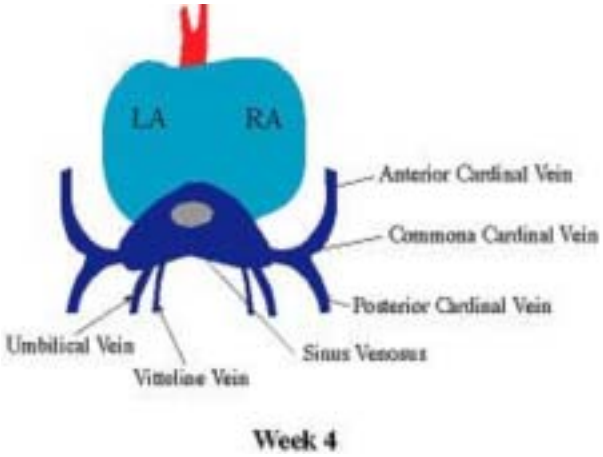


Fig. 24. (From Abdulla Ra-id. Embryology, Pediatric Cardiology. Rush Children's Heart Center Home Page

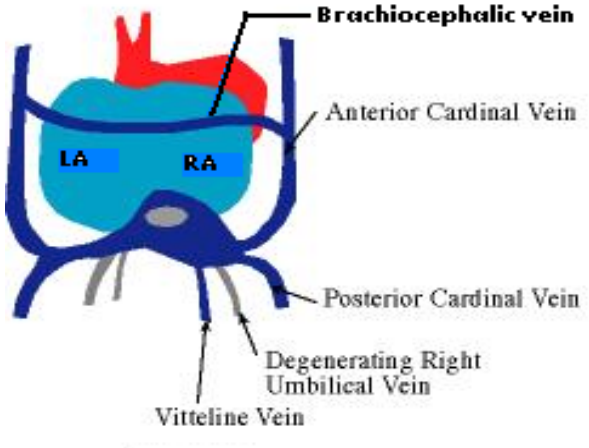


Fig. 25. (Modified From Abdulla Ra-id. Embryology, Pediatric Cardiology. Rush Children's Heart Center Home Page)

At 8th week (Figure 26), The distal end of the left cardinal vein degenerates and the more proximal portion of it will now connect through the anastomosing vein (left brachiocephalic vein) to the right anterior cardinal vein, thus forming the superior vena cava. The left posterior cardinal vein also degenerates, and the left sinus horn receiving venous drain from the heart become the coronary sinus. The right vitelline vein becomes the IVC (Inferior Vena Cava) and the right posterior cardinal vein becomes the azygos vein. All these is completed in the 8th week gestation.

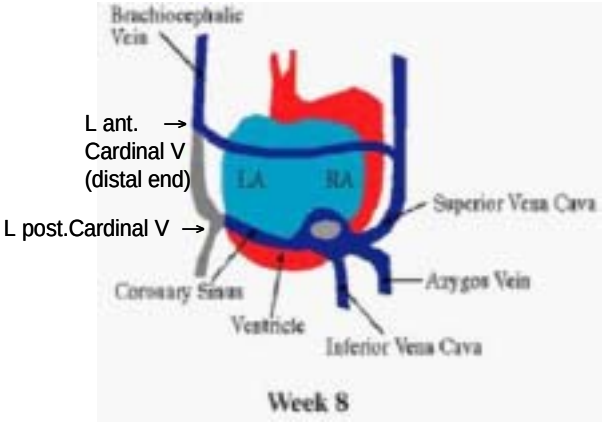


Figure 26. (Modified From Abdulla Ra-id. Embryology, Pediatric Cardiology. Rush Children's Heart Center Home Page)

In the case of our patient, these are the following anomalies seen: (Figure 27)

1. Bilateral SVC of good size, no innominate vein in between
2. Persistent left SVC drains to coronary sinus which then drains to the LA
3. Right SVC drains to LA
4. IVC drains to LA
5. Hepatic vein drains to LA

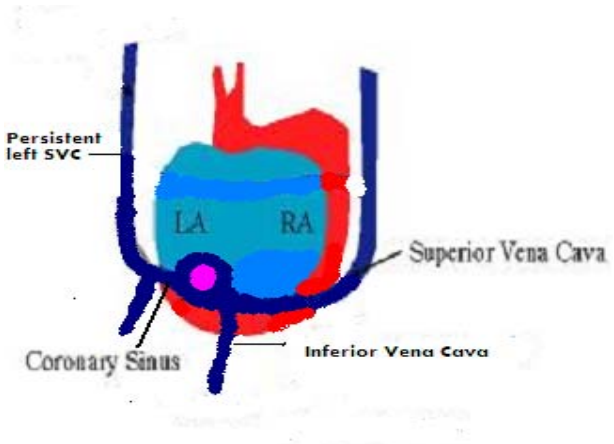


Figure 27. Schematic Diagram of Patients Systemic Venous Drainage Anomaly. . (Modified From Abdulla Ra-id. Embryology, Pediatric Cardiology. Rush Children's Heart Center Home Page)

Possible embryologic explanations of these anomalies are the following:

1. There is persistence of the left horn of the sinus venosus and the left common and anterior cardinal veins with incorporation of the sinus venosus into the left atrium. (By Miller, from Mayo Clinic Proceedings, 1965)[3]
2. This anomaly is also thought to result from malposition of the right horn of the sinus venosus in a leftward and cephalic direction, so that the dominant superior and inferior caval veins connect to the left rather than to the right atrium (Kirsch et al, 1961).[4]
3. There is persistence of the valves of the sinus venosus. In the normal heart, the remnants of the sinus venosus valves are the Eustachian and Thebesian valves and the crista terminalis. Pathologic overgrowth of the valves may cause complete subdivision of the right atrium; consequently, the inferior and superior vena cava and coronary sinus are excluded from the RA with channeling of the systemic venous return into the LA (By Gueron, Journal of Thoracic Cardiovasc Surg, 1969).[5]

Anomalous Systemic Venous Connection (ASVC)

Represents a wide range of malformations, whose physiological consequences may vary from nil to the most severe form of systemic arterial desaturation. They may occur in isolation or with other congenital cardiac anomalies, in situs solitus, or with cardiac malpositions with or without atrial isomerism.

Of considerable interest are the very rare instances just like in our case in which both the vena cava empty into the LA together with the coronary sinus and the pulmonary veins.

An organized classification of venous anomalies can be most easily achieved by using anatomic rather than embryologic subdivisions.

Classification of Systemic Venous Anomalies:

(From Anderson RA et al. Anomalous Systemic Venous Return. Pediatric Cardiology) [6]

I. Anomalies of the SVC
   a. Left SVC to RA
      - Bilateral Superior caval veins (slide)
      - absent right SVC (slide)
      - Left SVC with localized coronary sinus defect
   b. Left SVC to LA
   c. Right SVC to LA
   d. Superior caval veins accepting pulmonary veins
   e. Aneurysm of SVC

II. Anomalies of the IVC
   a. IVC to LA
   b. Absence of infrahepatic segment of the IVC with azygos continuation
   c. IVC accepting pulmonary veins

III. Anomalies of the Coronary sinus

IV. Total Anomalous Systemic Venous Return

V. Anomalies of the valves of the sinus venosus

Epidemiology

A review of literature revealed only 9 patients in the world literature with complete anomalous systemic venous drainage into the LA. Presence of an atrial septal defect is obligatory for survival. Pearl and Spicer reported the 9th case in 1980 (Southern Medical Journal 73: 259-261). De Leval et al[7]in 1975 who reviewed 100 patients with anomalous systemic venous connection who underwent operation reported only 3 patients with total anomalous venous connection to LA (Mayo Clinic Proceedings, 1975). They found out that associated cardiac anomalies were present in all patients except one. ASD is the most common associated cardiac anomaly. It has an equal sex distribution.

It is also worthwhile mentioning that persistence of a left SVC draining to the coronary sinus is the most common systemic venous anomaly. This lesion has been noted in 0.3-0.5% of the general population (Geissler and Albert, 1956; Burski et al, 1986) and is said to occur in 2-4.3% of patients with congenital heart disease. (Campbell et al[8] 1954; Fraos et al, 1961; Cha and Khoury[9] 1972). Electrocardiograms of patients with persistent left SVC show a leftward P axis in 35% (Momma & Linde[10]1969) to 70% (Hancock[11]1964) of patients. This abnormal P wave axis has been referred to as "coronary sinus rhythm" and may be a result of persistence of left-sided embryonic pacemaker tissue.

Pathophysiology:

Communication between the superior vena cava (Right and Left SVC) as well as the IVC and hepatic vein into the left atrium results in right to left shunts and a decrease in systemic arterial oxygen saturation, therefore cyanosis is obligatory.

In the normal circulation, the entire systemic venous return passes through the vena cava and enters the right side of the heart, while blood flow into the left side of the heart is derived entirely from pulmonary veins. If one of the cava enters the left atrium, the right side of the heart is effectively bypassed so that right ventricular output and pulmonary blood flow should fall. The ventricular output theoretically remains unchanged because the increment in anomalous caval flow into the left atrium is matched by a reciprocal decrement in pulmonary venous flow into the left atrium. In other words, as systemic venous return to the LA increases, pulmonary venous return decreases by the same amount so that total flow to the left side of the heart remains unchanged. In the absence of compensatory mechanisms, anomalous caval drainage into the LA should be associated with reduced pulmonary flow and normal systemic flow. These would explain why the ECG is normal with no cardiac enlargement as well as the CXR result in our patient.

Clinical Manifestations:

Physical appearance is normal except for symmetric cyanosis and digital clubbing. Growth and development are normal. All these characteristic findings are found in our patient.

Murmurs are absent or unimpressive. Theoretically, a soft midsystolic murmur might result from increased flow into the aorta, but left ventricular volume is seldom large enough to achieve such murmurs. In our patient we didn't appreciate any murmur. The second heart sound has been described as single just like our patient. To explain this observation, this is due to the reduced right ventricular stroke volume and decrease pulmonary capacitance result in early pulmonary valve closure and synchrony or near synchrony with aortic closure, thus producing a single S2. The intensity of the pulmonary component of the second heart sound is normal or diminished,

because pulmonary arterial pressure is normal or low. intensity of the pulmonary component of the second heart sound is normal or diminished, because pulmonary arterial pressure is normal or low.

Electrocardiogram

The ECG is often entirely normal. P waves are usually normal, but when a persistent left SVC connects to the coronary sinus just like our patient (P axis-75), there is often a leftward deviation of the P wave axis (+15 or less) with an incidence of 70-80% as opposed to 5-10% in normals (Hancock EW, 1964). Momma and Linde, reported an incidence of 35%, and Furuse et al[12]found out 37% of patients with persistent left SVC with superior leftward P wave and 67% in patients with absent IVC. Hence, in the presence of a superiorly leftward orientation of P wave vector, systemic venous anomalies must be carefully looked for. Thus, this would explain the leftward P axis of our patient.

Right ventricular hypertrophy is uniformly absent because flow into the right side of the heart is normal or reduced and pulmonary arterial pressure is normal or low. The increment in left ventricular flow is seldom sufficient to cause left ventricular hypertrophy.

CXR

In view of the relatively modest hemodynamic derangements, it is not surprising that the size and configuration of the heart are usually normal. Because pulmonary arterial flow tends to be reduced or usually normal, the vascularity of the lungs maybe reduced or normal.

A left superior vena cava may form a recognizable shadow before entering the left atrium or coronary sinus. This shadow is concave or crescentic as it emerges from beneath the middle third of the clavicle and passes downward toward the left upper border of the aortic arch.

Echocardiogram and Contrast Echocardiography

A non-invasive approach to the patient with CHD, which provides detailed information concerning systemic vnous return would be useful. Alerted to the presence of one abnormal systemic venous segment, the echocardiographer will pay particular attention to the cardiac connections of all the systemic and pulmonary veins. The first stage in any systematic approach in the diagnosis of systemic venous abnormalities must be diagnosis of the atrial arrangement (situs) which may be accurately predicted based on the position and connections of the inferior caval and hepatic veins. Particular attention to the suprasternal examination should also be emphasized to identify abnormalities in superior caval segments and their connections.

Contrast echocardiography is a very useful technique to diagnose anomalous systemic venous connection to the left atrium. Just like what we did in our patient. When a left superior vena cava drains directly into the left atrium, injection of a bolus of agitated saline into the left antecubital vein is followed by immediate opacification of the left atrium. Conversely when a right SVC drains directly into the left atrium, injection of agitated saline into the right antecubital vein promptly opacifies the left atrium. When the inferior vena cava connects to the left atrium, injection of contrast material into the femoral vein, the left atrium opacifies first. Thus, with the use of these contrast echocardiographic studies, we were able to arrive at the diagnosis of anomalous systemic venous connection to the left atrium. It could not be determined, however, whether an isolated right SVC or persistent left SVC alone was present or whether both were present.

Cardiac Catheterization and Angiography

Cardiac catheterization and angiography remains to be the most useful procedures to confirm the diagnosis. It provides precise definition of systemic venous connection which is important in congenital heart disease to enable proper surgical correction. Complete knowledge of the systemic venous connections before commencing to open heart surgery certainly enables the surgeon to plan venous cannulation and the surgical approach in a better fashion. The table below showed the summary of reported cases of TASVC to LA from different authors, the common presentation was cyanosis and clubbing, the cardiovascular findings were essentially normal as reported by Rojas and Pierre Vart, while single S2 was noted in a report of Gueron just like our patient, while Miller and Roberts reported a holosystolic murmur. The CXR in almost all authors showed normal or slightly enlarged heart with normal PVM. The ECG were usually normal, however leftward P axis were reported by Gueron, Roberts & Pierre Vart which is also found in our patient.

Surgical Options

Surgical correction of Total anomalous systemic venous connection to LA is succesfully achieved byapplying similar principles to those that are used for TAPVR. A baffle repartitioning using a pericardial patch in such a way that the pulmonary veins drained into the left atrium and the systemic veins and coronary sinus drained into the right atrium. The operation can be performed safely under profound hypothermia and circulatory arrest.

Other surgical option is bidirectional glenn shunt of right or left SVC or both. This had the same principle of patients who will undergo univentricular repair like Fontan. Since our patient had hypoplastic and underdeveloped RA and RV thus it can't accommodate all the systemic venous return. Thus BGS done, followed by intra-atrial baffle using pericardium to redirect IVC drainage, hepatic vein and CS to the RA.

Table. Reported Cases of Total Anomalous Systemic Venous Connection to the Left Atrium

Author/ Date/ Place	**Age**	**Sex**	**Presenta -tion**	**Cardio- vascular**	**X-ray**	**ECG**	**Angiography**	**Intra-op findings**	**Surgery**	**Results**
Miller et al[1] 1965 London, England	5	F	Cyanosis, clubbing	Gr 3/6 SM left LSB	Fullness L upper part of mediastin um	Normal	ASD, persistent L SVC, absent R SVC	L SVC to CS then to LA, IVC Pulm. veins drains to LA, absent R SVC, ASD	Septal defect enlarged, intra-atrial baffle to redirect veins to RA	Successful
Gueron[3] 1969 Israel	15	M	Cyanosis, clubbing, mild dyspnea on exertion	S2 single, no murmur	Mod cardiome galy normal PVM	LVH by voltage P wave inverted in II III aVF RCL P axis (-) 45	ASD, obstruction at TV suspected	Both vena cava drains to LA, ASD secundum, RA small	Septal defect enlarged intra-atrial baffle redirect veins to RA	Successful
Roberts[12] 1972 England	5	F	Cyanosis, clubbing, Dyspnea on exertion	Gr 3/6 HSM right LSB	Slightly enlarged heart	P axis (-)125	L SVC, R SVC, IVC, azygos, CS drains to LA ASD, Dextroversion	Small R SVC to CS, Huge L SVC drains to LA, no IVC but 2 hepatic veins entered to LA, huge azygos vein joined L SVC, ASD Dextroversion	Septal defect enlarged pericardial baffle redirect veins to RA, coronary sinus cut back	Successful
Rojas[13] 1965 Connecticut	20	F	Cyanosis, Clubbing , Mentally retarded	Normal	Normal	Normal except for sinus tachy	R innominate vein joined w/ L innominate vein to L SVC which drains to LA, ASD, atresia of R SVC			
Pierre Viart[14] 1977 Belgium	3	M	Cyanosis, clubbing	Normal	Slightly enlarged heart, Normal PVM	Atrial rhythm	L SVC, IVC drains to LA, absent R SVC, ASD	L SVC, IVC & CS drains to LA, Absent R SVC, large ASD	Septal defect enlarged pericardial baffle redirect veins to RA,	Successful
Berba-Maape 2002 PHC, Philippines	**15**	**F**	**Cyanosis clubbing**	**S2 single, No murmur**	**normal**	**P axis (-) 75 P wave inverted in II,III,aVF**	**L SVC to CS then drains to LA; R SVC, IVC, hepatic vein drains to LA, ASD**	**L SVC to CS then drains to LA; R SVC, IVC, hepatic vein drains to LA, ASD**	**Septal defect enlarged, intra-atrial baffle with pericardium to redirect IVC, hepatic V and CS; Bilateral BGS**	**Successful**

A study done by Florentino Vargas et al[13] who reviewed 170 patients who underwent modified Fontan- Kreutzer procedure who had complex CHD (SV, D-TGA, L-TGA, DORV) with co-existent anomalous systemic venous return. The study revealed 17 patients with anomalous systemic and pulmonary venous connection. Of the 17 patients, 7 of them had bilateral SVC in which the left SVC drains to LA. Four patients underwent patch diversion of which 2 of them expired due to systemic venous return (SVR) obstruction. There were 3 patients who underwent modified Glenn shunt all of them were doing well.

Summary

A very rare case of Total Anomalous Systemic Venous Drainage to the Left Atrium was presented. The malformation is a form of a cyanotic congenital heart disease in which the only clinical significant features of the anomaly are cyanosis and clubbing with otherwise normal cardiac findings. The ECG is usually normal except for some cases of leftward deviation of the P wave axis. The CXR reveals a normal cardiac silhouette, normal or diminished pulmonary vascular markings. Contrast echocardiography establishes specific patterns of systemic vein connection to the left atrium which was seen in this patient and was confirm by angiography. The patient was then successfully operated upon and the anomaly was corrected.

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

References

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

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

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

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

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

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

Figures

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

Legends

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

Tables

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

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