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Original Article

Long-Term Clinical and Echocardiographic Follow-up of Patients after Percutaneous Mitral Balloon Valvotomy at PHC from 1989-1994

Alexander D. Ang MD, Ramoncito B. Tria MD, Leonard Warren S. Rondilla MD, Leila Diaz MD.

OBJECTIVES: *Percutaneous mitral balloon valvotomy has been accepted as an alternative for surgical mitral commissurotomy in the treatment of patients with rheumatic mitral stenosis. It produces immediate hemodynamic and clinical improvement in majority of patients and its long-term clinical outcome is encouraging.*

MATERIALS AND METHODS: *This is a retrospective cohort study over an 8-year period (January 1989 - December 1994) of cases at the PHC. This study described and analyzed long-term clinical and echocardiographic outcome of patients with rheumatic mitral stenosis after successful PMV. Patients' records were reviewed and long term clinical outcomes were analyzed in terms of death, mitral surgery, repeated PMV and functional impairment. Functional status using New York Heart Association Classification (NYHAC) was determined at baseline prior to intervention as well as on 2nd, 4th, 6th, and 8th year of follow-up. Echocardiographic outcomes such as restenosis and progression of regurgitation were also assessed.*

Survival analysis was performed to estimate event free survival and chi-square test or Fisher exact test was used to analyze predictors of major cardiac events. Ninety-eight patients, 74 females and 24 males were followed-up for 8 years with the mean age of 35+ 9.7 years old. There was a marked reduction of symptoms in almost all of the patients after successful PMV, and majority remained remarkably stable on follow-up. The major cardiac events noted were 2(2%) cases of death, 6(6.6%) mitral valve surgery, 3(3.1%) repeated PMV, 23(26.4%) cases of restenosis and 10(10.2%) cases of functional impairment. The event free survival was 67% at 8 years. Restenosis was noted in 2.3%, 11.3% and 26.4% of cases at the 3rd, 5th and 8th year follow-up respectively. Severity of mitral regurgitation did not change in 72.4% of patients.

RESULTS: *After successful PMV, more than two thirds of patients were in good clinical condition and free of any cardiac events at eight years of follow-up. Restenosis increased overtime whereas regurgitation did not tend to progress.*

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Keywords: percutaneous mitral balloon valvotomy; mitral valve; mitral valve stenosis

Mitral stenosis is a disabling disease, which is predominantly caused by rheumatic fever. If untreated, significant symptoms such as dyspnea, easy fatigability, and serious complications such as pulmonary edema, systemic arterial embolism, pulmonary hypertension and even death can occur. Surgical commissurotomy and open valvuloplasty were, for many years, the only methods by which mitral stenosis could be corrected. However, the recent development of a percutaneous balloon valvotomy technique has revolutionized the treatment of this disorder.[1]

Percutaneous mitral balloon valvotomy (PMV) was first introduced by Inoue in 1984[2] and since then it has been accepted as an alternative to definitive surgical repair or replacement in selected patients with symptomatic rheumatic mitral stenosis.[3-6] It has been shown to produce immediate satisfactory hemodynamic and clinical improvement,[7-8] and the long term follow-up data for those patients at various center appears to be favorable.[9-10] After a decade of experience with this technique, it is clear that PMV is a safe and effective alternative procedure for treatment of mitral stenosis.

In the Philippine Heart Center (PHC), where the study was conducted, PMV was started only in 1989[11]as a treatment option for rheumatic mitral stenosis. Since then it steadily gained ground as an alternative to surgical commissurotomy in this institution. In the local study reported by San Diego Jr. et al, immediate and short-term outcome of patients who underwent PMV in this institution showed excellent results.

Although some series have provided long-term clinical data regarding outcome of patients who underwent PMV as well as echocardiographic data concerning changes in mitral valve area and regurgitation long after the procedure, local studies regarding this aspect are still lacking. The study was undertaken to provide local data on long-term clinical outcome and echocardiographic follow-up of patients after

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successful PMV. The objectives of this study were: (1) to determine and analyze long term (8 years) clinical outcome of patients with rheumatic mitral stenosis after successful PMV in terms of cardiac deaths, subsequent mitral surgery, (mitral valve replacement, mitral valve repair, open and closed mitral commissurotomy) repeated PMV and functional impairments, (2) to assess restenosis and mitral regurgitation after PMV.

Materials and Methods

The study design is a retrospective cohort study, which included all patients aged 18 years old and above, who underwent successful PMV at the PHC between January 1989 to December 1994, and had followed up for 8 years. The following patients were excluded: patients aged less than 18 years old, those with insufficient opening of mitral valve after PMV, those who did not have 2DED study before PMV, and patients who developed immediate complication during PMV and required mitral surgery.

Patients' records were reviewed and long term clinical outcomes were analyzed in terms of death, mitral surgery, repeated PMV and functional impairment. Functional status using New York Heart Association Classification (NYHAC) was determined at baseline prior to intervention as well as on 2^{nd}, 4^{th}, 6^{th} and 8^{th} year of follow-up. Echocardiographic outcomes such as restenosis and progression of regurgitation were also assessed.

2DED study of the patients were evaluated which included the Wilkins score, mitral valve area (using pressure half time method)[12] and mitral regurgitation estimation (graded as none, mild, moderate or severe by color doppler semiquantitative method)[13] before, after the procedure and on follow-up. The mitral valve area (MVA) and mitral regurgitation post PMV were compared to the value obtained in subsequent 2DED study, taking note of the restenosis and mitral regurgitation progression.

Since doppler MVA determination immediately after PMV is not accurate because of acute changes in left atrial compliance, Doppler MVA determined after 6 months to one year was the one considered in this study when hemodynamic conditions was already stable as baseline for restenosis.

Reviewed data was encoded in Database 3. Statistical programs such as Epi Info and SPSS (Statistical Package for Social Sciences) were used for statistical analysis.

Statistical Analysis

Data were described in terms of mean, standard deviation, frequency and percent distribution. Event-free survival rate for several single and composite end points was estimated with the use of survival analysis and predictors of major event were identified using Chi Square or Fisher exact.

Based on an alpha value $\leq .05$, and survival rate of 40% with total width of confidence interval of 20%. Sample size computed should be equal or greater than 82.

Results

The records of 261 patients who underwent PMV were reviewed. One hundred twenty nine patients (129) had a successful PMV, while 58 patients were considered to have insufficient mitral valve opening. In 9 patients commissurotomy was not performed due to technical failure or inability to place or stabilize the balloon across the mitral valve. In 4 patients, the procedure could not be evaluated because of major complications (3 severe mitral regurgitation and 1 LV wall rupture). Seven of these patients underwent mitral valve replacement with repair of LV perforation in 1 patient and the other 6 patients underwent open mitral commissurotomy.

Sixty-one subjects were excluded in the study due to incomplete data such as unavailability of pre and post 2DED study.

Of the 129 patients discharged with successful PMV, 31 were lost to follow-up. The remaining 98 were followed-up and were the ones included in this study.

Table 1. Baseline characteristics of patients undergone successful PMV

	Mean	**SD**
Age (years)	35	9.7
Sex	**No.**	**Percent**
Male	24	24.5
Female	74	75.5
Functional Class		
1	0	0
2	74	75.5
3	21	21.4
4	3	3.1

Baseline characteristics of the patients are shown in Table 1. Of the 98 patients, 74 (75.5%) were female and 24 (24.5%) were male with mean age of 35+9.7 years. Most of them were symptom limited, 74 (75.5%) were NYHA FC2, 21 (21.4%) in FC3 and 3 (3.1%) in FC4.

Echocardiographic assessment of the MVA is depicted at Table 2. Ninety (91.8%) patients had a Wilkins score of < 8 and only 8 (8.2 %) patients had a Wilkins score of > 8. The mean MVA was .69 + .16 cm^2 prior to PMV with mean mitral valve gradient (MVG) of 17.1+5.8mm Hg.

After PMV, there was a marked reduction of symptoms in most of the patients. The functional status progressively improved after the succeeding year. The percent of patients in functional class I and II remained remarkably stable during follow-up as shown in Table 3. At the time of last follow-up, the number of patients who were free from mitral valve surgery, repeat PMV and death were 87 patients: 61 (62.2%)in FC I, 16 (16.3%) in FC II, 10 (10.2%) in FC III and non-in FC IV.

Table 2. Preprocedural and postprocedural echocardiographic data

Wilkins Score	Pre PMV No.	Pre PMV Percent	Post PMV
5	3	3.1	
6	13	13.2	
7	37	37.8	
8	37	37.8	
9	7	7.1	
10	1	1.0	
Mitral Valve Area (cm^2)	0.69+ .16		1.73 + .31
Mean mitral valve gradient	17.1 + 5.8		5.8 + 2.2
Mitral regurgitation	**No.**	**Percent**	**No.** **Percent**
None	43	43.8	23 23.5
Mild	52	53.1	65 66.3
Moderate	3	3.1	10 10.2
Severe	0	0	0 0

The MVA significantly improved after the procedure to 1.73 + .31 cm^2 as well as the MVG, which significantly decreased to 5.8 + 2.2 mm Hg. Only 87 patients were able to have complete echocardiographic follow-up after PMV hence for the analysis of restenosis and progression of MR, only these subjects were included. On follow-up, the restenosis was noted on 2.3% of patients on the 3rd years, 11.3% on the (Table 4 and Fig.1). Mitral regurgitation did not change significantly during follow-up for the whole population. It remained unchanged in 63 (72.4%) patients, increased by 1 grade in 13 (14.9%) and decreased in 6 (6.9%), usually from mild to moderate and vice versa. In 5(5.7%) patients there was a well documented > 2 grade increase in mitral regurgitation severity usually progressive overtime.

Follow-up events were: (1) Death: 2 patients died, 1 because of prosthetic valve dysfunction and the other after mitral valve replacement. (2) Mitral valve surgery: 6 patients underwent surgery because of restenosis, (3) Repeat PMV: 3 patients had a repeat PMV because also of restenosis. (4) Restenosis: 23 (26.4%) patients meet restenosis definition

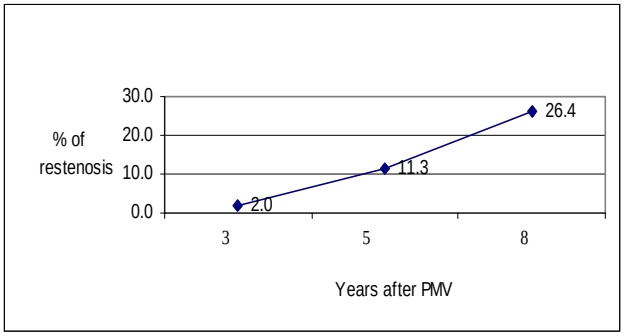

Figure 1

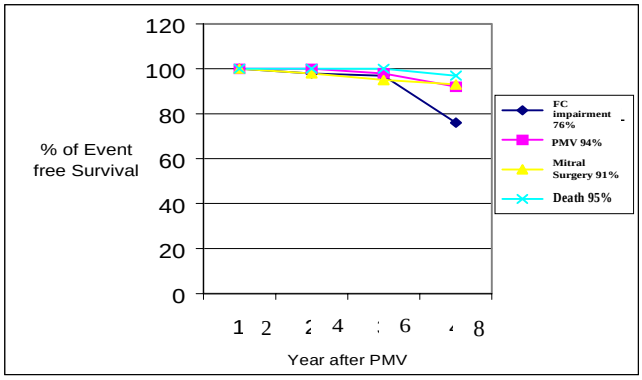

Figure 2

Table 3. Percentage of patients in NYHA functional classes I to IV before PMV and on follow-up.

Functional Class	Pre PMV	2 yrs	4 yrs	6 yrs	8 yrs
1	0	92 (93.9%)	85 (86.7%)	64 (65.3%)	61 (62.2%)
2	74 (75.5%)	6 (6.1%)	10 (10.2%)	27 (27.6%)	16 (16.3%)
3	21 (21.4%)	0	2 (2.0%)	1(1.0%)	10 (10.2%)
4	3 (3.1%)	0	0	0	0

(5) functional impairment occurred in 10 (10.2%) patient. The survival free of major events was 67% at 8 years, and the event-free curves for several end points are presented in Figure 2.

Discussion

Our report involves successful PMV in a population majority of which were middle-aged female with severe mitral stenosis, symptom limited, mostly FC2 to FC3 with good valve score. This study provided us information regarding the long-term clinical outcome and mitral valve changes overtime on patient who underwent successful PMV.

Clinical improvement was the rule for patients with sufficient mitral valve opening as reported by other literature.[3,5,7,8,14] As seen in our study, most of our patients improved after PMV and remarkably remained in functional class 1 to 2 over the years.

Disease progression in rheumatic mitral disease may be the result of low-grade subclinical rheumatic process and/or abnormal turbulence generated by already deformed valve.[15] Both mechanisms might contribute to further commissural fusion, thickening and calcification of valvular and subvalvular structures of the native valve. This also holds true in previously commissurotomized valves, which cause a progressive loss or decrease in MVA that might lead to restenosis. Restenosis is rare during the first early years after the procedure as stated by Vahanian et al, which showed 4% restenosis[16] and Al Zaibag et al, which reported no restenosis[17] in their studies. Data from the study of Hernandez et al, also support the fact that restenosis is rare within 3 years after the procedure especially with a good mitral valve opening. These results are in concordance with our study, which showed 2.3% restenosis rate in 3 years. A higher rate was obtained by Abascal et al, at 20%[18] and Desideri et al, at 21%.[4] This difference is likely due to differences in baseline characteristics of the subject included in the different studies such as age, echocardiographic score, and MVA after PMV which might cause the difference in the rate of progression in valvular disease. As evident in other studies, older age group and small valve area after PMV as well as high valve score are independent predictors for restenosis.[4,6,9] In contrast, the study made by Hernandez et al, failed to showed that postprocedural MVA is a good predictor of restenosis. Our study showed lower restenosis in the early years probably because our population consisted of younger age group with majority having a good valve score and sufficient mitral valve opening. However, we failed to show baseline characteristic that can predict restenosis. Restenosis increased over time reaching 11.3% at 5 years and 26.4% at 8 years and this is comparable to the reports made by other studies.[7]

Mitral regurgitation did not tend to progress in most of the population (94.2%), although it appeared to increase in 14.9% and decrease in 6.9% of patient. This change was only of 1 grade that might be caused by interobserver variability of the method rather than in the regurgitation in itself. Our event free survival defined as freedom from death, mitral valve surgery, repeated PMV and functional impairment, is 67% at 8 years, comparable with the reports of Hernandez et al, at 69% at 7 years and Jung et al,[19] at 76% at 5 years. Cohen et al,[20] found a 51% event free survival at 6 years, Dean et al,[8] described 60% event free for 4 years andTuzco et al,[10] had a 40% at 3 years. All of these studies showed a slightly lower event free survival compared to our study. This is probably caused by the differences in the study population in which patients with insufficient valve opening were included in their study. variability of the method rather than in the regurgitation in variability of the method rather than in the regurgitation in itself. Our event free survival defined as freedom from

death, mitral valve surgery, repeated PMV and functional impairment, is 67% at 8 years, comparable with the reports of Hernandez et al, at 69% at 7 years and Jung et al,[19] at 76% at 5 years. Cohen et al,[20] found a 51% event free survival at 6 years, Dean et al,[8] described 60% event free for 4 years andTuzco et al,[10] had a 40% at 3 years. All of these studies showed a slightly lower event free survival compared to our study. This is probably caused by the differences in the study population in which patients with insufficient valve opening were included in their study.

Limitation of the Study

In our study we could not compare the outcome of patients with good valve score on patients with high valve score. This is because of the limited number of patients with high valve score included in the study. Regarding average mitral valve area loss per year, we could not compute for it because of the limited 2DED study done on follow-up.

Conclusion

This study showed that PMV is an effective procedure for patients with symptomatic mitral stenosis, producing good long-term clinical outcome. Restenosis increases overtime whereas regurgitation did not tend to progress.

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Original Article

Relationship of Low Ankle-Brachial Pressure Index with Coronary Artery Disease

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BACKGROUND: ***The ankle-brachial pressure index is a measure of generalized atherosclerosis and peripheral artery disease in the lower extremities. If its association with coronary artery disease will be established, it will become an important tool for assessing coronary artery disease among high risk patients.***

This study aims to determine the relationship of low ankle-brachial pressure index with coronary artery disease and the effects of athero-sclerotic risk factors of low ankle-brachial pressure index coronary artery disease.

MATERIALS AND METHODS: ***This is a cross sectional study of the relationship of low ankle-brachial pressure index with coronary artery disease. From August 1 2002 to September 15, 2003, a total of 154 patients who underwent coronary angiogram were included in the study. Patients with history of CABG, coronary angioplasty, carotid surgery, CVA and vascular surgery of the abdomen or lower extremities were excluded. The ABI used is the minimum of the two values. Value less than 0.9 is considered low and abnormal. The extent of CAD was coded according to the number of coronary vessels with significant obstruction.***

RESULTS: ***Both the univariate and multivariate analysis were used for statistical analysis. Among the risk factors tested, the presences of hypertension, dyslipidemia, smoking, the duration of diabetes of more than 5 years and high BMI were associated with low ABI (p value <0.05). Furthermore, low ABI (<0.9) was associated with the presence of CAD. A multiple logistic regression analysis further identified hypertension, dyslipidemia and smoking as independent risk factors of low ABI (p value <0.05).***

CONCLUSION: ***Low ABI was associated with the presence of CAD. The presences of hypertension, dyslipidemia, smoking, the duration of diabetes of more than 5 years and high BMI were identified as risk factors of low ABI using the univariate analysis. Using a multiple regression analysis, hypertension, dyslipidemia and smoking were independent predictors of low ABI.***

Phil Heart Center J 2003;10:6-12

Keywords: coronary artery disease; atherosclerosis; peripheral vascular diseases; ankle brachial pressure

Cardiovascular events such as stroke and acute myocardial infarction remain a significant problem of the society despite a comprehensive campaign of prevention. Coronary artery disease (CAD) causes nearly half of these cardiovascular deaths and several atherosclerotic risk factors are identified to be related to coronary artery disease such as hypertension, diabetes, dyslipidimia, age, sex, and smoking.[1]

The ankle-brachial pressure index has been used to assess the patency of the lower extremity arterial system. Studies showed that it is also associated with generalized atherosclerosis.[2] If its association with coronary artery disease will be established, it will become an important screening tool for evaluating patients' high risk of coronary artery disease.

Review of Related Literature

Previous studies showed that low arterial brachial pressure index was associated with several atherosclerotic risk factors. Low arterial brachial pressure index (0.80) among elderly men in the presence of hypertension and cigarette smoking was strongly associated with coronaryartery disease.[3] Even among asymptomatic middle-aged males, low arterial-brachial pressure index (0.90) was associated with age, serum cholesterol, body mass index (BMI), smoking and diabetes.[4] Furthermore, low arterial brachial pressure index was associated with intermittent claudication, smoking, high mean systoloic blood pressure and mean palsma triglycerides and high cardiac event rate.[5]

Low arterial brachial pressure index was an important predictor of morbidity and mortality among older adults withsystolic hypertension,[6] and had important prognostic significance for mortality due to atherosclerotic heart disease in older men and women.[7] Finally, low arterial brachial pressure index was indicative of generalized atheros-clerosis.[8]

Research Objectives

1. To determine the relationship of low ankle brachial pressure index with coronary artery disease.

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2. To determine the effects of atherosclerosis risk factors such as hypertension, diabetes, dyslipidemia, age, sex, and smoking affect the relatioship of low ankle brachial pressure index with coronary artery disease

Research Hypothesis

1. Low ankle brachial pressure index is inversely related with the severity coronary artery disease

2. Different atherosclerotic risk factors such as hypertension, diabetes, dyslipidemia, age, sex, and smoking affect the relationship of low ankle brachial pressure index with coronary artery disease

Materials and Methods

Study Design

This is a cross sectional study of the relationship of low ankle brachial pressure index with coronary artery disease.

Study Sample

All patients who underwent coronary angiogram for evaluation of coronary artery disease (CAD) were included in the study. Patients with history of coronary artery bypass grafting (CABG), coronary angioplasty, carotid surgery, cardiovascular artery (CVA), and vascular surgery of the abdomen or lower extremities were excluded from the study. Informed cosent was obtained from the subjects.

Study Setting and Time Period

From August 1, 2002 to September 15, 2003, patients who underwent coronary angiogram at the Philippine Heart Center and fit in the inclusion criteria were included in the study.

Sample Size and Basis for Calculation

Previous studies showed that the incidence of coronary artery disease among elderly patients with low ankle-brachial pressure index was 15%.

Confidence Interval, @ = 0.05	N
5%	784
10%	196
15%	87
20%	49

Identification of Study Variables

a. independent variable - low ankle-brachial pressure index

b. dependent variable – coronary artery disease

c. confounding variable – atherosclerotic risk

Table 1. Baseline characteristics of the study population

Variables		Number (154)	Frequency
Age	<60	77	50
	≥60	77	50
Sex			
male		94	61
female		60	39
Smoking Hx	(-)	83	53.9
	(+)	71	46.1
Hypertension	(-)	64	41.6
	(+)	90	58.4
Diabetes	(-)	120	77.9
	(+)	34	22.1
Dyslipidemia	(-)	99	64.3
	(+)	55	35.7
ABI	<25	80	51.9
	≥25	74	48.1
CAD	<0.9	79	51.3
	≥0.9	75	48.7
	Normal	51	33.1
	abnormal	103	66.9

Detailed Description of Data Collection

Patients were interviewed and examined by the investigator based on the research questionnaire provided. The status of the coronary artery disease were evaluated and atherosclerotic risk factors were noted.

All patients were evaluated in supine position after at least 15 minutes of rest. Ankle brachial pressure index was determined from measurements of the systolic blood pressure taken from the right arm and in each ankle using a mercury sphygmomanometer.[3] The means of two measurements in the arm and in each ankle were used to calculate the ABI for both the left and right sides as a ratio of an ankle blood pressure measurement divided by the arm measurement.[3] The ABI used is the minimum of the two values.[9] Value less than 0.9 is considered low and abnormal.[10]

All patients underwent coronary catheterization using the standard Judkins or Sones techniques. Coronary angiographies were interpreted visually and the extent of coronary artery disease was interpreted by the angiographer and coded according to the number of coronary vessels with significant obstruction. A reduction of the luminal diameter by >50% for left main coronary artery and >70% for left anterior descending, left circumflex and right coronary arteries were considered significant obstruction.

Statistical Analysis

Univariate analysis using chi-square or t-test was used to examine the association of risk factors with low ankle brachial index and the relation of low ankle brachial index with the presence of coronary artery disease. Multiple logistic regression analysis was used to isolate the independent effects of different risk factors with low ankle brachial pressure index.

Baseline variables used in the analysis were age, sex, smoking, hypertension, diabetes, dyslipidemia, body mass index, ankle brachial index and the presence of coronary artery disease.

Results

The baseline characteristics of the subjects are shown in Table 1. Included in the study were 94 (61%) males and 60 (39%) females while 77 (50%) patients were 60 years old and above and 77 (50%) patients were less than 60 years old. Smoking history showed 71 (46.1%) patients were smokers, and 83 (53.9%) patients were non-smokers.

Furthermore, 90 (58.4%) patients had hypertension, 34 (22.1%) patients had diabetes, 55 (35.7%) patients had dyslipidemia, and 74 (48.1%) patients had abnormal body mass index.

Ankle brachial index measurements revealed that 79 (51.3%) patients had low ABI (<0.9) while 75 (48.7%) patients had normal ABI. Coronary angiogram revealed 51 (33.1%) patients had normal, and 103 (66.9%) patients had abnormal results.

Among patients more than 60 years old (Table 2), 35 (44.3%) had low ABI while 42 (56%) had normal ABI. For patients less than 60 years old, 41 (58.7%) had low ABI while 33 (44%) had normal ABI. Fifty-three (67.1%) male patients had low ABI while 31 (54.7%) had normal ABI; whereas 26 (32.9%) female patients had low ABI while 34 (45.3%) had normal ABI. Both age and sex were not associated with low ABI with p value of 0.197 and 0.157 respectively.

Among patients with hypertension (Table 3), 58 (73.4%) had low ABI while 32 (42.7%) had normal ABI. For patients without hypertension, 21 (26.6%) had low ABI while 43 (57.3%) had normal ABI. The presence of hypertension was associated with low ABI with p value of 0.000.

Furthermore, among patients with hypertension of more than 5 years, 47 (81%) had low ABI while 15 (46.9%) had normal ABI. For patients with hypertension of less than 5 years, 11 (19%) had low ABI while 17 (53.1%) had normal ABI. The presence of hypertension for more than 5 years was also associated with low ABI with p value of 0.002.

Table 3. Relationship of hypertension to ankle-brachial pressure index

Risk Factor	Low <.9		Normal > .9		TOTAL	P-value	OR (95% CI)
HPN	No	%	No	%	90	0.000***	3.71(1.79-7.75)
Present	58	73.4	32	42.7	64		
Absent	21	26.6	43	57.3		0.036*	
Duration of HPN (yrs)	X	SD	X	SD			
	7.76	4.62	5.51	5.19			
	No.	%	No.	%			
> 5 yrs	47	81	15	46.9	62	0.002*	4.84(1.69-14.17)
< 5 yrs	11	19	17	53.1	28		

****significant at p-value <0.05***

Table 2. Relationships of age and sex to ankle-brachial pressure index

Risk Factors	Low <.9		Normal > .9		TOTAL	P-value	OR (95% CI)
	X	SD	X	SD			
AGE	60.2	11.21	57.68	11.07		0.104NS	
AGE GROUP	No.	%	No.	%	No.		
> 60	35	44.3	42	56	77	0.197 NS	0.63 (0.31-1.24)
< 60	41	58.7	33	44	77		
Sex							
Male	53	67.1	41	54.7	94	0.157 NS	1.69 (0.84 –3.43)
Female	26	32.9	34	45.3	60		

*significant at p-value <0.05

Table 4. Relationship of diabetes to ankle-brachial pressure index

Risk Factor	Low <.9		Normal ≥ .9		TOTAL	P-value	OR (95% CI)
Diabetes	No	%	No	%	34	0.234 NS	1.73(0.74-4.05)
Present	21	26.6	13	17.3	120		
Absent	58	73.4	62	82.7			
Duration of	X	SD	X	SD		0.086 NS	
Diabetes (yrs)	5.9	2.94	3.85	3.69			6.75 (1.15-
> 5 yrs	15	75	4	30.8	19	0.031*	44.82)
< 5 yrs	5	25	9	69.2	14		

*significant at p-value <0.05

Table 5. Relationship of dyslipidemia to ankle-brachial pressure index

Risk Factor	Low <.9		Normal > .9		TOTAL		P-value	OR (95% CI)
Dyslipidemia	No	%	No	%	No.	%		
Present	40	50.6	15	20.0	55	35.7	0.000***	4.10(1.89-8.99)
Absent	39	49.4	60	80.0	99	64.3		
Duration in	X	SD	X	SD				
(Yrs)	2.30	1.46	1.28	1.45			0.040*	
> 5 yrs	5	12.8	1	8.3	6	11.8	1.000 NS	1.62 (0.15-40.68)
< 5 yrs	34	87.2	11	91.7	45	88.2		

*significant at p-value <0.05

Table 6. Relationship of smoking to ankle-brachial pressure index

Risk Factor	Low <.9		Normal > .9		TOTAL		P-value	OR (95% CI)
Smoking	No	%	No	%	No.	%		
Yes	47	59.2	24	32.0	71	46.1	0.001***	3.12(1.53,6.40)
No	32	40.5	51	68.0	83	53.9		
Duration In	X	SD	X	SD			0.563 NS	
(yrs)	13.69	9.57	15.29	12.17			0.766 NS	
> 10 yrs	16	35.6	9	42.9	25	37.9		0.74(0.22,2.41)
< 10 yrs	29	64.4	12	57.1	41	62.1		
Pack yrs	X	SD	X	SD				
	13.87	11.80	16.15	10.49			0.435 NS	
Pack yrs	No.	%	No.	%	Total			
>10	17	37.0	11	47.8	28	40.6	0.64 NS	0.64(0.21,1.98)
5-10	28	60.9	10	43.5	38	55.1		
< 5	1	2.1	2	8.7	3	4.3		

significant at p-value <0.05

Table 7. Relationship of BMI to ankle-brachial pressure index

Risk Factor	Low <.9		Normal > .9		TOTAL		P-value	OR (95% CI)
BMI	No	%	No	%	No.	%		
> 25	52	65.8	22	29.3	74	48.1	0.000***	4.64 (2.23,9.74)
< 25	27	34.2	53	70.7	80	51.9		

*significant at p-value <0.05

Table 8. Relationship of ankle-brachial pressure index to CA

	Low <.9		Normal ≥ .9		TOTAL		P-value	OR (95% CI)
CA	No	%	No	%	No	%		
Abnormal	78	98.7	25	33.3	103	66.9		
Normal	1	1.3	50	66.7	51	33.1	0.000***	1.56(21.27-3192.57)

significant at p-value <0.05

Table 9. Sensitivity and specificity of low ABI for CAD

	CAD		Total	PPV	NPV
ABI	(+)	(-)			
<0.9	78	1	79	99	
>0.9	25	50	75		67
Total	103	51			
Sensitivity	75.73				
Specificity		98			

The sensitivity and specificity of low ABI for CAD were 76% and 98% respectively. The PPV and NPV were 99% and 67% respectively.

Table 10. Multivariate analysis of different atherosclerotic risk factors

Variable	B	S.E.	Wald	df	Sig	R	Odds Ratio
Hypertension	1.3998	.4118	11.5570	1	.0007*	.2116	4.0544
Dyslipidemia	1.0339	.4322	5.7223	1	.0168*	.1321	2.8121
Smoking	1.0045	.4580	4.8110	1	.0283*	.1148	2.7307
BMI	.0191	.0571	.1122	1	.7376	.0000	1.0193
Age	.0127	.0184	.4795	1	.4887	.0000	1.0128
Sex	-.3833	.4768	.6464	1	.4214	.0000	.6816
Diabetes	.3999	.4700	.7240	1	.3948	.0000	1.4917
Constant	-2.5779	1.9832	1.6898	1	.1936		

**** significant at p-value <0.05***

Among patients with diabetes (Table 4), 21 (26.6%) had low ABI, while 13 (17.3%) had normal ABI. For patients without diabetes, 58 (73.4%) had low ABI, while 62 (82.7%) had normal ABI. Furthermore, among patients with diabetes of more than 5 years, 15 (75%) had low ABI while 4 (30.8) had normal ABI. For patients with diabetes of less than 5 years, 5 (25%) had low ABI, while 9 (69.2%) had normal ABI. The presence of diabetes for more than 5 years was associated with low ABI with P value of 0.031.

Among patients with dyslipidemia (Table 5), 40 (50.6%) had low ABI while 15 (20%) had normal ABI. For patientswithout dyslipidemia, 39 (49.4%) had low ABI while 60 (80%) had normal ABI. The presence of dyslipidemia was significantly associated with low ABI with p value of 0.00.

Among patients with smoking history (Table 6), 47 (59.2%) had low ABI while 24 (32%) had normal ABI. For patients without smoking history, 32 (40.5%) had low ABI while 51 (68%) had normal ABI. The presence of smoking history was associated with low ABI with p value of 0.001. However, the duration of smoking history and the number of pack years of smoking were not statistically significant.

Among patients with high BMI (≥25) (Table7), 52 (65.8%) had low ABI while 22 (29.3%) had normal ABI. For patients with BMI < 25, 27 (34.2%) had low ABI while 53 (70.7%) had normal ABI. High BMI was significantly associated with low ABI with p value of 0.000.

Finally among patients with low ABI (Table 8), 78 (98.7%) had abnormal coronary angiogram, while 1 (1.3%) had normal coronary angiogram. For patients with normal ABI, 25 (33.3%) had abnormal coronary angiogram while 50 (66.7%) had normal coronary angiogram. The presence of low ABI (<0.9) was significantly associated with abnormal coronary angiogram with p value of < 0.00.

The sensitivity and specificity of low ABI for CAD were 76% and 98% respectively. The PPV and NPV were 99% and 67% respectively.

When these risk factors (Table 10) were subjected to multiple logistic regression analysis; hypertension, dyslipidemia and smoking were independent predictors of low ABI with an odds ratio of 4.05, 2.81 and 2.73 respectively.

Discussion

Ankle brachial pressure index is a marker of generalized atherosclerosis. It is used as a non-invasive method to assess the patency of the lower extremity arterial system and to screen for the presence of peripheral occlusive arterial disease.[2]

Several potential risk factors were identified to be related to atherosclerosis, and subsequently with low ankle brachial pressure index. These include old age, male patients, smoking, high body mass index, hypertension, diabetes and dyslipidemia.

Studies showed that the prevalence of low arterial brachial pressure index (<0.9) increases with age and it increases the risk of death from cardiovascular disease.[11] Old age is not synonymous with coronary artery disease, but the incidence of CAD increases in the elderly.[11]

In this study, 65 (52.4%) patients included were 60 years old and above, the mean age of patients with low ankle brachial pressure index is 61+11. This issue is of increasing importance as the population ages.

Among the potential risk factors for atherosclerosis tested in this study, the presences of hypertension, dyslipidemia, smoking, the duration of diabetes of more than 5 years and high body mass index (BMI) were associated with low ankle brachial pressure index and coronary artery disease. Using a multiple logistic regression analysis, hypertension, dyslipidemia and smoking were independent predictors of low ABI.

Hypertension is often identified a silent cardiovascular risk factor. Many hypertensive patients evade diagnosis and not all receive effective treatment. The blood pressure maybe elevated for sometime but not detected because the patient is symptom free or without blood pressure monitoring. Only then when complications set in and the blood pressure elevation is documented. It is consistently correlated with increased risk of stroke and myocardial infarction.[1] Previous study revealed that low ankle brachial index is highly predictive of subsequent cardiovascular morbidity and mortality in patients with hypertension or peripheral vascular disease both in middle aged or older patients.[9] This study identified hypertension to be significantly associated with low ABI, particularly when it is present for more than 5 years or more. The risk increases with the duration of hypertension.

Dyslipidemia plays a central role in the development of atherosclerosis with numerous trials supported this hypothesis.[1] It is an important constituent of plaque formation responsible in the pathogenesis of different cardiovascular diseases. Furthermore, a positive linear relation between dyslipidemia and coronary mortality had been demonstrated.[12] Dyslipidemia then predicted coronary heart disease risk, although the absolute level of significant clinical events associated with atherosclerosis was quite variable. Dyslipidemia is an independent risk factor of low ABI in this study.

It is known that smoking is the major risk factor for the development of peripheral arterial disease. It increases the mortality rates for symptomatic peripheral arterial disease and is associated with high mortality among elderly.[9] Smoking was independently and significantly related with low ankle brachial pressure index.[3,5,8] In the study done by Abbot et al, the relation of low ABI was strongest in the presence of hypertension and in men with history of cigarette smoking. It is one of the independent risk factor of low ABI in this study.

Diabetes causes a distal, multisegmental, and polystenotic type of atherosclerosis.[13] Previous study showed that age, smoking and diabetes are independent predictors of peripheral arterial disease,[14] and low ankle brachial pressure index.[3,5,8] Results of this study showed that diabetes of more than 5 years is associated with low ankle brachial index.

Obesity is associated with increased cardiovascular risk and a direct linear relation between body mass indexes with subsequent risk of coronary heart disease has been proven.[15] Even modest weight gain in adult population increases risk of coronary disease among men and women.[16] A study done by Konitzer, et al identified high body mass index as one of the factors associated with low ABI aside from age, serum cholesterol, smoking and diabetes. This study also showed that high BMI is associated with low ABI.

Data of this study revealed that ankle brachial pressure index of <0.9 is associated with coronary artery disease. This low ankle brachial pressure index is not only associated with CAD but also with atherosclerotic changes in extra coronary arteries and the prognosis of patients with CAD.[8]

The computed sensitivity and specificity of low ABI for CAD in this study population were 6% and 98% respectively. In a study done by Abbot, et al among men aging 70 and above, the sensitivity and specificity of ABI <0.8 for CAD were 17% and 94% respectively.

Simple measurement of ankle brachial pressure index even

in an out-patient setting detects not only peripheral vascular disease but also identifies patients who are high risk for coronary artery disease. In such patients, further evaluations of the coronaries are warranted considering the presence of abnormal coronary angiogram results among patients with low ABI.

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Original Article

Reference Values for the Six-Minute Walk Test in Filipino Adults

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The six-minute walk test (6MWT) has enjoyed widespread clinical application because of its convenience of administration, its closer similarity to activities of daily living than tests of maximal exercise capacity, and the lack of need for sophisticated equipment.

OBJECTIVES: This study aims to establish a reference value for the 6-minute walk test (6MWT) in terms of six-minute walk distance (6MWD) in healthy Filipino adults by: 1) knowing the best 6MWD after 2 repetitions in a group of subjects 20 – 65 years old, 2) investigating the effects of demographic and anthropometric measurements on the best 6MWD, and 3) formulating a reference equation for computing the ideal 6MWD.

MATERIALS AND METHODS: Two 6MWTs were performed on the same day in a 50-meter corridor by 88 male and 115 female healthy volunteers. Oxygen saturation (SaO_2), pulse rate, and the degree of dyspnea (modified Borg scale) were determined before and at the end of the walk. The greater 6MWD by each subject was analyzed.

RESULTS: The best 6MWD averaged 619 ± 65 m for men and 526 ± 37 m for women. This was inversely related to age (r = -0.23; p= 0.001), and directly related to height (r = 0.50; p=0.000), weight (r = 0.25; p=0.000), waistline (r = 0.15; p=0.034),with the resulting gender-specific regression equations: for men, 6MWD = (1.44 x $height_{cm}$) – (0.43 x age) – (0.05 x $weight_{kg}$) – (0.40 x $waistline_{cm}$) + 429m, for women, 6MWD = (1.81 x $height_{cm}$) – (0.97 x age) – (0.94 x $weight_{kg}$) – (0.73 x $waistline_{cm}$) + 387m.

CONCLUSION: This study was able to establish a reference value for 6MWT among healthy Filipino adults. The factors that could affect the distance walked are age, sex, height, weight and waistline.

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The ability to walk for a distance is a quick and inexpensive performance-based measure and an important component of quality of life since it reflects the capacity to undertake day to day activities or, conversely, functional limitation.[1]

The objective utility of the 6-minute walk test in evaluating the functional capacity of patients with chronic lung disease has enjoyed widespread clinical acceptance. In 1976, McGavin et al[2] introduced the 12-minute walk test to evaluate disability in patients with chronic obstructive pulmonary disease (COPD). Shortly thereafter, this was modified by Guyatt et al[3] to the 6MWT. The outcome measure commonly reported is the distance traveled in the allotted 6 minutes. The test can be performed with ease and with simple instructions by most patients, young or old, frail individuals or those with severe limitations due to an underlying medical problem without the need for expensive or sophisticated equipment. It is a test that has closer similarity to activities of daily living than tests of maximal exercise capacity.

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Commonly employed as a tool for assessment of exercise capacity in patients with COPD (pre and post reha- bilitation program),[4] congestive heart failure,[3,5] neuro- muscular disease, and those undergoing surgical interventions i.e. pre and post lung volume reduction surgery (LVRS) and lung transplantation,[6,7] the 6MWD in these patients are most often reduced. Most studies previously conducted utilized the 6MWT in patients with cardiac and/or pulmonary diseases. Few studies were done in healthy adults and most investigations were done on Caucasians.[8,9] The anthropometric factors of age, weight, and height were independently associated with the distance walked.[8] Other factors that could affect a 6MWD include body mass index (BMI), sex, and waist size.

Objective:

The purpose of this study is to establish a reference value for the 6MWT test in healthy Filipino adults by:

1. knowing the best 6MWD after 2 repetitions in a group of subjects with age ranging from 20 – 65 years old
2. investigating the effect of demographic and anthropometric measurements on the best 6MWD

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3. formulating a reference equation for computing the ideal 6MWD.

Materials and Methods

Study Population

A sample of 203 asymptomatic healthy Filipino volunteers' age 20 to 65 years old were included in the study. Data regarding age, sex, height, weight, waistline, smoking history, exercise history, medication use, medical history, and pertinent physical examination were gathered. A review of the subjects' medical records when available was done.

Exclusion criteria included the following: history of asthma, COPD (based on GOLD guidelines[9]) or any pulmonary disorders, any cardiovascular disease including arrhythmias and hypertension, neuromuscular disease, arthritis, and recent thoracic surgery. Informed consent was obtained from each subject before participation in the study.

Pulmonary Assessment

Spirometry was performed on all subjects using the Micro Loop (Micro Medical Limited, England) prior to the initiation of the test.

6-Minute Walk Test

The 6MWT was conducted in an internal hallway. The 50-m distance was marked on the floor with a colored tape and the subjects were instructed to walk from one end to the other at their own pace, while attempting to cover as much ground as possible in the allotted 6 minutes. The subjects were allowed to stop and rest at any time during the test but were instructed to resume walking as soon as they were able to. The subjects were encouraged with the standard statements "You're doing fine" or "Carry on the good work." The researcher or research assistant timed the walk and recorded the distance traveled. The oxygen saturation (SaO_2) was continuously monitored using a handheld pulse oximeter (BCI International, Wisconsin, USA). Blood pressure and pulse rate were recorded at the start and end of the test. The subjects were asked to indicate their current degree of shortness of breath on a scale of 0-10 (0 = nothing at all, 5 = severe, 10 = very, very severe) using the modified Borg dyspnea scale (see App. A) at the end of the walk. The subjects were also asked after the test if they experienced any of the following specific symptoms: dyspnea, chest pain, light headedness, or leg pain.

The test was done twice at 30 minute intervals. The test with the longer distance covered was recorded.

Statistical Analysis

Mean and standard deviation were determined.

Associations of the 6MWT with demographic and anthropometric parameters were carried out using correlational analysis and t-test. Regression equation determined for prediction of 6MWD given the different anthropometric and demographic parameters that were significantly independently associated with 6MWD was used. A p-value ≤0.05 was considered significant.

Results

Demographic, Anthropometric and Spirometric Data

These data from 203 healthy subjects are presented in Table 1. Eighty-eight of the subjects were men and 115 were women. All of these subjects were lifelong nonsmokers. Only 2 subjects reported performing regular exercise at least twice a week in the month preceding study participation. Spirometry results were normal.

Table 1. Characteristics of healthy subjects

Age	20 –65 years old
Gender	88 men, 115 women
Body Size	
Height	160.48 ± 8.33 cm
Weight	61.32 ± 12.69 kg
Waistline	78.12 ± 7.45 cm
Spirometry	
FEV_1 (L)	2.60 ± 0.65
FEV_1 (%P)	97.09 ± 9.3
FVC (L)	92.92 ± 0.73
FVC (%P)	93.72 ± 9.83
FEV_1/FVC (%)	88.37 ± 56

FEV_1- forced expiratory volume in 1 sec, FVC – forced vital capacity, L – liters, %P – percent of predicted

6MWD in Healthy Adults

Each patient completed the 6MWT in the hospital corridor. The mean distance covered for all patients was 566.2 ± 75.9 meters. The male subjects walked an average of 618.6 ± 65.1m while the female subjects covered 526.1 ± 56.8 meters in 6 minutes. Correlational techniques were used to investigate the relationships among pulmonary function, age, sex, height, weight and waistline (Table 2). There was significant inverse relationship between 6MWT and age (r = -0.23, p = 0.001). A significant direct relationship was found between 6MWT and height (r = 0.50, p = 0.000), weight (r = 0.25, p = 0.000), FEV_{1L} (r = 0.48, p = 0.000) and FVC_L (r = 0.54, p = 0.000). The effect of gender on the 6MWT in the healthy Filipino adults is shown in table 3. The 6MWD is significantly greater Waistline was weakly correlated with 6MWT (r = 0.15, p = 0.034).

in healthy men (618.64 ± 65.11m) than the healthy women (526.11 ± 56.73m) by an average of 92m. (p=0.000). Table 3 also shows the stratification of the best 6MWD by age and gender. The anthropometric factors that were significantly independently associated with 6MWT are reflected in the gender-specific reference equation for the 6MWD in healthy adults (Table 4).

Table 2. Correlation between 6MWD and anthropometric measures

	r value	P value
Age	-0.23	0.001
Height	0.50	0.000
Weight	0.25	0.000
Waistline	0.15	0.034
Pulse rate (pre)	-0.25	0.000
(post)	0.14	0.043
Systolic BP (pre)	0.10	0.123
(post)	0.22	0.001
		0.000
FEV_1 (L)	0.48	0.000
FVC (L)	0.54	

Table 3. Stratification of 6MWD by age and gender

Subject Age	Male		Female		P value
Subject Age	**Mean**	**SD**	**Mean**	**SD**	
20 – 29	628.26	76.7	555.97	46.3	0.000
30 – 39	628.89	61.5	519.05	58.5	0.000
40 – 49	606.78	38.6	513.22	58.2	0.000
50 >	576.86	71.7	504.39	45.2	0.004
All Ages	618.64	65.1	526.11	56.8	0.000

Table 4. Reference equations for 6MWD in healthy filipino adults

Men:

$$6MWD = (1.44 \times height_{cm}) - (0.43 \times age) - (0.05 \times weight_{kg}) - (0.40 \times waistline_{cm}) + 429\,m$$

Women:

$$6MWD = (1.81 \times height_{cm}) - (0.97 \times age) - (0.94 \times weight_{kg}) - (0.73 \times waistline_{cm}) + 387\,m$$

Discussion

The six-minute walk test has been validated by high correlation with workloads, heart rate, oxygen saturation, and dyspnea responses when compared to standard bicycle ergometry and treadmill exercise tests.[1,8,10-13] The self-paced 6MW test assesses the submaximal level of functional capacity and because most activities of daily living are performed at submaximal levels of exertion, the 6MWT may better reflect the functional exercise level for daily physical activities.[15]

Reference values are already available for 6MWT in healthy individuals of a wide range of age[8,10,16] but these published studies have involved American and European subjects only. This present study is the first to establish a reference value for healthy Filipino adults 20-65 years old. The anthropometric factors of age, weight, height and waistline were independently associated with the distance walked. The shorter distance walked by the elderly subjects is probably due to the gradual reduction of skeletal muscle mass and strength that generally occurs with aging as well as the presence of subclinical morbidity.[17,18]

Taller men generally walk with a longer stride, potentially affecting the efficiency of ambulation and resulting in longer distance walked[8,11]. The body weight also directly affects the work/energy required to perform the work.[14] However, if the subjects are obese and with bigger waistlines a shorter distance may be walked because of the increased workload imposed by these parameters.

The reference values from this study are lower as compared to those from Enright and Sherrill,[8] Troosters et al,[16] and Gibbons[10] et al probably because our populations are of relatively shorter height. As expected, the present study confirmed the work of others, that several demographic and anthropometric factors influence 6MWT in healthy subjects. Our result show that the 6MWT is inversely related to age, directly related to height, weight and waistline, and was greater in men than women in all age groups.

For the past ten years that the Pulmonary Rehabili- tation Program has been in existence at the Philippine Heart Center, the 6MWT has been used to assess the patients' degree of functional impairment at program entry and to quantify the degree of improvement after two months of exercise training intervention. The subjects were generally noted to walk short distances only but we did not have a reference value by which we could compare their 6MWTs, so we decided it was high time to establish a reference value for Filipinos. By knowing the reference value for the 6MWT we could provide a more accurate grading of the patient's disability. Also, the expected degree of improvement in 6MWD that is possible with an exercise training intervention in patients involved in cardiac and pulmonary rehabilitation could be more realistic. This could be done by comparing the entry 6MWT with the corresponding reference 6MWT for each patient.

Conclusion

To the authors' knowledge this study is the first study to provide reference values for 6MWT in healthy Filipinos 20 – 65 years old. The factors that could affect the distance walked are age, sex, height, weight and waistline with inverse correlation to age and a direct relationship with height, weight and waistline.

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Appendix A

The Modified Borg scale	
0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (maximal)

Original Article

Midterm Outcome of Off-pump Coronary Artery Bypass: a Multicenter Study

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BACKGROUND: ***The early outcome of OPCAB is widely accepted to bring benefits to patients by reducing the complications of a cardiopulmonary bypass. The procedure is relatively new in the Philippines and is increasingly gaining popularity. It is the objective of this study to determine the midterm outcome of patients who underwent Off-pump coronary artery bypass.***

MATERIALS AND METHODS: ***From January 2001 to December 2002, medical records of patients from 3 centers who underwent pure OPCAB surgery were reviewed. Their demographic, perioperative and postoperative data were collected. Patients were followed-up from a period of 12 to 30 months. It was done by interview through telephone and at the attending physicians' clinic. Event-free survival and the association between the co-morbidities and cardiac events were determined using appropriate statistical analysis.***

RESULTS: ***A total of 68 patients were included in the study. Midterm outcome showed 5 patients with cardiac related events. Only one patient had repeat revascularization via angioplasty. Overall result was satisfactory with event free survival of 90% at 30 months. No cardiac related death was reported. The co-morbidities, which showed significant statistical association with the outcome, were the presence of unstable angina and left ventricular dysfunction.***

CONCLUSION: ***OPCAB is a safe procedure with promising results. However, a greater number of subjects and longer follow-up period are needed to establish its superiority against the conventional CABG.***

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Keywords: coronary artery bypass; cardiopulmonary bypass; coronary artery bypass, off-pump

Myocardial revascularization without cardiopulmonary bypass is fast becoming a popular procedure in cardiac surgery. It has gained the attention of cardiac surgeons and likewise the cardiologists due to its relative safety and efficiency.

The use of cardiopulmonary bypass continues to be a cause of morbidity associated with cardiac surgery. It has been linked to a systemic inflammatory response that may play a role in undesirable patient outcomes. Associated morbidity with this inflammatory response may involve multiple organ systems such as the heart, brain, blood, lung, kidney, or gastrointestinal tract. Keeping the heart beating during the surgical procedure may eliminate this reaction during the coronary artery bypass operation.[1]

In a series of 300 patients who underwent off-pump coronary bypass, there was a significant reduction in intraoperative blood transfusion requirements, as well as a significant reduction in the incidence of neurologic, renal, and prolonged ventilatory complication.[2] For instance in a study by Patel et al, off-pump patients had a substantially reduced risk of post-op stroke and a significant reduction in post-op hospital stay.[3] The incidence of deep sternal wound infection in the off-pump coronary artery bypass (OPCAB) group was likewise reduced in the study by Peskan et al.[4] Furthermore, a multicenter study showed significantly lower rates of post-op atrial fibrillation and lower need for intraoperative and postoperative intraaortic balloon pump.[5] It is therefore concluded by several studies that off-pump coronary artery bypass grafting (OPCABG) is safe, cost-effective, and associated with excellent early clinical outcomes.[3,4,5]

The basic question therefore is whether OPCAB, which carries enough benefit for the patient, will be able to sustain good results such as maintaining graft patency. It is known that the technical aspect of this approach plays a very important role in the early as well as the long-term success of off-pump CABG. One has to take into account that coronary artery bypass surgery on a beating heart is a microsurgical procedure on a moving target and technically somewhat demanding when the procedure is performed through a limited access. It is basically easy to perform an anastomosis to the left anterior descending (LAD), diagonal branches, right coronary artery (RCA), and the first marginal branch without cardiopulmonary bypass (CPB). But the technical challenge arise when there

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is a need to revascularize the more distal and even posteriorly located marginal branches, since major displacement of the heart may cause hemodynamic instability.[8] Thus, the advantages and disadvantages of OPCABG would also depend on the surgeon. The anastomosis in the beating heart do require skill and experience and therefore not a technique for everybody. In our experience, the purpose of this study is to evaluate the midterm outcome of patients who underwent OPCABG procedure from different institutions under surgeons with special interest with this approach.

Objectives:

General

To determine the midterm outcome (12 months to 21/2 years) of patients who underwent OPCABG from three centers.

Specific

To determine the non-cardiac and cardiac-related events early post-operative and at midterm of patients who underwent OPCABG.

Materials and Methods

Study Design: Retrospective Cohort Study

Medical records of all patients who underwent OPCAB from Jan. 2001 to Dec 2002 were reviewed retrospectively. Only patients of surgeons with particular interest with OPCABG were included. Three centers participated in this study namely: Philippine Heart Center, Asian Hospital and Medical Center, and St. Luke's Medical Center.

The demographic characteristics, perioperative, and postoperative data of each patient were collected and analyzed accordingly. However, those who underwent redo-bypass, those converted to bypass, and patients with concomitant cardiac and non-cardiac surgery (i.e. aneurysms and valve replacement) were excluded. One to two and half-year follow-up of patients was undertaken through telephone interview and attending physicians' clinical follow-up records.

The primary endpoint of the pooled analysis will be all-caused mortality or a cardiac-related event at mid-term follow-up. Cardiac-related events include the need for further coronary revascularization (whether reoperation or angioplasty), coronary angiogram, myocardial infarction, congestive heart failure, arrhythmia, and recurrence of angina. The recurrence of angina was assessed clinically by interview and confirmed with a laboratory exam such as a coronary angiogram or stress test if possible. Non-cardiac events such as neurological and renal complications were likewise recorded.

Event-free survival was obtained with the use of survival analysis. Univariate analysis was used to determine the association of the co-morbidities to midterm outcome.

Surgical Technique

The chest is opened through a mid-sternal incision. The sternum is opened from the sternal notch to the xiphoid using a Sarn's saw. Bone wax applied over free edges of the sternum and periosteal bleeders are cauterized. The Falvalro retractor is then applied to the left hemisternum for proper exposure. Direct harvest of the left internal mammary artery (LIMA) was done simultaneously with the saphenous vein graft (SVG) harvesting. Unfractionated heparin (150 units/kg bodyweight) is given prior to the cutting of the LIMA distally.

After preparation of the LIMA and SVG, the mediastinum is exposed with a sternal retractor and the pericardium is opened at the midline. The pericardial sac edge is then sutured to the subcutaneous tissue or the sternal retractor using Silk-0 sutures. Inspection and palpation of the lesions is then performed and the target vessels are identified. For further exposure, the heart is lifted partially from its pericardial bed by tagging the posterior pericardium with a series of silk-0 sutures (3-4 deep posterior pericardial sutures) and clamped on the left side of the sternal incision. The octopus tissue 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 and reperfused for another 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 myocardial contractility is achieved by giving a short acting beta-blocker (esmolol with a dose of 0.5 -1 mg/kg BW). The heart rate should be maintained at a range of 100-110 systolic and this may be achieved by giving nitroglycerine (NTG) drip.

An octopus III tissue stabilizer is used to achieve mechanical stabilization. Stabilization is accomplished by suction domes underneath two parallel paddles, which are attached by tubing to a suction apparatus. The ideal suction should be able to generate a pressure of negative 400 mm Hg to fix the target site. The suction paddles are applied on both sides of the target vessel. The suctioning effect lifts up the heart rather than push is 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. 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, which is applied proximally and distally. The proximal aorto-SVG anastomosis is accomplished under partial occlusion using continuous running prolene 6-0

suture. During aortic partial cross clamping, there maybe transient increase in blood pressure and this may be controlled by deliberated hypotension by giving NTG, nicardipine or esmolol. Upon release of the aortic cross clamp, the patient is given sodium bicarbonate
(1 mg/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 contraction is treated with lidocaine bolus given at 1 mg/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 trendelenberg maneuver (redistribution of blood volume), fluid supplemen-tation or inotropic drug support.

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.

Table 1. Baseline characteristics

	N= 68
Male sex	53 (77.9%)
Age (years)	59 +/- 10.6
Diabetes	27 (39.7%)
Previous myocardial Infarction	20 (29.4%)
< 14 days	8 (40%)
> 14 days and < 30 days	2 (10%)
> 30 days	10 (50%)
Hypertension	42 (62.7%)
Hypercholesterolaemia	22 (32.4%)
Smoking history	44 (64.7%)
Unstable angina	
Angina class (CCS)	16 (23.5%)
I	8 (16.3%)
II	36 (73.5%)
III	5 (10.2%)
IV	0
Left Main	10 (14.7%)
LV Dysfunction	18 (26.5%)

A total of 68 patients with complete charts and follow-up were included in the study. Table 1 summarizes the baseline characteristics. The average age of the cohort was 59+/-10.6 years old, predominantly male population (77.9%), more than half (64.7%) were smokers, with main operative indication being chronic stable angina (CCS II) (73.5%). Hypertension represents to be the next main risk factor (62.7%), followed by diabetes mellitus (39.7%), then hypercholesterolemia at 32.4%. Left ventricular systolic dysfunction was seen in 26.5% of patients, while left main involvement exceeding 50% was present in 10 cases (16%).

The pre-existing co-morbidities are shown in Table 2.

Table 2. Other co-morbid factors

	N = 68
CVA	3
Carotid Artery Disease	1
AF, TIA, Carotid artery dse	1
Chronic Renal Insufficiency	1
Age > 75yrs	7
Malignancy	1
S/P TCT	1
COPD/Bronchial Asthma	2
TOTAL	17

Three patients already had non-hemorrhagic stroke prior to operation. All of them were hypertensive and smokers. One of them, a 62-year old male, with 3-vessel bypass developed a new stroke early post-op. His operation (OR) duration was 4.5 hours and was on ventilator for 8 hours only. No arrhythmias noted. Another patient with a history of transcient ischema attack (TIA), chronic atrialfibrillation and associated carotid artery disease pre-op developed another episode of TIA at the recovery room. She developed pneumonia post-op but otherwise well on follow-up. She underwent 4-vessel bypass graft involving the distal left circumflex (CLX) with OR time of 5 hours and ventilation time of 16 hours. A patient with isolated carotid artery disease on the other hand did not develop any neurologic complications. Two patients with chronic pulmonary disease did not require prolonged ventilatory support. They also did not develop pneumonia. Chronic renal insuficiency (CRI) was also found in another patient but did not progress post-operatively. Furthermore, a patient with renal tumor also underwent bypass with uneventful course and good follow-up. Lastly, a 53 year old male, nondiabetic, with old myocardial infarction (MI) and left ventricular dysfunction (LVD) underwent transcatheter therapy (TCT) a year prior to bypass. Patient developed pneumonia as well as wound infection postoperatively. His OR time was 7 hours and was on ventilation for 48 hours. He underwent bypass of the left anterior descending (LAD), right posterior descending artery (RPDA), and Optious maginaries (OM). On follow-up patient had recurrence of chest pain and shortness of breath. An average of 2.82+/-0.765 grafts per patient was achieved. Majority of patients had triple bypass grafts (57.4%). Table 3 summarizes the distribution of bypass grafts performed. LIMA was used in 96.6% of patients as a vascular conduit to bypass the LAD. Except in one case, SVG was used because LIMA was judged not suitable due to atherosclerosis and calcifications. In the rest of the coronary territories, SVG was

Table 3. Intraoperative characteristics

Graft Distribution	N=68
Grafts per patient	2.82 +/- 0.765
Number of grafts	
1	4 (5.9%)
2	14 (20.6%)
3	39 (57.4%)
4	11 (16.2%)
LIMA to LAD grafts	65 (96.6%)
SVG to	
LAD	1 (1.5%)
LAD branch	23 (33.8%)
RCA	22 (32.4%)
RPDA	24 (35.3%)
Distal Cx grafts	18 (26.5%)
Other arterial grafts	4 (5.9%)

Table 4. Early clinical outcomes

Outcome	N = 68
CP arrest (secondary to VT)	1 (1.4%)
Myocardial Infarction, Hemodialysis	0
Post-operative requirements for inotropes	
< 24 hours	21 (30.9%)
> 24 hours	11 (16.2%)
Arrhythmia	
Atrial fibrillation	10 (15%)
Neurologic complications	
Transient ischemic attack	2 (2.9%)
Stroke	2 (2.9%)
Infection	
Wound	2 (2.9%)
Pneumonia	5 (7.4%)
UTI	1 (1.4 %)
Reoperation for bleeding	2 (2.9%)
Transfusion (units/patient):	0.971 +/- 1.17
FWB	0.647 +/- 1.45
Packed cells	0.324 +/- 1.03
FFP	0.191 +/- 0.83
Platelets	
OR duration	4.22 +/- 1.24
Intubation (hrs)	7.59 +/- 6.48
RR/ICU stay (days)	3.26 +/- 3.27
Hospital stay (days)	7.58 +/- 3.60
Medication	
Beta-blocker	46 (68.8%)
Calcium antagonist	9 (13%)
Nitrate	35 (51.5%)
Aspirin/Plavix	60 (88.2%)
ACE-inhibitors	37 (54.4%)
Statins	24 (35.3%)
Others	21 (30.9%)

utilized. However there were 4 cases wherein radial artery and right internal mammary artery were used as surgeon's preference.

Early outcome is summarized in Table 4. Post-operatively, low doses of inotropics were used in 32 patients.30.9% of whom did not require it for more than 24 hours. No severe hypotension due to myocardial failure was noted and insertion of intraaortic balloon was never required. Ten patients experienced non-fatal arrhythmia, which consisted of acute atrial fibrillation. Unfortunately, one patient, a 68 year old female, suddenly had ventricular tachycardia post operatively and went into cardiopulmonary arrest. Patient was found to be hypokalemic. She was revived but had to be reopened because of arterial bleeding. Patient developed pneumonia and had prolonged hospital stay.

Reoperation for bleeding was again necessary in another patient who had cardiac compressive shock, a slipped knot in SVG was found. Patient had an episode of TIA after the repair and was discharged within a week.

No incident of perioperative myocardial infarction was identified. However, early postoperative stroke occurred in 2 patients. One of whom was already described above while the other was a 76 year old male with previous MI and LVD who also underwent triple bypass (LAD, RCA, and OM). His OR and ventilation time averaged 3.5 and 5.25 hours respectively. Transient ischemic attack was likewise noted in 2 patients as described earlier.

Infection was still reported in a small percentage of patients. Five had pneumonia, 2 had wound infection, and one had urinary tract infection (UTI). Only 3 of the patients with pneumonia had prolonged ventilatory support (14 to 48 hrs) and an extended hospital stay (9 to 14 days). They were diabetics with an OR time of 5 to 7 hours and 3-4 vessel grafting. Two of the patients were already described previously.

The average ventilation duration of all patients was 7.59 +/-6.48 hours which was fairly less than the mean duration of ventilatory support of conventional CABG at Philippine Heart Center (14.03+/-7.91).[7] Furthermore, the mean recovery room and intensive care unit stay was 3.26+/-3.27 days which was again comparatively less than the average ICU stay of patients who underwent conventional CABG (4.76+/-2.76days) at PHC.[7] Mean hospital stay from surgery to discharge was 7.58+/-3.60 days.

Blood transfusion requirement on the other hand was comparable with that of the foreign literature. Also summarized in Table 4 were the medications prescribed on discharge. Eighty-eight percent (88%) were prescribed with antiplatelet, followed by beta-blockers, ACE-inhibitors, nitrates and lastly statins. There was no early post operation in this study.

The midterm outcome of patients within 1-2 years is shown in Table 5. No cardiac related mortality was noted. The only mortality reported was that secondary to lung cancer

Table 5. Midterm clinical outcome

Outcome	N = 68
Death	
Cardiac related	0
Non-cardiac	1 (1.4%)
Cardiac events only	
Recurrent angina only	1 (1.4%)
Angina +PTCA	1 (1.4%)
Angina+Congestive heart failure	1 (1.4%)
Angina+Abnormal stress echo	1(1.4%)
Abnormal stress test with no angina	1(1.4%)
Myocardial infarction, coronary angiography, Redo CABG, arrhythmia	0
Non-cardiac event	2 (2.9%)
Stroke	0
Hemodialysis	
Total	**7**

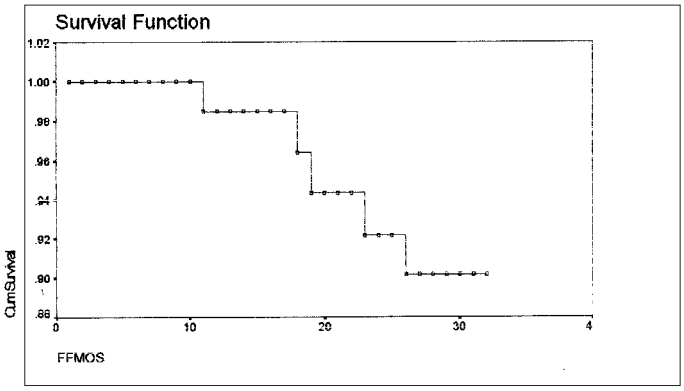

Figure 1. **Event survival curve**

which was discovered a year after the bypass surgery.

Five patients experienced recurrence of angina. First was a 53 year old male with a history of MI, LVD and TCT prior to surgery (described earlier) who presented with unstable angina. His postoperative course was complicated with pneumonia and wound infection. Patient experiencedrecurrence of chest pain 8 months post-op. Next was a 62 year old female also with history of heart failure who underwent 1-vessel bypass (LIMA to LAD). She continued to experience occasional shortness of breath with chest pain. Repeat 2-D echo showed an EF of 30% from the initial 37% (pre-op). Coronary angiogram was advised but did not comply. Third was a 76 y.o. male with 2-vessel graft (LAD/LCX) who submitted to a stress echo due to recurrence of angina. The result was abnormal. A stress test was likewise done in an asymptomatic patient, which also showed abnormal results. He is a 59 y/o male with hypertension and prior MI who had 4-vessel bypass graft in which a radial artery was used. No further work-up nor intervention done in both patients. Lastly, a 55 y/o hypertensive male who also presented with unstable angina underwent a 2-vessel bypass grafting (LIMA-LAD/SVG-RCA) with an uneventful peri and postoperative course. He had recurrence of angina and was subjected to TCT of the RCA and POBA of the ostial PDA 17th month post-op. The LIMA graft remained patent but the SVG was totally occluded at its origin. Patient was asymptomatic until the follow-up study (14 months after the angioplasty).

The event free survival is 90% at the end of the study (Fig.1). Univariate analysis showed that unstable angina and left ventricular dysfunction were the variables significantly associated with the occurrence of both cardiac and non-cardiac events with p-value of 0.03 and 0.04 respectively. Correlation with other co-morbidities such as age, sex, hypertension,diabetes, hyperlipidemia, previous MI, OR duration and arrhythmia was not statistically significant.

Discussion

OPCAB is relatively a new alternative procedure to the standard CABG in the Philippines. Conversely, other centers have been performing OPCAB a few years earlier than Philippine Heart Center. It is only in 1999 that the procedure was introduced using the Medtronic Octopus II Tissue Stabilizer System. Since then there was a growing interest toward the use of the procedure.

Several published data suggests that OPCAB outcomes is indeed equal if not better than those achieved with standardCABG in terms of reducing morbidities related with the use of CPB. In fact, local data regarding its early outcome at Philippine Heart Center showed lesser perioperative complications, lesser transfusion requirement, shorter operative and ventilation time as well as ICU and overall hospital stay.[7] This therefore translates to a lower hospital cost.

However, our main concern at present is whether the reduction of early morbidity with off-pump surgery will be at the expense of long-term benefits. As stated earlier, operating on the beating heart, with difficult access and exposure, might compromise the quality of anastomosis.

This paper assessed the midterm outcome of the beating heart surgery without CPB from 3 centers in the Philippines. There are minor variations in the operative technique but the overall outcome seems to be satisfactory.

Operative morbidity and mortality were gratifyingly low. There was no note of perioperative mortality, no conversion to conventional CABG was observed, and the use of inotropics was kept to minimal. Furthermore, there was no incidence of renal failure requiring hemodialysis. However, the incidence of atrial fibrillation (15%), stroke (2.9%), pneumonia (7.4%), and 2 cases of reoperation secondary to bleeding cannot beignored. Unfortunately, as per limitation of this study, no

comparison with the standard CABG was made. The above results are nonetheless comparable with foreign data. Majority of patients (57.4%) have a 3-vessel disease, which is therefore demographically representative of a regular population referred for coronary artery revascularization.

Though no angiographic assessment was done to better evaluate the patency of the graft, follow-up study yielded only 5 out of 68 patients with cardiac events while the rest remained asymptomatic. Only 2 had a non-cardiac event (Table 5). As observed, patients with cardiac events were mostly male, hypertensive, with prior MI and LV dysfunction, and anastomosis to the LAD/LCX/RPDA system. Unexpectedly, none of them was diabetic. All of them were maintained on anti-ischemic regimens. However, of interest was the patient who underwent repeat revascularization by angioplasty of the native vessels. Although the LIMA graft was patent, the SVG was totally occluded at its origin and the distal segment of a native vessel as well. These findings may be attributed to either the surgical technique or accelerated atherosclerosis, or both. Though it is difficult to isolate which one is the cause, the surgical technique may well be a factor since the vein graft was occluded at its origin. Anastomosis of the vein to the aorta does entail it more difficult in OPCAB than when done using the standard approach. On the other hand, consider that both the vein graft and the native vessels were occluded so that atherosclerosis may possibly play a role too.

Nonetheless, the presence of unstable angina and LV dysfunction prior to operation was the co-morbidities that demonstrated statistically significant correlation to the cardiac events using univariate analysis. This finding raises some concern regarding the safety of low ejection fraction in OPCAB. Though there are no hard data as to indication and patient selection for OPCAB, some authors are proposing that patients with LVD may be appropriate candidates for OPCAB because the depressing effects of cardioplegia are eliminated. Two foreign studies already addressed this issue and concluded that the immediate results were satisfactory but long-term follow-up is still mandatory.[9,10] Our study therefore suggests that caution should be made when subjecting patients with LVD to off-pump bypass in lieu of its relationship to the cardiac events.

The number of grafts and the target vessels did not have significant statistical correlation with the cardiac events. A number of patients in this study did receive multivessel grafting and the RCA/RPDA and distal CX were not spared (Table 3). As mentioned, grafting these vessels is quite difficult because it would entail elevating the heart vertically. This procedure did not increase the OR duration nor produced significant morbidities such as hypotension, perioperative MI nor acute graft occlusion.

Midterm follow-up of patients is also satisfactory. The results simply imply the advancing proficiency gained by the surgeons on the off-pump technique as well as higher quality of mechanical stabilization.

Presently, overall midterm outcome is gratifying. Our cumulative event free survival is 90%. Though the sample size is small, the result is almost comparative to foreign published data which showed 95-96% survival-rate.[11,12]

It is concluded that OPCAB is a safe technique, which can provide good early and midterm results. This approach should not be viewed in competition with CPB since both has a place in myocardial revascularization. Our data does not unquestionably establish superiority of OPCAB to conventional CABG at midterm even if the data showed no cardiac related mortality. A larger sample size and longer follow-up are necessary to demonstrate its validity in the long-term using this technique. In addition, careful patient selection and surgeon's experience are major factors that would definitely improve future outcome.

Recommendation

Aside from increasing the study population and having a longer follow-up period, it is recommended that a control group be included to have a better comparison between the benefits of OPCAB and the standard CABG.

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Original Article

Preservation of Tissue Heterografts: Comparison between Normal Saline-Treated and Glutaraldehyde-Treated grafts

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Use of biological grafts in cardiovascular surgery is an indispensable armamentarium in repairs. Faced with the dilemma of scarcity in the supply of autogenous conduits, we were encouraged by reports describing successful use of human venous allograft as an alternative conduit. Improvements in techniques of vein procurement and preservation have renewed interest in the glutaraldehyde preserved saphenous vein allograft.

OBJECTIVE: To evaluate and compare the acute and chronic reaction of subcutaneously implanted glutaraldehyde vs. normal saline preserved human saphenous veins in rabbits.

MATERIALS AND METHODS: Greater saphenous vein collected and divided into 2 groups. Stored in container with 0.6% glutaraldehyde and 0.9% isotonic saline solution respectively. Preserved grafts were implanted subcutaneously in thirty rabbits. Explantation was done after 5th, 14th and 30th day and examined grossly and under light microscopy for foreign body reaction, neovascularization and evidence of inflammatory reaction in the intima, media and adventitia statistical analysis using Mann-Whitney and Kruskal-Wallis.

RESULTS: Acute reactions to glutaradehyde treated grafts showed no inflammatory cells, no foreign body reaction and almost no neovascularization. Chronic reaction was minimal. Reactions to NSS- preserved grafts showed significant inflammatory cells in both acute and chronic phases. Foreign body reaction was prominent on the 14th to the 30th day. Neovascularization was consistently observed from the 5th to the 30th days post-explantation.

CONCLUSION: This study indicates that unmodified veins are normally antigenic and that this antigenicity is reduced with glutaraldehyde treatment. The glutaraldehyde treatment had significant influence on antigenic suppression of arterial homografts which may play a significant role in graft patency.

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Keywords: transplantation, heterologous; tissue preservation; sodium chloride; glutaral;

The use of biological grafts in cardiovascular surgery be it homografts or heterografts is an indispensable armamentarium in repairs. Widespread use of these grafts has resulted in excellent outcomes. The use of autogenous greater saphenous vein has remained to be the preferred graft material for the majority of vascular reconstructions.[1] Recently, the use of saphenous vein graft as an alternative material for shunts and other reconstruction in congenital heart disease has come into play.[2,3,4]

Unfortunately, the use of available autologous vein may become difficult in many patients. Patient's vein may be unsuitable for use because of occlusion from thrombophlebitis, dilatation from varicosities, inadequate vein caliber, and deficient as a result of previous vein stripping and/ or venous anomaly.[5]

The use of prosthetic conduit has been a surgical practice by some as an alternative graft for patients with unsuitable autogenous veins.[6] Despite the obvious advantage of these grafts their use has not given promising results in graft patency comparable to those of autogenoussaphenous veins.[5] Their high propensity for prosthetic graft infections is another issue. Complications such as serous leakage, graft kinking and pseudoaneurysm formation are common to these grafts.[7,8,9] Although a prosthetic conduit can be used for arterial reconstruction in the presence of an overt infection, it is imperative that it is positioned in a sterile extra anatomic plane remote from the infected field. When remote bypass is not feasible, the use of autologous tissue grafts has been proven to be durable and resistant to infection and it represents the best material for direct reconstruction in an infected field.

Having faced with the dilemma of scarcity in the supply of autogenous conduits, we were encouraged by earlier reports describing successful use of human venous allografts as an alternative conduit.[5,6] Recent improvements in techniques of vein procurement and preservation have renewed interest in the glutaraldehyde preserved saphenous vein allograft as an alternate conduit.

The importance of antigenic differences between donor and recipient is largely taken into consideration. Considerable evidence indicates that allograft antigenicity plays a major role

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in the failure of venous allografts when used as arterial replacements.[10]

The choice of appropriate preservatives in these biological grafts remains a significant influence in their patency. The effect of glutaraldehyde pretreatment, a cross-linking type of fixative, is known to preserve the morphological integrity and renders a graft less permeable to antibodies.[11] Recent reports suggest that glutaraldehyde preservation of venous allografts may reduce allograft antigenicity while preserving allograft viability.[12,13]

Objective

To evaluate and compare the acute and chronic reaction of subcutaneously implanted glutaraldehyde vs. normal saline preserved human saphenous veins in rabbits.

Materials and Methods

Saphenous Vein Collection and Preservation

The greater saphenous vein was collected during coronary artery bypass operation in patients operated from March 2002 to August 2002. Patients enrolled in the study were aged 40-60 years old. Non-diabetic, no history of peripheral arterial occlusive disease and any deep vein insufficiency nor thrombosis, no greater saphenous vein varicosities. Informed and written consents of the study were made prior to the operation.

The greater saphenous vein was harvested using the no-touch technique and dilated with a normal isotonic solution with its branches ligated. It was stored in heparinized autologous blood at room temperature until revascularization procedure was completed. The unused vein was collected under sterile condition, pre-cut to 5 mm length and rinsed with isotonic (0.9%) saline solution. The final product was placed in sterile sealed glass container-A with 0.6% glutaraldehyde in phosphate buffered saline (PBS) and a second sterile sealed glass container-B with isotonic saline solution. These grafts were kept in the refrigerator at 4^{o}C for 3-38 days prior to implantation.

Blood Examination

Blood samples were taken from all donor patients and serologic test for hepatitis, HIV, cytomegalovirus and syphilis as part of the preoperative evaluation was requested. Positive results from these tests were discarded and excluded from the study.

Graft Implantation and Explantation

Thirty (30) healthy rabbits were selected for the study. The rabbits were given pre-op antibiotic (Ampicillin IV) computed to their weight. Right and left inguinal areas were shaved, prepped and anesthetized with 2% lidocaine. Two to three centimeter inguinal incision made and implantation of the preserved vein grafts. Using a glutaraldehyde preserved graft on one inguinal area and a NSS preserved graft on the other.

The preserved graft was prepared prior to implantation by rinsing them to a previously prepared 3 basins with the 1st basin with a gentle back-and-forth motion for 2-3 minutes and repeated in the remaining basins. Samples for gram stain and culture was obtained and submitted to the laboratory. Implantation in the subcutaneous area and anchored with prolene 6-0 suture.

Explantation of the tissue sample was done under sterile set-up after the 5th, 14th, and 30th day. Ten rabbits were allotted for each explantation day. All tissue samples acquired was fixed using formalin, labeled and coded. All tissues were sent to the pathologist for histological study.

Histologic Study

The tissue was examined by gross examination and under light microscopy after staining with hematoxylin and eosin by periodic acid shiff (PAS) method. Evidence of inflammatory reaction in the intima, media, and adventitia were noted. Foreign- body reaction, and neovascularization were also observed.

Statistical Analysis

Comparison between two groups was made with Mann-Whitney . Analysis of variance using Kruskal-Wallis H. A value of $p<0.05$ was considered significant.

Results

All samples of vein grafts collected for gram staining and culture showed no bacterial growth after 48 hours of incubation except for 2 vein grafts preserved in normal saline (NSS) which showed a growth of coagulase negative staphylococcus. These 2 vein grafts were later discarded and were not included in the study.

All explanted vein grafts from the inguinal area showed neither gross signs of tissue necrosis nor signs of mineralization for both glutaraldehyde (Grp-A) and NSS (Grp-B) preserved groups.

Microscopic examination of the intima of the veins in Grp-A showed no signs of inflammatory reaction on the 5th day post explantation but there was a trend of increasing tissue reaction by the 14th to 30th day post explantation (Table 4) ($p=0.048$).

At the 14thday, mild reaction with presence of lymphocytes was noted with Grp-A. Presence of plasma cells and monocytes signifying chronic reaction was seen on the 30th day post explantation (Table 2 & 3). Group-B showed

constant mild to moderate reaction to inflammatory cells from the 5th-30th day post explantation. With presence of minimal neutrophilic infiltration in the intima on the 5th day, lymphocytes and macrophages on the 14th day and plasma cells and monocytes on the 30th day (Table 1,2,3 & 4) (p=0.18).

There was a significant difference of inflammatory reaction on the intima between the 2 groups. Occurring predominantly in the NSS preserved group (NSS) (Grp-B) and much less in the glutaraldehyde group (Grp-A) (p=0.0005, p=0.53, p=0.014 on the 5th, 14th and 30th respectively).

Media and adventitia of the vein showed no inflammatory reaction on the 5th day on Grp-A with gradual mild reaction by the 14th- 30th day post explantation (p=0.012 and p=0.045 respectively) (Table 4,5 & 6). Group-B showed no significant difference on tissue inflammatory reaction on the media and adventitia from the 5th-30th day of explantation. It showed a constant significant inflammatory cell reaction (p=0.54 and p=0.89 respectively) (Table 5 & 6).

Foreign body reaction was not observed in Grp-A. Group-B showed significant difference on the 14thday (p=0.003) (Table 7).

Neovascularization was noted more with time implanted on Grp-A. While in Grp-B neovascularization was noted from the start, 5th-30th day with no significant difference (p=0.303) (Table 7).

Discussion

Saphenous vein homograft has proved to be an acceptable conduit for arterial reconstruction since initial description of its use. Many authors have become less enthusiastic because of suboptimal long-term outcome, probably related to chronic rejection of the donor graft.14

We designed experimental models to study whether the preservation process alters antigenicity.

In our experiment, samples of the explanted graft at 5, 14 and 30 days were compared between glutaraldehyde-preserved grafts and NSS-preserved as controls.

The glutaraldehyde treated grafts showed significantly less infiltration of inflammatory cells than the NSS graft in the intima, media and adventitia. This was prominent more during the acute phase with some infiltration on the chronic phase but still with a significant difference between the NSS group.

Glutaraldehyde, commonly being used as a cross-linking fixative, has a characteristic of rendering samples better preservation of morphological integrity and give less permeability of antibodies.[11,14,15,16] The antigenicity of the glutaraldehyde-treated grafts is very poor, almost undetectable.[17,18] Microscopic examination suggests that the mechanism of rejection of the glutaraldehyde treated grafts is similar to that operating in the rejection of an inert foreign body.[19,20,21] Cellular structures are preserved by combining with lipids, especially in membranes and by insolubilizing some proteins without coagulation.

The microscopic examination of neovascularization formation on the glutaraldehyde preserved group showed almost no reaction on the acute phase (5thday). No significant difference on neovascularization was seen from the 14th-30th days between the 2 groups.

Chemical reactions of gluraldehyde with proteins is fast (minutes to hours), but the larger molecule penetrate the tissue slowly thus needing longer immersion time.[22] This will show soft but becoming progressively stiffer with minimal shrinkage in size as seen in the glutaraldehyde-preserved grafts.

NSS-preserved grafts showed significant consistency in inflammatory cells infiltrating the whole layer of the vein graft. From the 5th to the 30th day, the presence of neutrophilic infiltrates and lymphocytic infiltrates to transmural infiltration of macrophages were noted. This signifies acute and chronic rejection.

The degree of antigenicity is related to the degree of inflammatory cell infiltration, neovascularization and foreign body reaction.

Acute reactions to glutaradehyde treated grafts showed no inflammatory cells, no foreign body reaction and almost no neovascularization. Chronic reaction was minimal with inflammatory cells. No foreign body reaction to glutaraldehyde treated group was seen during the acute and chronic phases.

Reactions to NSS-preserved grafts showed significant inflammatory cells in both acute and chronic phases. Foreign body reaction was prominent on the 14th to the 30th day post-explantation.

Conclusion

This study indicates that unmodified veins are normally antigenic and that this antigenicity is reduced with glutaraldehyde treatment. The glutaraldehyde treatment had significant influence on antigenic suppression of arterial homografts which may play a significant role in graft patency.

Studies to pursue will include the graft patency of these glutaraldehyde preserved heterografts when exposed to arterial (high pressure) and venous (low pressure) environment. Recommendation of the study is the use of these glutaraldehyde preserved allografts in congenital cardiac surgery as alternative materials for prosthetic grafts in shunt surgery. Proven to be lesser antigenic and more resistant to infections thus increasing patency.

Clinical implication of the study include use of glutaraldehyde tissue preservation in allografts and heterografts as an alternative to cryopreservation, which may pave way to a tissue bank in a third world country.

Table 1. Grafts Explanted at 5th day post-implantation. (A-Glutaraldehyde preserved grafts; B-NSS preserved grafts ; + Mild ++ Moderate +++ Severe; For foreign body & neovascularization:- Negative + Positive)

RABBIT	Intima	Media	Adventitia	Foreign Body Rxn	Neovasculari-zation
Rabbit 1					
A	-	-	-	-	-
B	++	++	++	-	+
Rabbit 2					
A	-	-	-	-	+
B	+	+	+	-	+
Rabbit 3					
A	-	-	-	-	-
B	+	+	+	-	+
Rabbit 4					
A	-	-	-	-	-
B	+	-	+	-	+
Rabbit 5					
A	-	-	-	-	-
B	+	++	-	-	+
Rabbit 6					
A	-	-	-	-	-
B	+	+	+	-	+
Rabbit 7					
A	-	-	-	-	-
B	+	+	+	-	+
Rabbit 8					
A	-	-	-	-	-
B	+	+	+	-	-
Rabbit 9					
A	-	-	-	-	-
B	-	+	+	-	+
Rabbit 10					
A	-	-	-	-	-
B	+	++	++	-	+

Table 2. Grafts Explanted at 14th day post-implantation. (A-Glutaraldehyde preserved grafts; B-NSS preserved grafts);+ Mild ++ Moderate +++ Severe; For foreign body & neovascularization: - Negative + Positive)

RABBIT	Intima	Media	Adventitia	Foreign Body Rxn	Neovasculari-zation
Rabbit 1					
A	+ PM	-	++ PMN	-	+
B	-	-	+ PMN	-	-
Rabbit 2					
A	-	-	+	-	-
B	-	-	+	+	+
Rabbit 3					
A	-	-	+	-	+
B	+	+	+ PM	+	+
Rabbit 4					
A	-	-	-	-	+
B	-	+	-	-	+
Rabbit 5					
A	-	-	-	-	+
B	++	++	++	-	+
Rabbit 6					
A	-	-	-	-	+
B	+	+	+	+	-
Rabbit 7					
A	-	-	-	-	-
B	+	+	+	+	+
Rabbit 8					
A	-	-	-	-	-
B	-	+	+	++	-
Rabbit 9					
A	-	-	-	+	-
B	+	+	+	+	+
Rabbit 10					
A	-	-	-	-	+
B	-	++	++	++	-

Table 3. Grafts Explanted at 30th day post-implantation. (A-Glutaraldehyde preserved grafts; B-NSS preserved grafts;+ Mild ++ Moderate +++ Severe; For foreign body & neovascularization:- Negative + Positive)

RABBIT	Intima	Media	Adventitia	Foreign Body Rxn	Neovasculari-zation
Rabbit 1					
A	-	+	+	-	+
			PMN		
B	-	-	+	-	-
Rabbit 2					
A	-	-	+	-	-
B	+	+	+	-	-
Rabbit 3					
A	+	+	+	-	+
B	+	+	+	-	+
			PMN		
Rabbit 4					
A	++	-	-	-	+
B	++	-	-	-	+
Rabbit 5					
A	++	++	++	-	+
B	++	++	+	-	+
Rabbit 6					
A	-	-	-	-	-
B	++	+	+	-	+
Rabbit 7					
A	+	+	+	-	-
B	+	+	+	-	+
Rabbit 8					
A	-	-	-	-	+
B	+	++	++	-	-
Rabbit 9					
A	-	-	-	-	+
B	+	+	+	-	+
Rabbit 10					
A	-	-	-	-	+
B	++	++	++	-	+

Table 4. Comparison of inflammatory cell reactions on the INTIMA between glutaraldehyde-preserved group (A) and NSS-preserved group(B)

	INTIMA	5th	14th	30th	P value
A	No Reaction	10	9	6	0.048997
	Mild	0	1	4	
	Moderate	0	0	0	
	Severe	0	0	0	
B	No Reaction	2	5	1	0.181125
	Mild	7	4	7	
	Moderate	1	1	2	
	Severe	0	0	0	
	P value	**0.00045**	**0.053266**	**0.013751**	

Table 5. Comparison of inflammatory cell reactions on the MEDIA between glutaraldehyde-preserved group(A) and NSS-preserved group (B)

	MEDIA	5th	14th	30th	P value
A	No Reaction	10	10	6	0.011545
	Mild	0	0	4	
	Moderate	0	0	0	
	Severe	0	0	0	
B	No Reaction	1	2	2	0.536536
	Mild	6	6	7	
	Moderate	3	2	1	
	Severe	0	0	0	
	P value	**0.000150**	**0.000514**	**0.058297**	

Table 6. Comparison of inflammatory cell reactions on the ADVENTITIA between glutaraldehyde-preserved group(A) and NSS-preserved group (B)

	ADVENTITIA	5th	14th	30th	P value
A	No Reaction	10	6	5	0.044215
	Mild	0	3	5	
	Moderate	0	1	0	
	Severe	0	0	0	
B	No Reaction	1	1	1	0.892724
	Mild	7	6	7	
	Moderate	2	3	2	
	Severe	0	0	0	
	P value	**0.000132**	**0.0301778**	**0.029948**	

Table 7. Comparison of foreign body reactions and neovascularization between glutaraldehyde-preserved and NSS-preserved grafts

A. GLUTARADEHYDE-PRESERVED GRAFT		5th	14th	30th	P value
FOREIGN BODY REACTION	No Reaction	10	4	9	0.003099
	With Reaction	0	6	1	
NEOVAS-CULARI-ZATION	No Reaction	1	4	3	0.30325
	With Reaction	9	6	7	
B. NSS-PRESERVED GRAFT					
FOREIGN BODY REACTION	No Reaction	10	10	10	1.00
	With Reaction	0	0	0	
NEOVAS-CULARI-ZATION	No Reaction	9	4	3	0.0157
	With Reaction	1	6	7	

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Original Article

Association of the Intima-Media Thickness of the Common Carotid Artery and Brachial Artery Flow-Mediated Dilation with the Extent, Severity, and Jeopardy Score of Coronary Artery Disease

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Measurement of the carotid artery intima-media thickness (IMT) assesses the extent and severity of atherosclerosis. It is directly correlated with cardiovascular disease affecting the cerebral, peripheral, and coronary artery vascular beds. Vascular endothelial function exemplified by flow-mediated dilatation (FMD) plays a pivotal role in the pathogenesis of atherosclerosis and enhances the risk of future cardiovascular events.

MATERIALS AND METHODS: Forty-six patients who underwent coronary angiography at the Philippine Heart Center (PHC) had quantitative measurement of the distal common carotid artery IMT and brachial artery FMD. Relation between carotid artery IMT and brachial artery FMD with the extent, severity, and jeopardy scores of CAD.

RESULTS: There were 40 (87%) men and 6 (13%) women included in the study with a mean age of 60 ± 11 years. Seven patients (15.7%) had no coronary vessels with ³70% stenosis and 26 (56.5%) had three-vessel disease. The mean extent of CAD score was 28.87 ± 15.08 (range, 0 to 64.5). The mean jeopardy score was 7.70 (range, 0 to 12). The mean maximum IMT of the distal common carotid artery was significantly correlated with the extent score of CAD IMT (r=0.309, p=0.037) but was not significantly correlated with the severity and jeopardy scores of CAD. Age and the number of pack-years in the smoking history were found to be significantly correlated with maximum IMT (r=0.417, p=0.004 and r=0.396, p=0.034, respectively). A significant positive correlation was found between FMD and the severity score of CAD (r=0.321, p=0.030) but not with the extent and jeopardy scores of CAD.

CONCLUSION: This study shows a significant positive correlation between the mean maximum IMT of the far wall of the distal common carotid artery with the extent score of CAD, age and the number of pack-years in the smoking history.

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Keywords: carotid arteries; coronary artery disease; jeopardy score; brachial arteries;

Coronary angiography and standard functional tests have been the cornerstone of the diagnosis and management of coronary artery disease. Given that early atherosclerosis involves the endothelium of many arteries, a noninvasive test may provide information about arterial anatomy that may be pertinent to the coronary arteries.[1] Measurement of carotid artery IMT using ultrasound assesses the extent and severity of atherosclerosis. [2]

The intima-media thickness (IMT) of the carotid artery is defined as the distance between the lumen-intima interface and the media adventitia interface.[2,3] Carotid ultrasound measurement of the IMT is a safe, standard, and validated method that permits qualitative measurements.[3] This may have clinical application as a marker of atherosclerosis development in the setting of various risk factors, a marker of response to therapy for atherosclerosis, and a marker of advanced vascular disease.

In the Cardiovascular Health Study, carotid IMT was independently associated with left ventricular mass after adjustment for other factors.[4] Among men and women 65 years of age or older without a history of cardiovascular disease, increased carotid IMT was directly associated with an increased risk of myocardial infarction and stroke.[5] Another study with a mean follow-up of among subjects ≥55 years provides evidence that an increased common carotid IMT was associated with future cerebrovascular and cardiovascular events.[6]

Several prospective, controlled population studies have shown that a reduction in IMT based on the use of lipid-lowering therapy correlated with reduced cardio-vascular events. Slowing of IMT progression also decreases the risk

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of coronary events as evidenced by the long-term follow-up of the Cholesterol Lowering Atherosclerosis Study (CLAS) cohort.[7]

As a surrogate marker of atherosclerosis, carotid IMT may provide a noninvasive assessment of the presence of cardiovascular disease and the rate of progression or regression of atherosclerosis. Nevertheless, the predictive accuracy of carotid IMT as a surrogate marker of coronary artery disease may be debatable. In a study of 350 patients undergoing coronary angiography, mean carotid IMT was weakly but significantly correlated to both severity and extent of CAD (r=0.26, p<0.0001).[8] In a community study, the common carotid IMT was increased in older subjects with asymptomatic myocardial ischemia as evidenced by exercise ECG alone or in combination with thallium scan. Further regression analysis revealed that for each 0.1-mm increase in IMT was associated with a 1.91-fold (95% CI, 1.46 to 2.50; P<0.0001) increased risk for concordant positive exercise tests or manifest CAD, independent of other significant predictors of CAD.[9]

Endothelial dysfunction plays a pivotal role in the pathogenesis of atherosclerosis. The vasodilator response in conduit arteries to an increase in blood flow is thought to be endothelium dependent. This flow-mediated dilation has been demonstrated in the epicardial coronary arteries. High-resolution ultrasound has been used to assess brachial artery response to the increase in blood flow that occurs after 5 minutes of ischemia (upper arm occlusion), the normal brachial artery increases its diameter by up to 20%. This has been used in patients with atherosclerosis, cardiac risk factors, and depression. This technique is sensitive and reproducible.[10,11,12,13]

Flow-mediated vasodilation in the brachial artery has been demonstrated to have a close relation to coronary artery endothelium-dependent vasomotor responses. Other strong predictors of reduced brachial dilator responses to flow were baseline brachial artery diameter, the presence of coronary artery disease, and cigarette smoking. The positive predictive value of abnormal brachial dilation (<3%) in predicting coronary endothelial dysfunction is 95%.[14]

The study outcomes may vary among different cultures. It may be difficult to extrapolate findings among individuals with different ethnic backgrounds. This study hopes to determine the correlation of the carotid IMT and flow-mediated brachial artery vasodilation with the extent, severity, and jeopardy score of CAD among Filipinos. The result of this study may help us predict the extent, severity, and/or jeopardy scores of CAD based on a simple, non-invasive measurement of the carotid IMT and brachial artery FMD. If a significant correlation is indeed found, this may usher in prospective studies that may help us in the prognostication of a patient with CAD for occurrence be done in conjunction with this is improvement of these noninvasive measurements with intensive risk-factor modification. This may later help the clinician in the follow-up of patients' prescribed intensive treatment to decrease the atherosclerotic burden.

Research Objectives

a. General Objective

To determine the correlation of carotid IMT brachial artery FMD with the extent, severity, and jeopardy scores of CAD.

b. Specific Objectives

1. To determine the carotid IMT among patients who underwent coronary angiography at the Philippine Heart Center.
2. To determine the brachial artery FMD among patients who underwent coronary angiography at the PHC.
3. To determine the severity, extent, jeopardy scores of CAD among patients who underwent coronary angiography at the PHC.

Materials and Methods

Study Population

We studied 46 patients who underwent coronary angiography at PHC from August to October 2003. Patients who have previously undergone coronary artery bypass surgery were excluded. Patients who had requests for carotid duplex scan on top of the coronary angiography were included. Eligible patients who signed the informed consent form were included in the study.

Research Design

This is a cross-sectional study.

Carotid IMT measurement

All measurements of the carotid IMT were done at the Vascular Laboratory of the PHC. High-resolution B-mode carotid ultrasonography was performed using Logiq 700 machine (General Electric) with 7-MHz linear-array transducer. The subjects were examined in the supine position. The right and left common carotid arteries (CCA) were examined with the head turned approximately 45 degrees to the contralateral side. The transducer was manipulated so that the near and far walls of the CCA will be parallel to the transducer footprint and the lumen diameter maximized in the longitudinal plane.[1,2,7,8,9]

A region about 1.5 cm proximal to the carotid bifurcation was identified, and the video image was digitized by a frame grabber attached to a personal computer. Two measurements of the IMT of the far wall of the distal common carotid artery on each side were performed using a computerized edge detection system. The mean of the maximum IMT measurements were used in the analysis.[1,2,7,8,9] Duly trained vascular sonographers, who were not aware of the coronary arteriography results, performed the measurement.

Brachial Artery FMD

Flow-mediated dilation of the brachial artery was determined with the patient in the supine position. Images were obtained using a cuson machine with linear array transducer. After baseline measurements, a blood pressure cuff was inflated to 200 mm Hg over the proximal portion of the right forearm for 5 minutes. The lumen diameter of the brachial artery was again measured 45 to 60 seconds after the release of the cuff. Four determinations for each stage were made coincident with the R wave and then averaged. The end of the measurement was the percent change in diameter in response to reactive hyperemia. The percent change was computed by dividing the difference of the post- and pre-reactive hyperemia diameters by the pre-reactive hyperemia diameter then multiplied by 100. All measurements were performed by either of three trained vascular sonographers, who were unaware of the CAD status of the patient. [11,12,13]

Coronary Angiography

Coronary angiographies were performed at the Invasive Cardiology division by the designated angiographers or attending physicians via the femoral artery using the standard Judkins technique.

Data Collection

The data on the IMT measurement of the patients were collected by the researcher. Two angiographers graded the severity, extent, and jeopardy scores of the coronary lesions. They were not informed about the IMT and FMD measurements of the subjects. The data sheet also contained the patient's name, age, sex, diagnosis, and risk factors for CAD. (See Appendix A)

Coronary angiograms were interpreted visually and scored according to three techniques, as follows:

a) Severity score

This pertained to the number of vessels with a significant stenosis (≥70% reduction in lumen diameter). Scores ranged from 0 to 3, depending on the number of vessels involved. Left main stenosis ≥50% was scored as two-vessel disease.[15]

b) Extent score

This score was developed to indicate the proportion of the coronary arterial tree involved by angiographically detectable atheroma. The proportion of each vessel involved by atheroma, identified as luminal irregularity, will be multiplied by a factor for each vessel: left main artery, 5; left anterior descending artery, 20; main diagonal branch, 10; first septal perforator, 5; left circumflex artery, 20; obtuse of future cardiovascular events. Another study that can marginal and posterolateral vessels, 10; right coronary artery, 20; and main posterior descending branch, 10. When the major lateral wall branch was a large obtuse marginal or intermediate vessel, this was given a factor of 20 and the left circumflex artery, a factor of 10. When a vessel is occluded and the distal vessel not fully visualized by collateral flow, the proportion of vessel not visualized was given the mean extent score of the remaining vessels. [15] The scores for each vessel or branch were added to give a total score out of 100 that is the percentage of the coronary intimal surface area involved by atheroma. [15]

c) Jeopardy score

For purposes of determining the jeopardy score, the coronary circulation is considered as six arterial segments: the left anterior descending artery, the major anterolateral (diagonal), the first major septal perforator, the left circumflex artery, the major circumflex marginal branch and the posterior descending branch. In patients with a left dominant system, the right coronary artery was assigned no points. Each segment with a 70% or greater stenosis was given a score of 2 points. Each vessel distal to a 70% or greater stenosis was also given a score of 2 points. The maximal number of possible points was 12.[16]

Data Analysis

Data analysis was performed with SPSS for Windows 10.0 in the Preventive Cardiology Division of this institution. Descriptive data were expressed as mean ± SD. Univariate analysis of the associations between CAD scores, atherosclerotic risk factors and medications with carotid IMT or FMD was done using Spearman correlation coefficient for continuous variables and ANOVA for nominal variables.

Limitations

The variability between invasive cardiologists in the conduct of the study cannot be accounted for in this study. Lipid determinations were available in only 52.2% of subjects.

Results

There were 40 (87%) men and 6 (13%) women included in the study with a mean age of 60 ± 11 years. Fourteen (30.4%) were current smokers and 18 (39.1%) were former smokers. The average dose of smoking among the 32 smokers was 33.7 ± 23.7 pack-years. Only 11 patients (23.9%) had diabetes mellitus, but 33 (71.7%) hadhypertension. Eighteen (39.1%) had a positive family history of premature coronary heart disease. Dyslipidemia was noted in 23 of the 24 patients with lipid studies. Table 1 describes the demographic profile of the subjects.

Seven patients (15.2%) had no coronary vessels with ≥70% stenosis, 6 (13.0%) had single-vessel CAD, 7 (15.2%) had two-vessel CAD, and 26 (56.5%) had three-vessel CAD. The mean extent score of CAD was 28.87 ± 15.08 (range, 0 to 64.5). The mean jeopardy score was 7.70 ± 4.28 (range, 0 to 12).

Table 1. Clinical characteristics of the study patients

	N (%)
Age, *years ± SD*	60.33 ± 11.37
Male/female	40/6
BMI, *kg/m²*	24.31 ± 2.92
Hypertension	33 (71.7)
Family History of Premature CHD	18 (39.1)
Former smokers	18 (39.1)
Current smokers	14 (30.4)
Diabetes mellitus	11 (23.9)
Dyslipidemia *(n=24)*	23 (95.8)
Total cholesterol, *mg/dl (n=24)*	193.1 ± 39.2
LDL-cholesterol, *mg/dl (n=21)*	125.1 ± 35.2
HDL-cholesterol, *mg/dl (n=21)*	50.3 ± 19.9
Triglycerides, *mg/dl (n=22)*	148.9 ± 101.2
Ejection fraction, *%*	56.86 ± 15.07
Mean maximum CCA IMT, *mm*	1.10 ± 0.12
Flow-mediated dilatation, %	11.46 + 12.35
Predilatation brachial artery diameter, *mm*	4.97 ± 0.79
Medication use:	
Aspirin	29 (63.0)
Nitrates	28 (60.9)
Statins	26 (56.5)
ACE inhibitor	26 (56.5)
Beta-blocking agent	24 (52.2)
Clopidogrel	18 (39.1)
Angiotensin receptor blocker	10 (21.7)
Dihydropyridine calcium channel blocker	7 (15.2)
Nondihydropyridine calcium channel blocker	6 (13.0)

Correlation of Carotid IMT with CAD and Risk Factors

The mean maximum IMT of the distal common carotid artery was significantly correlated with the extent score of CAD IMT (r=0.309, p=0.037) but was not significantly correlated with the severity and jeopardy scores of CAD. Age was found to be significantly correlated with maximum IMT (r=0.417, p=0.004) as well as the number of pack-years in the smoking history IMT (r=0.396, p=0.034). The other major traditional atherosclerotic risk factors for CAD were not shown to have significant correlation with the mean maximum IMT measurement. The antithrombotic, antihypertensive, and hypolipidemic medications taken by the patients were also found to have no significant correlation with mean maximum IMT. (See Appendix F)

Correlation of FMD with CAD and Risk Factors

A significant positive correlation was found between FMD and the severity score of CAD (r=0.321, p=0.030). The extent and jeopardy scores of CAD and the traditional CAD risk factors were not shown to be significantly correlated with FMD. The antithrombotic, anihypertensive, and hypolipidemic medications taken by the patients were lso found to have no significant correlation with FMD. (See Appendix F)

Discussion

In this study, the mean maximum IMT of the far wall of the distal common carotid artery was found to be correlated with the extent score of CAD despite its small sample size. This was in agreement with the study by Adams et al which showed a significant but weak correlation between CAD and common carotid IMT when this was measured as a continuous variable.[8] The Atherosclerosis Risk in Communities (ARIC) study has also shown a consistently greater carotid far wall IMT in subjects with prevalent clinical cardiovascular disease.[17]

The extent score of CAD used by Sullivan et al indicated the proportion of the coronary arterial tree involved by angiographically detectable atheroma.[15] The severity and jeopardy scores, on the other hand, only considers areas with ≥70% stenosis in the coronary arterial system.[15,16] The mean maximum CCA IMT in this study was shown to be correlated only with the extent score rather than the severity and jeopardy scores of CAD. This points out that the IMT may be a marker of atheroma burden rather than the presence of hemodynamically significant coronary lesions.

The use of beta-blockers, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, nitrates and antithrombotic drugs was not shown to be correlated with a significantly less mean maximum common carotid artery IMT and brachial artery FMD. Studies on regression of CCA IMT with therapy, like the European Lacidipine Study on Atherosclerosis (ELSA), showed a greater efficacy of carotid IMT progression after four-year treatment with lacidipine compared with atenolol.[18]

Endothelial dysfunction, on the other hand, relates to the risk for an initial or recurrent cardiovascular event rather than the anatomical lesion severity.[19] Brook et al have demonstrated that flow-mediated vasodilation in the brachial artery has a close relation to coronary artery endothelium-dependent vasomotor responses with a positive predictive value of 95%.[14] In our study, the severity score of CAD was surprisingly found to have a significant positive correlation with brachial artery FMD. The extent andjeopardy scores of CAD did not show a correlation with the brachial artery FMD. This finding in our may also is due to a small sample size or probably due to an actual lack of correlation between endothelial function with the anatomical lesions in CAD and endothelial function but rather with coronary endothelial function.

Both FMD and IMT also did not show a correlation with the traditional CAD risk factors in this study.

Conclusion

This study shows a significant positive correlation

between the mean maximum IMT of the far wall of the distal common carotid artery with the extent score of CAD. Age and the number of pack-years in the smoking history were also shown to have a significant positive correlation with the mean maximum IMT. This finding may provide some evidence for the use of the carotid IMT measurement as part of the screening regimen for patients with suspected CAD.

Recommendations

Since this study had a very small sample size, the results are not very conclusive. The author recommends continuation of the study to fulfill the computed sample size. With a larger sample size, a more conclusive result may be obtained.

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Original Article

Percutaneous Coronary Intervention Versus Coronary Artery Bypass Surgery in Patients with Multivessel Disease: Clinical and Economic Outcomes -The Philippine Heart Center Experience 2000-2002

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BACKGROUND: ***Recent randomized controlled trials have shown that percutaneous coronary interventions (PCI) with stenting has similar mortality and myocardial infarction rates with coronary artery bypass surgery (CABG) in the management of multivessel disease. The overall cost on these revascularization strategies in our local setting is uncertain.***

MATERIALS AND METHODS: ***This is a retrospective, matched cohort study comparing the in-hospital clinical and economic outcomes of multivessel stenting and bypass surgery. One hundred eighty (108) patients who underwent stenting of at least 2 major coronary arteries at our institution were included. The CABG group consisted of 108 patients who underwent bypass surgery matched for at least 2 of 3 characteristics, namely, age, sex, and presence of diabetes mellitus.***

RESULTS: ***There were no significant differences noted between the stent and CABG groups for mortality rates (1.9 vs. 1.9%), development of MI (0.9% vs. 1.9%), and renal failure (3.7% vs. 3.7%). Patients in the CABG group had significantly longer total 12.4 vs. 6.8 days) and ICU (6.4 vs. 1.8 days lengths of stay than those in the PCI group (p<0.001). The calculated total hospital costs were significantly higher for the CABG group compared to the PCI group (₱ 251, 746.00 vs. ₱ 240,657.29, p<0.001).***

CONCLUSION: ***Multivessel stenting and CABG have comparable risks of -n-hospital deaths and myocardial infarction. Multivessel stenting was significantly less costly compared to CABG and results to shorter hospital stay faster recovery and better qualify of life.***

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Keywords: coronary artery bypass; myocardial infarction; quality of life; coronary artery bypass surgery

Over the past decade, seven randomized controlled trials have been published comparing percutanous transluminal coronary angioplasty (PTCA) tocoronary artery bypass graft (CABG) surgery.[1-7] A meta-analysis of these trials showed that patients undergoing either procedure have similar outcomes in terms of myocardial infarction and mortality rates, but patients treated with bypass surgery needed fewer additional interventions.[8] Subsequent improvements in both percutaneous and surgical techniques may, however, now limit the validity of the drawn conclusions from such studies.

Reevaluation may be especially needed in the case of angioplasty, since several studies show that coronary stenting.[9, 10] Another reason to reevaluate these surgical and percutaneous techniques is the growing concern about the cost of health care, especially in developing countries like ours. Increasingly, the additional effects of new therapies must be weighed against their costs.[11-13]

The recent ARTS Trial concluded at 1 year follow-up after the procedure, coronary stenting for multivessel disease is less expensive than bypass surgery and offers the same degree of protection against death, stroke, and myocardial infarction. However, stenting is associated with a greater need for repeated revascularization.[14] The smaller Argen-tine ERACI-II Trial revealed that PTCA with stent implantation showed better survival and freedom from myocardial infarction than did conventional surgery, but repeat revascularization procedures were higher.[15]

Objective of the Study

To the address the need to obtain local data on both revascularization techniques in our country, we performed a

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cohort study to compare the clinical, in terms of in-hospital mortality and complication rates, and economic outcomes of coronary artery disease in our center.

Materials and Methods

Study Population

A total of 108 consecutive patients without previous CABG or PTCA who underwent multivessel percutaneous coronary intervention (PCI) at the Philippine Heart Center from January 2000 to October 2002, were included in the study. For the purposes of this study, multivessel PCI was defined as angioplasty with stent placement in two major coronary arteries (or their major branches) during a single procedure.

For each patient in the PCI group, a patient with contemporary CABG was matched for at least 2 out of the 3 clinical and demographic variables known to influence clinical outcomes and costs of care: age (within 5 years), sex, and presence of diabetes mellitus.[16]

Data Collection

The baseline demographic and clinical data were obtained by chart review, which coronary risk factors, extent of coronary artery involvement, and ejection fraction. In hospital clinical outcomes, which include death, periprocedural myocardial infarction (MI), need for repeat revascularization, vascular and bleeding complications, development of renal failure requiring dialysis, and stroke were noted.

Determination of Costs

For PCI procedures, resource utilization (including the number of balloon catheters, stents, guiding catheters, guidewires and contrast) were obtained from the cardiac catheterization lab and billing section records and verified through the MedTrak, the network of the Philippine Heart Center. The total procedural costs of CABG were obtained from the operating room bad billing section records and also verified through the MedTrak. The physicians' professional fees for in-patient services (admission, daily care), and procedures (interventional and surgical), including anesthesia, however, were not included.

Statistical Analyses

Discreet data were reported as frequencies while continuous data were reported as mean +/- SD. Selected cost data were computed as mean +/- SD. Continuous variables were compared by means of t-tests and categorical variables by Fisher exact tests. The analyses of the costs were done using ANOVA.

Results

Study Population

A total of 216 patients were included in the final cohort. The mean age of the population was 61 years, and more than 75% of the patients were males. The mean left ventricular ejection fraction was 56%. In both groups, 41% were diabetics and there were more patients with 2-vessel involvement in the PCI group compared to the CABG group (45% vs. 28%). In contrast, there were more patients with 3-vessel involvement in the CABG group compared to the PCI group (72% vs. 55%). These differences, however, were not statistically significant (p=0.012). (Table 1)

Revascularization Procedures and Methods

PCI procedures were done in keeping with the standard clinical practice for the period of the study. An average of 2.4 stents (range=2-7) and 3.7 angioplasty balloons (range 2-8) were used. Seven of these patients underwent direct stenting. Glycoprotein IIb/IIIa antagonists were used in only 4% of the cases. CABG procedures were done using the conventional method, except for six, which were done without the use of the cardio-pulmonary bypass machine (off-pump method).

The left anterior descending artery (LAD) was the most common target for revascularization in both groups receiving either a stent or left internal mammary artery (LIMA) graft in 82% and 100% of the procedures, respectively.

In-hospital Clinical Outcomes

There were no significant differences noted between the stent and CABG groups for mortality rates (both 1.9%), development of periprocedural MI (0.9% vs. 1.9%) and renal failure requiring dialysis both 3.7%. One patient in the CABG group had stroke while for patients in the PCI group had vascular complications. There were incidences of a need for repeat revascularization in both groups before discharge. (Table 2)

Resources Utilization and Costs

Patients in the CABG group had significantly longer total (12.4 vs. 6.8 days) and ICU (6.4 vs. 1.8 days) lengths of stay than those in the PCI group ($p<0.001$). The calculated total hospital (procedural and ancillary) costs were significantly higher for the CABG group compared to the PCI group (Php251,746.00 vs. Php240,657.29, $p<0.001$). This does not include, however, the professional fees of the physicians, which when extrapolated, could further widen the cost difference. (Table 3)

Subgroup Analysis

We performed subgroup analysis comparing the lengths of stay and total costs of patients who underwent the off-pump CABG method (OPCAB) with the conventional CABG and PCI procedures. Compared to the conventional CABG

group, those who underwent OPCAB had shorter total and ICU lenghts of stay but were not statistically significant. However, the OPCAB group had statistically significant lower total procedural and ancillary costs compared tot he conventional CABG group (₱180,770 vs. ₱225,792.28, p<0.01). (Figs. 1 & 2))

The OPCAB group, compared to the PCI group, had longer total and ICU lengths of stay (6.8 and 1.8 vs. 10.0 and 4.3 days, p<0.01). The total hospital costs for the OPCAB group, excluding the physicians' professional fees were lower than the PCI group but the differences was not statistically significant (₱182,964.35 vs. ₱240,657.29, p=0.037). (Figs. 1 & 2)

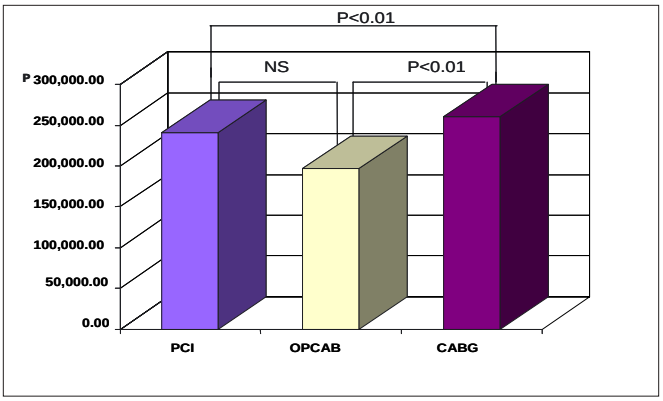

Figure 2. **Total procedural and ancillary costs (excluding physicians' professional fees): PCI vs. OPCAB vs. CABG**

Table 1. Baseline demographic and clinical characteristics

Characteristics	PCI (n=108)	CABG (n=108)	P
Age (yr)	60.82 +/- 12.8	60.56 +/-9.8	NS
Sex (% male)	78.7	83.3	NS
Diabetes mellitus (%)	40.7	40.7	NS
Hypertension (%)	70.4	64.8	NS
Dyslipidemia (%)	78.7	79.6	NS
Smoking history (%)	64.8	54.6	NS
No. of diseased vessels			
Two-vessel (%)	45.3	27.7	NS
Three-vessel (%)	54.6	72.0	NS
LV Ejection Fraction (%)	57.3 +/-14.2	55.8 +/-12.1	NS

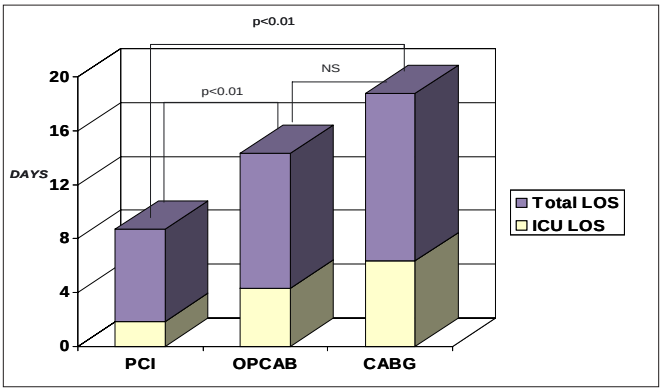

Figure 1. **Comparison of total and ICU lengths of stay**

Table 2. In-hospital post-procedural clinical outcomes

Clinical Outcomes	PCI (n=108)	CABG (n=108)	P
Death (%)	1.9	1.9	NS
Q wave MI (%)	0.9	1.9	NS
Repeat revascularization	0	0	
Vascular injury	3.7	0.9	NS
Stroke	0	0.9	NS
Renal failure requiring dialysis	3.7	3.7	NS

Table 3. Resource utilization and total procedural and ancillary costs

Costs	PCI (n=108)	CABG (n=108)	P
Post-procedure length of stay (LOS) (days)	6.84 +/- 4.12	12.41 +/-4.97	<0.01
ICU LOS (days)	1.84 +/- 1.31	6.38 +/- 4.21	<0.01
Total procedural and ancillary costs	₱ 240,567.29+/- 84,999.66	₱ 251,746.29 +/- 58,070.00	<0.01

Discussion

In our study, there is no significant difference in the rates of in-hospital deaths and development of periprocedural MI in both the PCI and CABG groups. These clinical findings are consistent with previous randomized trials comparing multivessel PCI and bypass surgery, which include the ARTS[14] the Beth Israel Deaconess Medical Center 9BIDMC) Trials.[17]

In the Argentine ERCI-II Trial, there was an unexpected higher perioperative death (5.7%) in the CABG cohort, which was explained by the investigators of that study due to the high 91% unstable angina rate.[16] Our study, on the other hand, excluded emergency PCI or CABG procedures, accounting for the lower mortality rates (1.9%), close to the figure in the ARTS Trial.

There was no note of any need for repeat revascularization procedures in our study. In contrast, there was a high rate of repeat revascularizations in the index hospitalization of the stent group in the BIDMC Trial (4%).

This may be due to the usage of the newer second and third generation stents in our study compared to the use of the older generation slotted tube design stents in the BIDMC Trial during the study period 1994 to 1998.[16] Furthermore, the use of the newer drug-eluting stents in the later half of 2002 in our study, could have contributed to this, although, we could not draw such definite conclusions because the number of patients were underpowered. The benefits of the use of glycoprotein IIb/IIIa antagonists could not deduced also because of similar reason.

Our study also showed longer duration of ICU and total hospital stay for CABG patients, both for conventional and OPCAB, compared to the PCI group. This is quite expected, because of the less invasive approach with PCI. Such findings are consistent with all other previous trials. This would indicate faster recovery and a better quality of line one month after the intervention.

In our study, the total hospital costs were >P10,000.00 per patient lower with multivessel stenting compared with CABG. This, however, excludes physicians' professional fees. If the professional fees were taken into account, the difference would be greater, approximately close to P90,000.00 + per patient, equivalent to about 20% lower with PCI.

In the subgroup of patients who underwent the OCAB, method which does not utilize the cardiopulmonary bypass machine, the cost is lowered by 28% compared to the conventional CABG with or without the physicians' professional fees added. When compared to PCI, however, this markedly lower cost with OPCAB was not statistically significant. Furthermore, if the physicians' fees were included, the difference in the costs between the two groups is nil.

The economic data from our study are not directly comparable to any of the previous studies comparing costs of multivessel stenting with bypass surgery. Resources utilization patterns (e.g. length of stay and room rates, PCI rates, unit costs, etc. may differ dramatically in cross-national studies, reflecting differences in medical infrastructure, practice patterns, health insurance programs and cultural factors.[18]

Limitation of the Study

Our study has some important limitations. Our retrospective cohort design does not provide the same assurance of baseline equivalence between the groups compared to a randomized controlled trial. The demographic and clinical data were all obtained based on records and documents.

We only evaluated the clinical and economic outcomes during the index hospitalization. Long-term follow-up of these patients is needed to document repeat revascularization procedures, which were found to be higher in the PCI group in previous studies.[14,16,17] This would have a major impact . on the long-term cost-effectiveness of PCI and CABG Phase II of this study aims to consider this.

Finally, our study is limited somewhat by the rapid evolution of techniques for both multivessel stenting and bypass surgery. Some recent modifications in both stenting (use of drug-eluting stents, glycoprotein IIb/IIIa inhibitors) and bypass surgery (off-pump method) were incorporated in our study to a limited extent only. This limitation is also true in all studies that attempt to evaluate outcomes of evolving technologies.

Recommendations

Our study concludes that multivessel coronary stenting or PCI is a clinically reasonable alternative to bypass surgery that reduces overall procedural and ancillary costs and shorten the recovery period. However, "cost" must be defined from the persepctive of the society as a whole, and each patient's preference must be considered in making individual decisions.

We recommend, though, that additional follow-up of these patients, to include outpatient visits, hospital re-admissions, repeat revascularizations and clinical outcomes, be done to provide us a total picture of long-term cost-effectiveness of both multivessel PCI and CABG.

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Original Article

Reversibility of Severe Pulmonary Hypertension among Pediatric Patients with Left-to-Right Shunts Using Milrinone–A Double-Blind Randomized Placebo-Controlled Interventional Study

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BACKGROUND: ***Preoperative assessment of pulmonary vascular reactivity among children with CHD specifically L-to-R shunts with pulmonary hypertension (PHT) is routinely performed to identify patients with fixed PHT who are at risk for heart failure and death after surgical correction. Several maneuvers aside from giving of 100% oxygen and nitric oxide, employs the use pharmacological agents to lower PVR have its own limitations and complications. The objective of this study to examine the feasibility of using Milrinone to test pulmonary vascular reactivity in pediatric patients with L-to-R shunt and severe PHT before the contemplated surgical correction. The hypothesis of this study is that Milrinone would lower PVR in pediatric patients with L-to-R shunts with severe PHT.***

MATERIALS AND METHODS: ***This preliminary, prospective, double-blinded, randomized, placebo-controlled, interventional study includes 24 pediatric patients age 1-15 years old with cardiac L-to-R shunts and severe PHT. Patients were randomly divided to receive either a single doe of 50ug/kg IV Milrinone bolus or an equal volume bolus of placebo in a double-blinded fashion to test reversibility of PHT.***

RESULTS: ***Nineteen out of twenty-four patients were included in the study. Using ANCOVA, 8 out of 15 variables tested in the Milrinone group had significant results: Increase in CO by 38.7% (0.046), 333% increase in the PBF (0.046), 10% decrease in PASP (0.002), decrease in diastolic PAP (0.019), decrease in mean PAP (0.010), decrease in Rp (0.013), decrease in Rp:Rs ratio (0.044,) and decrease in PVR (0.026). There was no significant change noted from the baseline in the placebo group.***

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Congenital cardiovascular defects affects approximately 32,000 infants each year,[1] can cause abnormal patterns of blood flow and influence structural and functional circulatory development.[2] Children with this type of cardiac disorder specifically large left-to-right shunts are frequently encountered in the practice of pediatric cardiology and cardiovascular surgery. Data from the Philippine Heart Center showed that 219 pediatric patients with either ventricular septal defect (VSD) or patent ductus arteriosus (PDA) were admitted from 1999 to 2000[3] underwent medical management of heart failure and/or surgical correction. Advances in cardiac surgery, including improved cardiopulmonary bypass (CPB), postoperative care, and repair of more complex defects have made surgical repair a primary therapy for an increasing number of pediatric patients with cardiovascular disease.[4] Despite all of this advancement, certain number of patients in this subgroup of congenital heart disease (CHD) develops pulmonary hypertension (PHT) secondary to increase in pulmonary artery pressure (PAP) and/or pulmonary vascular obstructive disease (PVOD). Pulmonary vascular resistance (PVR) is frequently elevated in patients with chronic heart failure, uncorrected shunt lesions, and other type of cyanotic heart disease.[5,6,7] PAP is the product of the PVR and pulmonary minute volume (Qp), such that pulmonary hypertension may develop as a result of an increase in either PVR or Qp or both.[8] Philippine Heart Center data from May 1, 2001 to August 31, 2001 showed that among the 79 pediatric patients with isolated VSD awaiting surgery, 30.4% had moderate-to-severe pulmonary hypertension that requires

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cardiac catherization.[9,10] Because fixed pulmonary hypertension is a risk factor for right heart failure and death after corrective surgery,[11,12] preoperative pharmacologic assessment of the reversibility of pulmonary vascular hypertension by cardiac catherization has become a requisite part of the preoperative evaluation.

At present, the Section of Invasive Cardiology–Cardiac Catheterization and intervention of the Department of Pediatric Cardiovascular Medicine of the Philippine Heart Center employs only the use of inhaled 100% oxygen to assess reversibility of severe pulmonary hypertension PVOD prior to contemplated surgical correction of the cardiac lesion. Nitric oxide (NO) and IV Prostcyclin, although available in our center, were limited due to its prohibitive cost.

Milrinone, a nonglycoside, noncathecolamine bipyridine derivative that possesses both potent positive inotropic and systemic vasodilating effects. A selective phosphodiesterase III inhibitor that indirectly results in an increase in intracellular cyclic adenosine monophoshate production[13,14] thereby improving cardiac muscle contractile force and vascular relaxation through positive inotropic and vasodilatory effects. Experimental animal study of this drug in dogs with pulmonary hypertension showed that Milrinone decreased the mean PAP significantly.[15] But it did not change the mean PAP in dogs with normal PAP, indicating that it has a selective pulmonary vasodilatory effect only in subjects/dogs with pulmonary hypertension.[15] In the recent years, several hemodynamic studies in human subjects confirmed this findings, both in the pediatric and adult population: in the management of heart failure,[16,17] neonates and children post cardiopulmonary bypass (CBP) / post-cardiac surgery,[18,19,20] post-cardiac surgical patients with pulmonary hypertension,[21,22] pediatric patients with septic shock,[23,24] and in patients with cardiomyopathy whom were considered for heart transplant[25] at risk of developing right-sided heart failure secondary to fixed PHT and consequently, death post-operatively.

All studies mentioned, collectively concluded that Milrinone reduces PVR, mean PAP and pulmonary artery wedge pressures, increase the cardiac output (CO), cardiac index (CI) and left-ventricular stroke volume index. Furthermore, studies also found that Milrinone causes no change in the heart rate; systemic blood also found out that Milrinone causes no change in the heart rate, systemic blood pressures (SBP), diastolic blood pressure (DBP), and mean systemic artery pressures even in neonatal and pediatric population.

Extensive electronic data search on the use of Milrinone to test for the reversibility of severe pulmonary artery hypertension among patients with left-to-right shunts prior to corrective surgery, disclosed no published or reported foreign studies/trials. Only the local at the Philippine Heart Center reported the use of Milrinone on similar subjects with severe pulmonary hypertension, limited by its non-randomized controlled nature of the study [26] and the use of another vasodilator in combination with Milrinone to lower the PVR.[26] It is therefore the objective of this study is to investigate whether Milrinone alone can be used to test for reversibility of pulmonary vascular hypertension in pediatric patients with large left-to-right shunts. Specific emphasis will be placed on obtaining hemodynamic assessments via cardiac catheterization among this subgroup of patients who needed it as a requisite prior their corrective cardiac surgery. To examine this possibility, the hypothesis that Milrinone will lower the PVR if administered as bolus and subse-quently as IV infusion, will be tested in the above mentioned patients who will undergo hemodynamic studies (cardiac catheterization).

Safety, Metabolism, Indications and Adverse Effects

Use of Phosphodiesterase Inhibitors in Neonates and Children.

Several large series of studies, including previously mentioned reports, have already documented the use, efficacy and safety of phosphodiesterase inhibitors. Phosphodiesterase inhibitors such as amrinone and its congener, Milrinone, exert their effects on cardiac performance by increasing cytosolic cyclic AMP independently of B-adrenergic receptors.[2,6,7,13,14,18] Unlike cathecolamines, these new nonglycoside and noncathe-colamine agents improve myocardial performance without raising myocardial oxygen consumption or increasing after load.[13,14,18] The overall effect of phosphodiestrerase inhibitors is multi-fold: a) increased inotropy as a result of cyclic AMP-mediated increase in trans sarcolemmal calcium influx; b) peripheral vasodilatation secondary to removal of free intracellular calcium into the sarcoplasmic reticulum; and c) increased lusitrophy from a mechanism probably related to improved actin-myosin dissociation during diastole.[18] The use Amrinone, the parent compound from which Milrinone is derived, has already been used in the past among neonates and infants, and was proven to be safe and efficacious.[27,28] Milrinone, a 2-methyl, 5-carbonitrile of the bipyridine, amrinone, is about 15 times more potent than its parent compound.[29] The dose recommended in pediatrics with normal renal function is 50 ug/kg as bolus given over for a period of 10 minutes with maintenance infusion of 0.25-0.75 ug/kg/min titrated to a desired hemodynamic response.[13] The elimination half-life is approximately 3 hours.[13] It circulates approximately 70% plasma protein bound, and the major route of elimination is renal.[13,18]

Indications of the use of Milrinone in infants and children include: in cases of low cardiac output after surgery wherein it was out to lower filling pressures, systemic and pulmonary arterial pressures, and resistances, while improving cardiac index without increasing oxygen consumption,[13,14,18] and incases of acute heart failure.[14] The main reported side effects of IV Milrinone in adults have included hypotension and ventricular or supraventricular tachyarrhythmias, all of which

were not observed with the use in children.[13]

The decision as to whether a patient with congenital heart disease would profit corrective surgery often hinges on the calculated PVR. Although each case must be evaluated on its own characteristics, many criteria for operability have been proposed.[30] The principal author for the purpose of this study therefore used several following terms. Severe PHT is arbitrarily defined as any or all of the following: mean PAP of > 75% compared to arterial systemic pressure,[26] resistance ratio (PVR/SVR ratio) > 0.75%,[35] and wedge angiogram results (Grade B-C) in correlation with morphometric studies of the lung.[31] Since no amount of oxygen or vasodilators can lower PAP or PVR in fixed PHT, reversible PHT is then defined as a fall of PVR more than SVR, with consequent increase in Qp:Qs ratio and a rise in the oxygen saturation.[32] This marked change is indicative of a very responsive pulmonary circulation.[31]

Specific Objectives:

1. Determine baseline hemodynamic measurements* among pediatric patients with left-to-right shunts and severe PHT by cardiac catheterization.
2. Determine efficacy and safety of intravenous (IV) Milrinone bolus in lowering PAP/PVR among patients with left-to-right shunts and severe PHT.

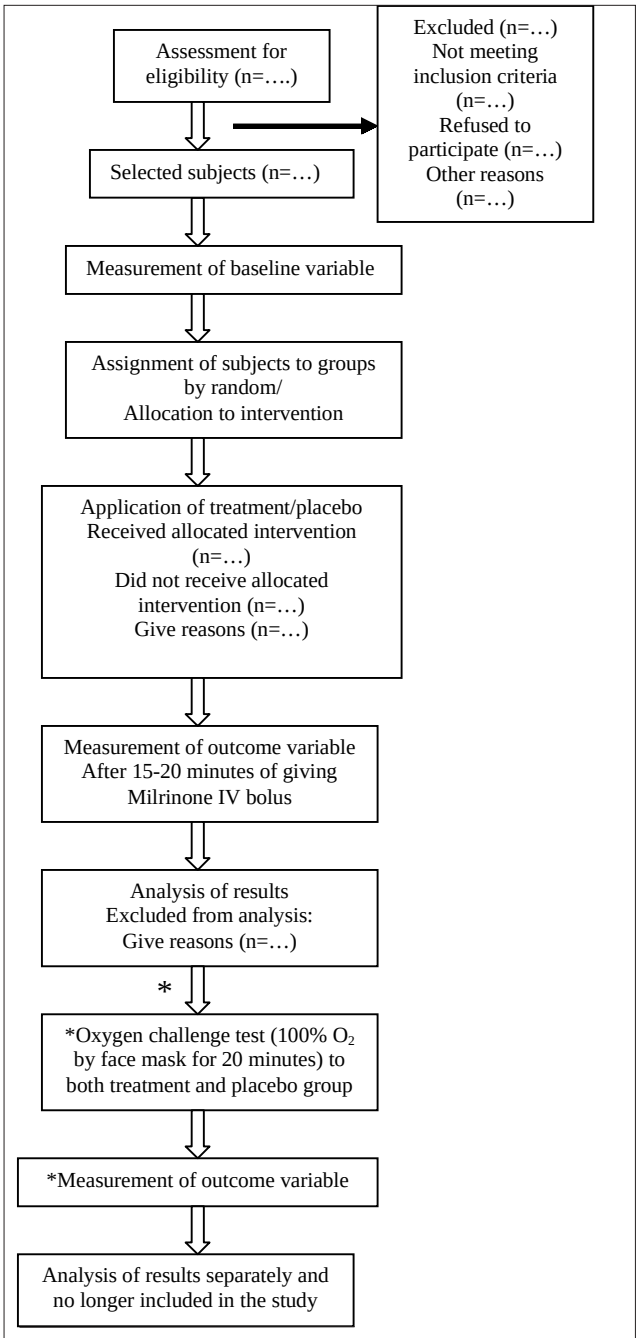
**Baseline measurements of the variable include the following: cardiac rate, arterial blood gas, oxygen saturations in all chambers and vessels entered, pressure recordings in the IVC, RA, SVC, RV, MPA, RPA, LPA, PCWP, LA, PV, LV, and aorta. Computation of the CO, CI, SVR, PVR, Qp:Qs ratio, PBF, SBF, RpRs ratio, oxygen consumption, and oxygen capacity.*

Materials and Methods:

Study Design

Double blind, randomized, placebo-controlled, interventional trial.

All pediatric patients age 6 months to 19 years of age with cardiac left-to-right shunt documented by recent 2D echocardiogram (Table 1) admitted to the Philippine Heart Center Department of Pediatric Cardiovascular Medicine, were assessed for the eligibility for inclusion in the study. 2D echocardiogram findings of all eligible patients for the study had an estimated mean PAP equal to or more than 75% compared to the systemic arterial pressure that necessitated hemodynamic studies by cardiac catheterization as primary reason for admission prior to contemplated surgical cardiac correction. Informed written consent (Appendix 1) from the parents was obtained prior to the study.



** The giving of 100% oxygen/Hyperoxia test/oxygen challenge test was done strictly for ethical consideration so that patients who received the placebo will benefit from the cardiac catheterization and hemodynamic study and likewise be tested for reversibility of severe PHT. Results of which were analyzed separately and no longer included for the purpose of this study.*

Figure 1. **Flow diagram of the progress through the phases of a randomized trial/parallel controlled trial [1,2]**

Exclusion criteria were as follows:

1. Patients with mild-to-moderate PHT
2. Patients in congestive heart failure (CHF)
3. Patients with lower respiratory tract infections as documented by both clinical and chest X-ray findings
4. Patients with prolonged bleeding parameters, i.e. thrombocytopenia, prolonged prothrombin and partial thrombolastin time.
5. History of supraventricular or ventricular dysrrhythmias
6. History of hyperthyroidism or hypothyroidism
7. History of chronic renal failure or serum creatinine concentration greater than 2.0mg/dL
8. Patients who are already receiving Milrinone or other Phosphodiesterase inhibitors prior to the study.
9. Patients who have hypotension immediately before the study drug administration. Hypotension is defined as a systolic BP (SBP) <50mmHg in patients <1 to 12 months old, or SBP <65 mmHg in patients > 12 months old. [35]
10. Patients with severe pulmonary hypertension who's shunt defect is predominantly right-to-left shunting by 2D echocardiography
11. Patients with documented cardiac left-to-right shunt defect but with suprasystemic right ventricular and pulmonary artery pressure measured by cardiac catheterization.

Table 1. Inclusion criteria: eligible CHD

Types of Cardiac Defects
⇙ Venticular septal defect (VSD)
⇙ Atrial septal defect (ASD)
⇙ Patent ductus arteriosus (PDA)
⇙ Endocardial cushion defect (ECD)
⇙ Double outlet right ventricle without pulmonic stenosis behaving as large VSD
⇙ Any combination of the above

Sample size was determined based on the local study done in this institution [26] with the following general formula [31]:

$$N = \frac{2t^2 \times SD^2}{(\alpha + \beta)^2}$$

For inference on the difference between means, where:

N = sample size

$\alpha + \beta$ = value of the t corresponding to alpha and beta errors

SD = standard deviation of the difference in the sample

E = the effect size, i.e. the chance/difference in the mean before and after intervention, which the investigator wishes to detect

In order to eliminate or equalize the influence of confounding factors and to ensure that equal number of subjects was assigned to the groups, blocked randomization 31 was employed. The total computed sample was divided into blocks of even-number size. The subjects as they come were randomly assigned to the groups in the first block. When six subjects had already been assigned to the one group the next subjects were assigned to the group until it also has six subjects. The process was repeated in the second block. Then the other block until the desired number of subjects has been selected and assigned to the groups.

Hemodynamic Measurements/Randomization

All selected and qualified subjects underwent right and left heart catheterization via percutaneous puncture in the femoral artery and femoral vein. All patients received IV Midazolam at 0.1 to 0.2 mg/kg as their pre-medication prior to cardiac catheterization. Subjects included in the study were placed in a fasting state for four-to-six hours before the procedure. Hemodynamic and oxygen transport data were measured from an arterial and venous catheter.

Measurements from the arterial catheter (left heart catheterization) include arterial blood gas (ABG) and pH, oxygen saturations in all vessels and chambers that were entered, systolic BP (SBP), diastolic BP (DBP), left atrial pressures (LAP), LV end diastolic pressures (LVEDP) and mean arterial BP (MAP). Measurements from the venous catheter (right heart catheterization) include oxygen saturations in all chambers and vessels that were entered. Superior vena cava and right atrial pressures (RAP), mean RAP, RV pressure, RV end-diastolic pressure (RVEDP), PAP, mean PAP and pulmonary capillary wedge pressures (PCWP). Once baseline measurements were taken, assignments of the subjects into the control/placebo (group A) or intervention/treatment group (group B) were done by random, double-blinded fashion (Fig. 1).

Milrinone 50 ug/kg were given as loading dose, followed by continuous IV infusion at 0.5 ug/kg/min to the group B, while group A received an equal volume loading dose and IV infusion of the placebo (normal saline solution). To maintain the investigators blind, a first research assistant prepared either the placebo or the Milrinone solution. He/she was in-charged of the proper coding of the solutions being prepared. The second research assistant, blinded to the content of the solution, got the allotted solution for a particular patient and was

in-charged in sending the solution to the cardiovascular laboratory (CV lab) during the hemodynamic procedure. Both the investigator and the nurse at the CV lab were blinded to actual content of the solution being tested.

Repeat measurements of the hemodynamic parameters were done 20 minutes after Milrinone bolus. Once the study were completed, the standard oxygen challenge test (Hyperoxia test/challenge) of this institution to check reversibility and to determine PVR and cardiac angiography were done on all patients, both the treatment and the placebo group. Exchange grouping or cross-over trial involving both drugs (Milrinone versus oxygen) and its effects on a subject was not applied in this study since the elimination half-life (T1/2)/ wash-out period (effects of treatment to disappear) of Milrinone is 3 hours,[13] which deemed not possible for each subjects to stay that long at the CV lab.

Hyperoxia test (Fig.1) was performed to all subjects (both the Milrinone and the placebo group) by giving 100% oxygen for at least 10 minutes[31,36,37] by face mask, after which, repeat measurements of the hemodynamic parameters was done. This procedure was done strictly for ethical consideration so that all patients specifically those who received the placebo benefited from cardiac catheterization and hemodynamic study, and likewise was tested for reversibility of severe PHT. Results of which were analyzed separately and no longer included for the purpose of this study.

Pulmonary blood flow, systemic blood flow, Qp:Qs ratio, PVR, SVR, pulmonary arteriolar/systemic vascular resistance ratio (Rp:Rs ratio), cardiac output, cardiac index, oxygen consumption, and oxygen capacity will be computed at baseline point, 10 and 20 minutes after Milrinone bolus, and likewise after the standard oxygen challenge test.

Statistical Analysis

Data was recorded in a standardized spreadsheet format (Data editor SPSS for Windows version 10.0) with clinical profile, outcome of interest was placed in columns, patient observation was placed in columns, and patient observation was place in rows. For the differences in the values of the outcome variable in the two independent groups, the following statistical tests were used: Independent t-test (interval/ratio data),[31,38] and Fisher's exact probability test and/or Chi-square (nominal data).[31,33]

Analysis of Covariance (ANCOVA) was used to control for the influence of a confounding variable.[34,38] In this study the baseline parameters (pre-intervention – whether placebo or test drug), acted as co-variates. Statistical analyses were done using the Statistical Packages for Social Sciences (SPSS) for Windows version 10.0, with level of significance set at $p=<0.05$.

Results

Twenty-four (24) pediatric patients were admitted at the Philippine Heart Center, a tertiary cardiac referral center, from February 1, 2003 to September 30, 2003 with cardiac left-to-right shunts who were eligible for hemodynamic studies prior to contemplated surgical correction. Two patients did not undergo cardiac catheterization because repeat 2D-echocardiographic study prior to the procedure showed only moderate pulmonary hypertension, and thus, underwent direct surgical correction of the cardiac defect. Twenty-two (22) patients underwent cardiac catheterization however; one patient, an 11-year-old patient with secundum type atrial septal defect was excluded from the study because PAP and RSVP recordings during the procedure only showed 30 mmHg. An additional two patients were excluded from the study because both became unstable during catheterization, and hence the procedures were prematurely terminated.

Nineteen (19) patients completed the hemodynamic study, and comprised the final study population in this preliminary report. Thirteen (68.4%) of the subjects were males, and six (31.6%) were females (Table 2). Mean age of patients under the treatment/Milrinone group is 5.6 years (SD +/-3.4 years), while mean age of patients under the placebo/control group is 8.4 years (SD +/-4.3 years). Mean weight of patients in the Milrinone group is 14.3 kg (SD +/-4.8 kg), while patients in the placebo group had a mean weight of 26 kg (SD +/-16 kg). Overall, 63.2% (12) of the subjects were from the charity service, while 36.8% (7) were from the pay service (Table 3).

Table 3 showed that majority of the patients who underwent cardiac catheterization (42.1%) in this study had isolated ventricular septal defect (VSD). Twenty-three percent (23.3%) of cases in the study population had a combination of VSD and patent ductus arteriosus (PDA). Isolated PDA was observed in 16% of cases, and a combination of VSD, atrial septal defect (ASD) and PDA was noted in one patient. ASD with cleft mitral valve were noted in two patients (Fig. 2) included in the study.

By paired sample statistics (t-tests), Table 4 demonstrates that there was no significant difference in the cardiac output (CO), PBF, SBF, QpQs ratio and cardiac index (CI) in the Milrinone-treated group and the placebo group from the baseline. Using the analysis of covariance (ANCOVA) in controlling the influence of the baseline parameters as a covariates or confounder, Milrinone significantly elevated the CO and the PBF (Figs.3 & 4). These were not observed in the placebo group. No change was noted in the SBF, CI and QpQs ratio in both two independent groups.

Table 2. Demographic profile of the subjects included in the study (n = 19)

Variable	Placebo Group (n = 7) Mean (SD)	Milrinone Group (n = 12) Mean (SD)	p – value
Age (years)	5.571 (SD+/-3.4087; Range 11)	8.417 (SD+/-4.2738; Range 13)	p >0.05
Sex Ratio (M: F)	1.4:1	6:1	p >0.05
Weight (kg.)	14.3286 (SD +/-4.8431)	25.9833 (SD+/-16.0373)	p >0.05

Table 3. Distribution of Subjects by Cardiac Lesion and by Patient Category (n = 19)

	Milrinone (n = 7)	Control/Placebo (n = 12)	Total(%)
Type of Cardiac Lesion: Ventricular Septal Defect (VSD)	2	6	8 (42.10%)
Atrial Septal Defect (ASD)	0	0	0
Patent Ductus Arteriosus(PDA)	2	1	3 (15.79%)
VSD + PDA	2	3	5 (26.31%)
VSD + ASD + PDA	0	1	1 (5.26%)
ASD with Cleft Mitral Valve	1	1	2 (10.53%)
Patient Category: Charity/Service	6	6	12 (63.16%)
Pay	1	6	7 (36.84%)

Table 4. Baseline releasing vs. post treatment comparison(T- test and analysis of covariance) used in the two independent groups in relation to blood flow and volume

	Baseline Reading vs. Post Treatment Comparison			ANCOVA
Variables		**Placebo** Mean SD	**Milrinone** Mean SD	**Main Effect p – value**
Cardiac output (CO) (L/min) **Paired t-test**	Baseline Post-intervention Paired Diff.	4.6208 1.3697 4.6458 1.4562 2.50 1.2600 **p = 0.065 NS**	4.5000 1.899 16.2429 3.9983 1.7429 2.3515 **p = 0.980 NS**	**0.046 Significant**
PBF (L/min) **Paired t-test**	Baseline Post-intervention Paired Diff.	9.3833 7.0374 9.500 7.2970 0.3333 3.9389 **p = 0.205 NS**	10.429 6.4768 34.714 42.488 24.286 38.900 **p = 0.150 NS**	**0.046 Significant**
SBF (L/min) **Paired t-test**	Baseline Post-intervention Paired Diff.	4.7083 1.5324 4.6667 1.4902 4.167 1.3708 **p = 0.918 NS**	4.6000 1.8556 6.1857 4.035 9 1.5857 2.4079 **p = 0.132 NS**	**0.075 NS**
Qp:Qs Ratio **Paired t-test**	Baseline Post-intervention Paired Diff.	2.2617 2.1803 2.1517 2.0467 0.1100 0.3382 **p = 0.284 NS**	2.3286 1.2352 5.2714 6.2891 2.9429 6.3432 **p = 0.266 NS**	**0.117 NS**
OTHERS				
Cardiac Index (L/min/m^2) **Paired t-test**	Baseline Post-intervention Paired Diff.	5.9583 2.9091 5.8750 2.4510 8.3330 1.2305 **p = 0.819 NS**	7.9857 4.9229 11.057 8.8703 3.0714 4.8531 **p = 0.145 NS**	**0.096 NS**

RVSP – right ventricular systolic pressure, LVSP – left ventricular systolic pressure, PASP – pulmonary artery systolic pressure, PA – pulmonary artery, PAP – pulmonary artery pressure, LVEDP – left ventricular end-diastolic pressure

Table 5. Summary of statistical analyses (T-test and analysis of covariance) used in the two independent groups in relation to ventricular and pulmonary pressures

Paired Samples Statistics				ANCOVA
Variables		**Placebo** **Mean SD**	**Milrinone** **Mean SD**	**Main Effect** **p – value**
RVSP	Baseline	90.083 10.457	87.143 8.0917	**0.107NS**
	Post-intervention	91.917 15.240	82.143 12.864	
Paired t-test	Paired Diff.	1.8333 1.9102	5.0000 9.1287	
		p = 0.358 NS	**p = 0.197 NS**	
LVSP	Baseline	97.083 5.8225	89.000 8.8694	**0.767NS**
	Post-intervention	102.08 10.544	97.143 12.199	
Paired t-test	Paired Diff.	5.0000 2.5376	8.1429 4.1829	
		p = 0.074 NS	**p = 0.100 NS**	
PASP	Baseline	91.250 11.104	87.571 8.3238	**0.002Significant**
	Post-intervention	91.583 13.905	79.000 10.893	
Paired t-test	Paired Diff.	0.3333 3.9389	7.5714 4.7909	
		p = 0.775 NS	**p = 0.006 Sig**	
PA diastolic	Baseline	42.500 13.229	40.000 9.5743	**0.019Significant**
	Post-intervention	41.667 12.673	31.857 10.205	
Paired t-test	Paired Diff.	0.8333 3.5887	8.1429 9.2633	
		p = 0.438 NS	**p = 0.059 NS**	
Mean PAP	Baseline	66.083 9.2093	62.429 8.4825	**0.001Significant**
	Post-intervention	65.583 11.453	49.286 9.9952	
Paired t-test	Paired Diff.	0.5000 4.2319	13.143 3.5686	
		p = 0.690 NS	**p = 0.010 Sig**	
LVEDP	Baseline	11.250 3.2228	11.857 5.8432	**0.247NS**
Paired t-test	Post-intervention	11.667 3.6013	11.286 3.860 7	
	Paired Diff.	0.4167 1.5643	0.5714 1.9881	
		p = 0.376	**p = 0.476**	

RVSP – right ventricular systolic pressure, LVSP – left ventricular systolic pressure, PASP – pulmonary artery systolic pressure, PA – pulmonary artery, PAP – pulmonary artery pressure, LVEDP – left ventricular end-diastolic pressure

Table 5 showed that RVSP, LVSP, PASP, mean PAP, diastolic PAP and LVEDP did not have a significant difference from the baseline in the placebo group. In the Milrinone-treated group however, both the PASP and the mean PAP had a significant decrease from the baseline. In both statistical analyses used, mean PAP decreased from 62 mmHg to 49 mmHg, and PASP decreased from 88 mmHg to 79 mmHg (Figs.5 & 6). In trying to eliminate the baseline variable as a confounder, by ANCOVA, diastolic PAP decreased significantly from mean of 40 mmHg to 32 mmHg. No change was observed in the LVSP, RVSP and LVEDP.

Table 6 showed that in the Milrinone-treated group, pulmonary arteriolar resistance (PAR or Rp) decreased significantly from the baseline of 528 dynes to 290 dynes, from the baseline Rp: Rs ratio of 0.41 to 0.24, and from the baseline PVR of 6 to 3.2 woods units (Figs.7&8). No change was noted from the baseline in the placebo group.

Generally, there were no major untoward incidents or reactions during the entire duration of the study. The effect of Milrinone is rapid in onset and generally well tolerated. No significant drop in the systolic blood pressure was noted in both the placebo and the Milrinone group. No occurrence of significant respiratory distress, arrhythmia or tachycardia/ supraventricular tachycardia was noted. Two cases however were excluded from the study after it was prematurely aborted, because both the RVSP and PASP were noted to be suprasystemic and both patients started to show signs of low cardiac output.

Discussion

Milrinone is an intravenously active Phosphodiesterase inhibitor that exerts both positive inotropic and direct vasodilator effects. In patients with severe heart failure, Milrinone increased cardiac output and reduced systemic vascular resistance (SVR) largely than other vasodilator agents such as nitroprusside when the agents were given at rates that caused matched reduction in arterial blood pressure. This observation suggests that if Milrinone is an effective

Table 6. Summary of Statistical Analyses (T – test, Analysis of Covariance) Used in the Two Independent Groups in Relation to Pulmonary and Systemic Resistance

Paired Samples Statistics				ANCOVA
Variables		**Placebo** **Mean SD**	**Milrinone** **Mean SD**	**Main Effect** **p – value**
Rp (PAR) (dynes/sec/cm^{-5}) **Paired t-test**	Baseline Post-intervention Paired Diff.	756.30 661.53 871.76 736.13 115.46 79.449 **p = 0.174 NS**	528.23 557.74 289.73 285.83 238.50 112.21 **p = 0.078 NS**	**0.013** **Significant**
Rs (SVR) (dynes/sec/cm^{-5}) **Paired t-test**	Baseline Post-intervention Paired Diff.	1265.0 370.18 1285.9 383.90 20.925 315.13 **p = 0.822 NS**	1226.6 381.92 1040.1 359.07 186.49 162.97 **p = 0.023 Sig**	**0.100** **NS**
PAR/SVR Ratio (Rp:Rs ratio) **Paired t-test**	Baseline Post-intervention Paired Diff.	0.7017 0.520 30.6092 0.4367 9.250 0.2920 **p = 0.296 NS**	0.4093 0.3195 0.2457 0.1803 0.1636 0.1840 **p = 0.057 NS**	**0.044** **Significant**
PVR (Wood units) **Paired t-test**	Baseline Post-intervention Paired Diff.	9.0292 8.3743 10.380 9.3915 2.7700 1.4242 **p = 0.100 NS**	5.9714 7.2330 3.2014 3.7256 2.7700 3.7680 **p = 0.100 NS**	**0.020** **Significant**

Rp – resistance pulmonary, Rs – resistance systemic, PAR – pulmonary arteriolar resistance, SVR – systemic vascular resistance, PVR – pulmonary vascular resistance

pulmonary vasodilator, it may be associated with a smaller decrease in systemic arterial pressure, for a given decrease in PVR, relative to nitroprusside. However, despite the clinical use of Milrinone for several years, there is always no information available regarding its effect on PVR.

The major finding in this study is that Milrinone effectively decreases the PAP, mean PA pressure, pulmonary arteriolar resistance (Rp), Rp:Rs ratio and most importantly the PVR. Systemic vascular resistance was noted to be significantly affected by Milrinone by t-test analysis, however by analysis of covariance (ANCOVA), the result was not significant. Cardiac output improved after the Milrinone bolus, as well as the PBF, indicating that reversible pulmonary vasculature.

Conclusion

1. The following were the baseline hemodynamic measurements among pediatric patients with CHD left-to-right shunts and severe PHT:

Variables:	Control/Placebo Group:	Milrinone Group:
CO	4.62 LPM +/-1.3697	4.5 +/-1.8991
PBF	9.4LPM +/-7.0374	10.43 LPM +/-6.4768
SBF	4.7083 +/-1.5324	4.6 +/-1.8556
Qp:Qs Ratio	2.3:1	2.3:1
Cardiac Index	5.96 L/min/m^2	7.0 L/min/m^2
PASP	91 mmHg +/-11.104	88 mmHg +/-8.3228
Diastolic PAP	42.5 +/-13.229	40 +/-9.5743
Mean PAP	66.083 +/-9.2293	62.429 +/-4825
Rp	756.30 dynes/sec/cm^{-5}	528.0 dynes/sec/cm^{-5}
Rs	1265 +/-370	1226.6 +/-381.92
Rp:Rs Ratio	Wood units +/-8.37	6 Wood units +/-7.2333

2. Analysis of Covariance (ANCOVA) showed that a single rapid bolus injection of Milrinone effectively lowers the PVR in pediatric patients with left-to-right shunts secondary to CHD accompanied by severe PHT. Likewise, with Milrinone bolus cardiac output improved as well as a marked increase in the PBF. PASP, diastolic PAP, mean PAP, Rp and as well as the RpRs Ratio were significantly decreased after the Milrinone bolus.

Milrinone is well tolerated, safe with no noted significant hemodynamic changes. It can be used to test for the reversibility of PHT in patients undergoing corrective cardiac surgery. No adverse reactions to Milrinone were observed in all patients tested.

Recommendation

The relative small numbers of subjects in this study maybe a disadvantage for some in the interpretation of the results and the conclusion even with statistically significant findings. It is therefore being recommended to continue this study to generate a much larger population or sample size for the benefit of this study in itself, but also for the clinicians who might also benefit from it.

Likewise, it is also being recommended to compare standard oxygen challenge test with Milrinone plus oxygen alone to determine which between the two maneuvers will effectively lower the PVR.

Acknowledgement

The author acknowledges and appreciates profoundly the enthusiastic help of Ms. Mercedita Parazo, Senior Science Research Specialist, Division of Preventive Cardiology of the Philippine Heart Center for the statistical aspect of this study. Similarly, in no small measure the author would like to extend its heartfelt gratitude to all patients and its parents involved in this study as subjects, without them the advances in the knowledge and management, and further understanding of this subtype of congenital heart disease will not be achieved.

PHILIPPINE HEART CENTER
East Avenue, Quezon City

Section of Cardiac Catheterization and Intervention
Division of Pediatric Cardiology

CONSENT FOR INCLUSION IN THE MILRINONE STUDY TO TEST REVERSIBILITY OF SEVERE PULMONARY HYPERTENSION AMONG PATIENTS WITH LEFT-TO-RIGHT SHUNTS UNDERGOING CARDIAC CATHETERIZATION – A DOUBLE BLIND RANDOMIZED PLACEBO-CONTROLLED TRIAL

Patient: _____ Hospital No._____ Date: _____

1. I hereby consent to the performance of upon myself/above patient the procedure:

   _____Cardiac catheterization_____
   (state nature)
2. I further consent to the performance of such additional procedure as stated in the heading as maybe considered necessary or desirable in the judgment of the attending Medical Staff of the above named medical institution
3. I attest that the above procedure or trial will be done in conjunction with the standard procedure, which is the OXYGEN CHALLENGE TEST, to test reversibility of pulmonary hypertension.
4. I also consent to the procedure/trial for the purpose of better decision-making, treatment options, and for the purpose of advancing medical knowledge.
5. I attest that the procedure/trial has been fully explained to me and I understand what will be done to me/above patient.

THE UNDERSIGNED CERTIFIES THAT HE/SHE UNDERSTANDS THE FOREGOING, AND IS THE PATIENT, OR IS AUTHORIZED BT THE PATIENT TO EXECUTE THE ABOVE AND ACCEPT ITS TERMS.

Signature of the Patient: _____ Date: _____
Signature of the Witness: _____ Date: _____

Because the above patient is a minor _____ years of age, or is unable to sign for the following reasons:
_____

Consent is given on the patients' behalf by:

Signature of Patient's Authorized Agent: _____
Relationship to the Patient: _____ Date: _____
Signature of Witness: _____ Date: _____

NOTE:
In case the patient/responsible party cannot understand and read English, the above must be translated to him/her in his/her own dialect.

Figure 1

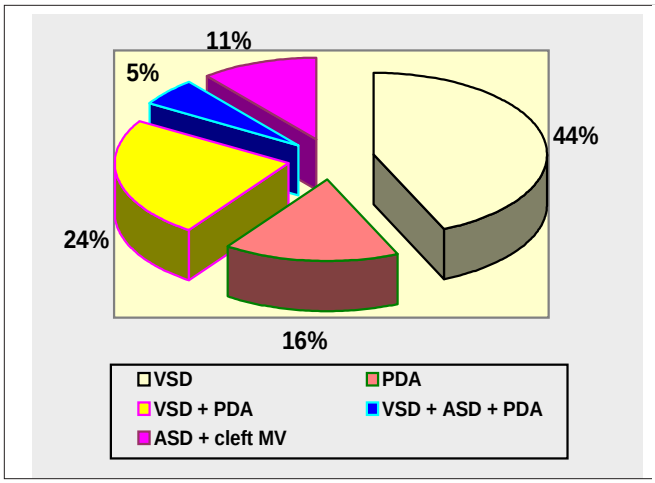


Figure 2. **Distribution of subjects in the study population according specific cardiac lesion (n = 19)**

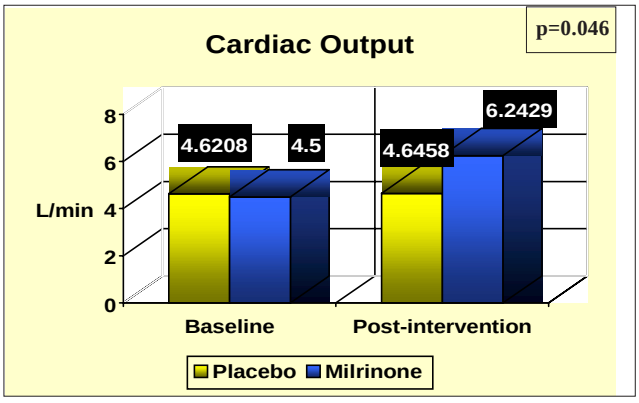


Figure 3. **Illustration of Means in Cardiac Output (L/min) adjusted using ANCOVA at Different Point in Time**

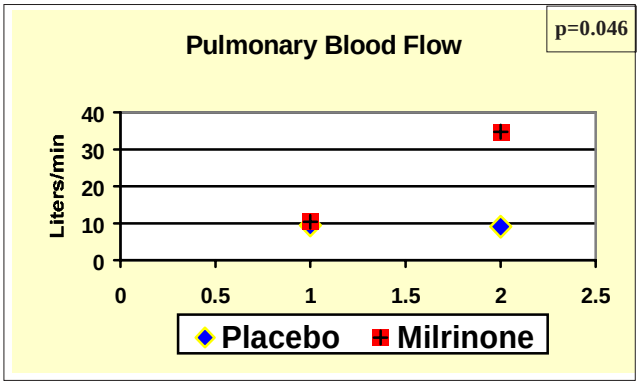


Figure 4. **Illustration of means adjusted using ANCOVA at different point in time, the baseline and the post-treatment – placebo or Milrinone.**

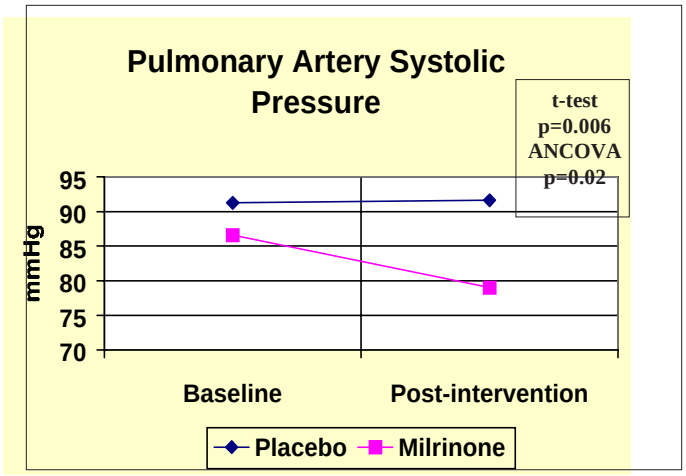


Figure 5. **Mean PASP at Different Point in Time**

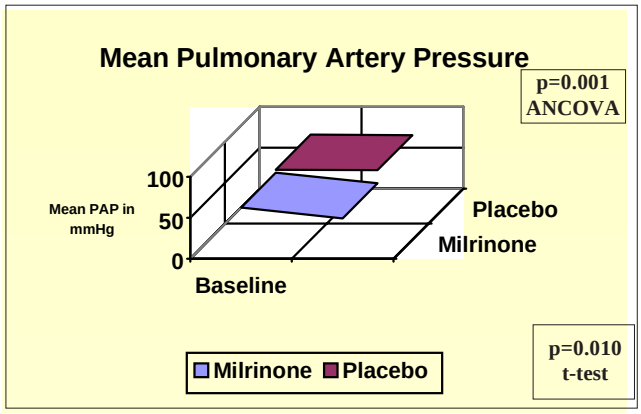


Figure 6. **Illustration of means adjusted using ANCOVA and Paired Sample t-Test**

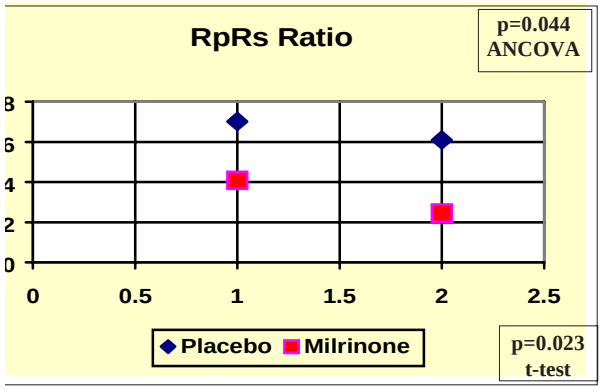


Figure 7. **Illustration of Means (RpRs Ratio) at different point in time**

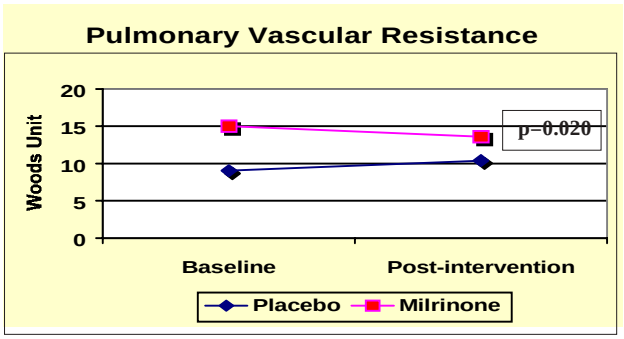


Figure 8. **Illustration of means in PVR adjusted using the ANCOVA**

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Original Article

Prognostic Scoring Index to Predict Outcome of Arterial Switch Operation in Filipino Children

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BACKGROUND: ***Transposition of the great arteries accounts for 5% to 7% of all congenital heart disease. It is the most common cyanotic heart disease and the most frequently diagnosed in the neonatal period. Arterial switch operation is the procedure of choice in patients with transposition of the great arteries. The purpose of this study is to identify variables that will undergo this procedure in patients.***

MATERIALS AND METHODS: ***This is a cross-sectional study involving 77 patients who underwent arterial switch operation from January 1991 to June 2002 at The Philippine Heart Center. Primary outcome measured was mortality. Patients were also classified into: transposition of the great arteries, transposition of the great arteries with intact ventricular septum, transposition of the great arteries with ventricular septal defect, and transposition of the great arteries with left ventricular outflow tract obstruction.***

RESULTS: ***Predictors of mortality were identified in patients who underwent arterial switch operation. Statistically significant pre-operative variables were pulmonary artery pressure and aorta: pulmonary artery annulus ratio; operative variable was bypass time and post-operative predictors were use of dobutamine (p=0.024), presence of acidosis (p=0.001) and bleeding (p=0.008). A clinical scoring index was formulated to predict outcome in patients who will undergo arterial switch operation. Variables included in the scoring system were sex (4.2125), left ventricular posterior wall thickness (3.7079) and aorta: pulmonary artery annulus ratio (4.6068) based on the result of multiple regression analysis. In the clinical scoring index developed, the cut off score was at eight, which has 37% sensitivity and 97% specificity for predicting mortality. At a score of 4-5; sensitivity is at 79%-58% and specificity of 54%-79%, and mortality is probable. At a score of 9-13; sensitivity is at 3%-29%, specificity is 100%, and mortality is definite.***

CONCLUSION: ***This study was able to identify predictors of mortality and developed a scoring index that will predict outcome in patients with transposition of the great arteries who will undergo arterial switch operation.***

Phil Heart Center J 2003;10:50-60

Keywords: sprognostic scoring index; arterial switch operation; congenital heart disease; children

Transposition of the great arteries (TGA) accounts for 5% to 7% of congenital heart disease (CHD), with a prevalence rate of 0.2 per 1000 live births and with a strong male preponderance. TGA is the most common cyanotic CHD diagnosed in the neonatal period and is responsible for 16% of all deaths from congenital cardiac disease.[2]

The genetic aspect of the pathogenesis of TGA is not considered strong, given that very few familial cases have been described and that genetic syndromes or extra-cardiac malformations are uncommonly associated with TGA. The mean precurrence risk for CHD among siblings of affected individuals with any type of TGA is 1.4%.[3]

Early intervention is warranted because without treatment, about 30% of affected infants succumb in the first week, 50% within the first month, 70% within the first 6 months and 90% within the first year of life.[4] In infants with VSD the early survival rate is higher, 91% at one month and 33% at one year.[2]

The transition and changing outcome from palliation to repair can be gleaned from experience with babies with complete transposition of the great arteries.[5] From 1950 to 1959, babies with complete TGA were palliated either with a Blalock-Hanlon atrial septectomy or one of the partial venous switch operations pioneered by Baffes and others. In the late 1950s and early 1960s, various atrial level physiological procedures were developed including Senning and Mustard procedure.[6] Senning first accomplished the atrial level switch in 1959, transposing the walls of the left and right atria without the use of prosthetic material. In 1964, Mustard devised an alternate technique for atrial level switch that involved excising the interatrial septum and creating a prosthetic baffle to redirect the systemic and pulmonary venous return. In 1966, Rashkind made a significant impact on the management of

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infants with D-TGA by the introduction of balloon atrial septostomy. In 1975, Jatene et al. reported the first successful arterial switch procedure in a patient with D-TGA and VSD. In 1977, Yacoub et al. introduced a two-stage repair comprising an initial pulmonary artery banding to retain the left ventricle, supplemented by a systemic-pulmonary artery shunt. In 1983, the concept of the primary neonatal arterial switch procedure was introduced by Castaneda et al.[2]

Therapy for TGA is one of the true success stories of congenital cardiac operation. Therapeutic options for all forms of TGA include palliative therapy, and physiologic and anatomic corrections. Palliative therapy like balloon atrial septostomy is most commonly performed in the first few days of life to improve mixing and cardiac output. This is followed by arterial switch operation within the first two weeks of life.

Anatomic correction (arterial switch operation) is the current state of the art and the ultimate management in patients with D-TGA. Proper selection of patients as to age at repair, weight, preoperative atrial septostomy, need for prostaglandin E2, preoperative echocardiographic left ventricular indices (left ventricle mass, posterior wall thickness, left ventricular end diastolic dimension (LVEDD), ejection fraction, fractional shortening), aorta: pulmonary artery ratio, pulmonary artery pressure, and associated cardiac defects, need for inotropic support and preoperative clinical status of the patient, should be considered when recommending ASO. Procedural variables like bypass and ischemic time, lowest temperature and anesthesia used are also contributory to mortality. Postoperative variables include presence of arrhythmia, seizures, acidosis, bleeding other metabolic problems (i.e. hypernatremia, hyperkalemia, hypoglycemia) and need for peritoneal dialysis.

Significance of the Study

An understanding of the physiology of the unique aspects of the circulation of the fetus and neonate, as well as the concept of the transitional circulation, had profound impact on the development of scoring system and treatment modalities in pediatric cardiology. Research led to an understanding of myocardial perfusion in the developing heart and the unique metabolic aspects of the neonatal heart, opened the way to efficient cardioplegia and myocardial protection, pharmacological circulatory support and neonatal cardiac resuscitation.

Arterial switch operation (ASO) started at the Philippine Heart Center in 1991. The criteria used in recommending ASO were based on the parameters from foreign studies. Only one local study entitled "Predictors of Outcome After Arterial Switch Operation" done in 1999 by Panergo et.al. was available to guide cardiologists in recommending the procedure.

As there is no definite criteria to prognosticate outcome of transposition of the great arteries after arterial switch operation, we will attemp to formulate a scoring index to predict its outcome. It is hoped that the development of a scoring index will help prognosticate outcome after ASO, so that cardiologists and surgeons would be alerted in recognizing poor prognostic factors in ASO.

Review of Related Literature

Several studies have identified factors that predict mortality in ASO.of transposition of the great arteries after arterial switch operation, the investigators will attempt to formulate a scoring index to predict its outcome.

In a study done by J.Losay et al. by-pass time, major intraoperative events, year of surgery before 1990 and type II abnormal coronary pattern has significant influence on early mortality.[7]

Risk factors for operative death were coronary artery patterns and preoperative instability according to Brown and Turrentine.[8]

The surgical repair of D-TGA beyond the age of 21 days is controversial. Concern that regression of left ventricular myocardial mass will render the left ventricle unable to cope with the acutely increased work of systemic perfusion has been considered contraindication to ASO.

Many patients are however, referred late for correction making them either high risk for surgery or inoperable due to development of irreversible pulmonary vascular obstructive disease. Therefore, it is important to recognize the ideal time for intervention. In admixture lesions like transposition of the great arteries, persistent truncus arteriosus or total anomalous pulmonary venous drainage, a very early intervention is needed so as to avoid development of severe hypoxia and early pulmonary vascular obstructive changes. Arterial switch operation is best performed in first two to three weeks of life stated by Shrivastava.[9]

In a study done by Rutledge et al., risks factors for mortality by univariate analysis included age at biventricular repair, complete atrioventricular (AV) canal defect, dextrocardia, moderate or severe tricuspid regurgitation and poor right ventricular (RV) function. By multivariate analysis, only complete AV canal defect and poor RV function remained significant risk factors for mortality. Significant tricuspid regurgitation (TR) and poor RV function are risk factors for poor outcome and provide convincing evidence that patients undergoing conventional biventricular repair are at risk for deterioration of tricuspid valve and right ventricular function.[10]

Left ventricular (LV) mass index, LV posterior wall thickness index, LV volume index, LV mass/volume ratio, patent arterial duct diameter > 2mm or coronary anatomy did not predict death, duration of mechanical ventilator or inotropic support according to Foran et al.[11]

Daebritz et al stated risk factors for operative mortality included complex anatomy, coronary anomalies and prolonged bypass time. Determinants of late mortality were coronary distribution, position of the great arteries, bypass time and aortic coarctation.[12]

Wernovsky and colleagues found that independent risk

factors for early death included less common types of coronary artery patterns, including single right coronary and inverted coronary patterns. Aortic arch repair, the year of surgery and circulatory arrest time were independent risk factors for increased mortality.[13]

An increased risk of death associated with abnormal coronary artery patterns and aortic arch obstruction was reported in a multicenter study of the Congenital Heart Surgeons Society.

ASO is now the operation of choice for typical D-TGA at the Children's Hospital, Boston. Operative mortality was 3% since 1985. Anatomic considerations suggesting the morphologically LV may well be a better pump than the morphologically RV which would favor ASO as opposed to the atrial switch operation are: (1) LV consists almost entirely of the sinus or pumping portion, and has only a minimal distal infundibular (conal) component while the RV has a relatively much larger infundibular component, the primary function being to prevent regurgitation rather than to pump, (2) phylogenetically, the LV is the ancient "professional" pump while the RV is a recent modification of the bulbus cordis, (3) the LV is a two coronary ventricle, the RV a one coronary ventricle, (4) the LV has much more compact myocardium than does the RV, (5) the mitral valve leaflets are better designed to occlude a circular systemic, atrio-ventricular orifice than are the tricuspid valve leaflets, (6) the papillary muscles of the LV are large, paired, well-balanced and both arise from the same ventricular wall - the LV free wall, while the papillary muscles of the RV are small, numerous, unbalanced, and arise from both ventricular septal and free walls, (7) the LV has two conduction system radiations, while the RV has only one.

Current anatomic contraindications to the arterial switch operation in typical D-TGA, includes: (a) unprepared LV, (b) aortic intramural left coronary artery arising from the right coronary sinus of valsalva, (c) pulmonary outflow tract stenosis or atresia, (d) aortic outflow tract stenosis with tubular hypoplasia of the aortic arch and preductal coarctation, (e) tricuspid or mitral valve atresia, (f) marked underdevelopment or absence of either the RV sinus or the LV sinus, (g) two major anomaly of the systemic and/or pulmonary veins, as in the heterotaxy syndrome with asplenia according to Van Praagh and Jung.[14]

Objective of the Study

General

To predict the risk of arterial mortality switch operation.

Specific

1. To determine predictors of mortality in ASO.
    a. Pre-operative variables
    b. Operative variables
    c. Post-operative variables
2. To correlate the predictors as to the classification of transposition of the great arteries.
3. To formulate a scoring index this could predict outcome of ASO.

Materials and Methods

Study Design

This is a retrospective cross sectional study which retrospectively identified clinical parameters predictive of mortality in patients undergoing arterial switch operation.

Study Setting

This study was conducted at Philippine Heart Center, East Avenue, Quezon City.

Study Population

Records of pediatric patients with diagnosis of D-transposition of the great arteries (D-TGA) who underwent arterial switch operation from January 1991 to June 2002 at Philippine Heart Center were identified from the pediatric admission and surgical logbooks. One hundred twelve (112) cases were identified but only eighty-three (83) charts were retrieved. Cases were individually reviewed by the principal investigator and only seventy-seven patients were included. Subjects were categorized into those who died and those who survived after ASO. Total enumeration was employed.

Subjects are divided into four groups: a.) transposition of the great arteries as a whole; b.) transposition of the great arteries with intact interventricular septum; c.) transposition of the great arteries those with ventricular septal defect and d.) transposition of the great arteries with restricted pulmonary blood flow.

Excluded from the study were those patients diagnosed to have D-TGA but did not undergo arterial switch operation and those with incomplete records.

Study Outcome Measures

Patient Characteristics

Demographic variables include age and sex. Clinical and laboratory variables cited in the literatures that predict mortality were evaluated. These included age at repair, weight, need for prostaglandin E2, associated cardiac lesions, pre-operative atrial septostomy (Balloon Atrial Septostomy), pre-operative inotropic support, echocardiographic left ventricle indexes (LV mass, LV posterior wall thickness, LVEDD, ejection fraction, fractional shortening) pulmonary artery pressure and preoperative clinical condition. Procedural variables were circulatory arrest time, bypass time, lowest temperature, and anesthesia used; and post-operative condition.

Primary Outcome Measure:

Main outcome measure was mortality after ASO.

Scoring Index Development:

A review of literature was done to identify variables to be included. Demographic, clinical and laboratory parameters identified were age, sex, weight, associated cardiac lesion, prior intervention (balloon atrial septostomy), need for prostaglandin and inotropic support, left ventricle indexes, aorta; pulmonary artery ratio, pulmonary artery pressure and preoperative clinical condition. Procedural variables were bypass time, ischemic time, lowest temperature and anesthesia used. Post-operative variables included presence of arrhythmia, seizures, acidosis, bleeding, metabolic disturbances and need for peritoneal dialysis.

In the formulation of the scoring index, eleven variables were initially included, all of which were the pre-operative variables identified. These were age, sex, left ventricular posterior wall thickness, left ventricular end diastolic dimension, left ventricular mass, ejection fraction, pulmonary artery pressure, aorta: pulmonary artery annulus ratio, fractional shortening, pre-operative intervention specifically balloon atrial septostomy (BAS) and use of dopamine. Age of repair was divided into more than 21 days and less than 21 days based on the study done by Shrivastav.[9] Other variables were divided into normal and abnormal based on the different criteria and/or empirical recommendations. Yasui et al. included performance as follows: before two to three weeks of age in patients with TGA/IVS, LV/RV pressure ratio of >0.8, LV pressure >65mmHg, LV mass >60% of normal, LVPW >4.5mm.[15] Left ventricular end diastolic dimension was divided into normal and abnormal based on the desired LVEDD for patient weight. Left ventricular mass was also divided into normal and abnormal based on the normal range for body surface area. Pulmonary artery pressure was classified into normal and abnormal based on the left ventricular pressure which is equal to, or above 70% of the systemic level (LV/RV ratio=/>0.7).[16] Ejection fraction was divided into normal and abnormal based on the normal mean ejection fraction of 74%, with 95% predictive limit of 64% to 83%.[17]

The study limited the clinical parameters into three from the result of multiple logistic regressions. Data on the three parameters, which were obtained on history and laboratory examination of the patient, were present seventy-seven patients included in the study.

Each of the three clinical parameters was analyzed using odds ratio. The score was developed using the odds ratio of logistic regression. The value of the ratio for a specific clinical parameter is defined as the probability of the clinical parameter in the presence of the outcome (mortality) divided by the probability of the clinical parameter in the absence of the outcome (survived). Odds ratio represents the degree of probability (how many times likely) a clinical parameter in our scoring system will be present in D-TGA patients who will succumb, as compared to those who will survive.

The highest possible score was thirteen (13) while the lowest possible score was four (4). The higher the score, the greater the probability of mortality. Odds ratio was calculated for every level of each of the three clinical parameters.

Analysis of Data

Data gathered were entered on SPSS. Frequency, percentage, means, median, standard deviation and 95% confidence intervals of variables were determined.

Differences in the different variables were determined by chi-square test and independent T- test.

Differences in the variables between those with ventricular septal defect, with intact ventricular septum and those with pulmonary outflow tract obstruction were determined and compared using the independent t-test. A p-value of less than 0.05 was considered statistically significant. Univariate analysis was used to determine association with the outcome. Multiple logistic regressions to determine the independent effect of each variable was also employed. The Kruskal-Wallis test, Mann-Whitney test, odds ratio, sensitivity, specificity, positive and negative predictive values were also used to analyze data gathered.

The proposed scoring system was tested on all patients included in the study. The score for each patient was obtained by adding up the specific values designated for the presence or absence of the clinical parameters.

Sensitivities and specificities for each clinical score in determining patients likely to die were computed. The values obtained were plotted in a receiver operator curve (ROC) to determine the cut off score. The ROC is a graph of the pairs of true positive rates (sensitivity) and false positive rates (specificity) that correspond to each possible cut-off, for the diagnostic test result.

Results

One hundred twelve patients underwent arterial switch operation from January 1991 to June 2002 but only eighty three charts were available for review. Seventy-seven patients were included in the study. The ages ranged from three days to one thousand eight hundred twenty five days (5 years). Most of the patients (76.6%) who underwent ASO were more than twenty-one days of age. Mean age of those who survived was sixty-eight (68) days while those who died were one hundred forty three (143) days (Appendix 1). In D-TGA with IVS, the youngest patient was three (3) days old and the oldest was sixty-seven (67) days old; both patients died. While in D-TGA with VSD, the youngest patient was six (6) days old and the oldest was five hundred fifty (550) days old; both patients survived. In D-TGA with LVOTO, the youngest was thirty-seven (37) days old and the oldest was 5 years. Both of them

died. Of the seventy-seven patients who underwent arterial switch operation, 51% survived and 49% expired. (Appendix 2).

Seventy-three percent (73%) were males and twenty-seven percent (27%) were females, with a male to female ratio of 3:1, with a p-value of 0.034 which is statistically significant. (Table 1).

Patients were classified into three categories and fifty percent (50%) were D-TGA with VSD (Appendix 3).

Several factors were included as possible pre-operative predictors of mortality of ASO. Of the several variables, pulmonary artery pressure and aorta: pulmonary artery ratio was noted to be statistically significant with p values of 0.04 and 0.01 respectively (Table 2).

Table 1. Distribution by sex (P value = 0.03425*)

	SURVIVED		DIED	
SEX	**FREQUENCY**	**%**	**FREQUENCY**	**%**
Male	33	43	23	30
Female	6	8	15	19
Total	39	51	38	49

Table 2. Factors Associated with the Outcome in D Trasposition of the Great Arteries

VARIABLES	**MEAN**	**S.D.**	**P VALUE**
AGE (Days) Died Survived	 144 68	 306 97	0.1465
WEIGHT (Kgs.) Died Survived	 4.325 3.84	 2.088 1.343	0.2290
LV MASS (Gms.) Died Survived	 96.50 96.217	 51.673 4.824	0.9863
LVPW (Systolic) Died Survived	 0.529 0.533	 0.151 0.138	0.9194
LVPW (Diastolic) Died Survived	 0.763 0.755	 0.209 0.195	0.8619
LVEDD Died Survived	 1.934 1.909	 0.553 0.538	0.8430
EF (%) Died Survived	 80.184 80.82	 11.411 11.56	0.8087
FS Died Survived	 48.421 47.641	 13.434 11.00	0.7810
PAP (mmHg) Died Survived	 76.50 70.61	 12.54 12.81	**0.0459***
A:P RATIO			**0.0134***

Associated cardiac lesions were identified as isolated, or in combination with other lesions. The most common associated lesion was patent ductus arteriosus and the least common was atrial septal defect. The presence of the associated cardiac lesion however did not affect the surgical outcome (Appendix 4).

Interventions like were done to improve and stabilize the clinical condition of the patient while awaiting ASO. These interventions however did not affect the surgical outcome of the patients (Appendix 5).

Clinical pre-operative variables identified were also noted which may affect the outcome; however, none was statistically significant (Table 3).

Of the procedural intra-operative variables, only bypass time was noted to be highly statistically significant with a p-value of 0.003 (Appendix 6). The mean bypass time for those who survived was shorter by eighty minutes compared to those who died. The other variables did not affect the surgical outcome. None of the anesthesia used during the procedure affect the outcome (Table 10).

Of the cardiac supports used after surgery, only the use of dobutamine was identified to have statistically affected the outcome with a p-value of 0.024 (Table 4). The use of cardiac supports was given in combination with another, and none was used alone.

Several medical and clinical conditions that developed during the post-operative course were identified. Of the several conditions that affected the surgical outcome of post-ASO patients, the variables that were highly statistically significant were the presence of acidosis with a p-value of 0.0001, followed by the development of bleeding with a p-value of 0.008 (Appendix 8).

Pre-operative variables including the demographic distribution, sex, echocardiographic parameters, presence of associated cardiac lesions, interventions done and the presence of medical problems in the three types of D-TGA were compared, but none of the several parameters affected the outcome. Procedural variables were also included: duration of procedure, anesthesia and cardiac supports used. The cardiopulmonary bypass time in patients with D-TGA with

VSD was statistically significant with a p-value of 0.01. The number of patients, (51%) that belonged to this group could explain our result. Other variables were not statistically significant.

Using the proposed clinical scoring index system, scores were calculated for each of the seventy-seven patients. The best cut-off score was determined with the use of receiver operator curve (ROC). At a score of four (4), the sensitivity is seventy-nine percent (79%), specificity of fifty-four percent (54%), positive predictive value of sixty-three (63%) and negative predictive value of seventy-two (72%). At a score of thirteen (13), sensitivity is three percent (3%), specificity of one hundred percent (100%), and positive and negative predictive values of one hundred percent (100%) and fifty-one percent (51%) respectively. The score of eight (8) was selected as the best cut-off score with sensitivity of thirty-four percent (34%), specificity of ninety-seven percent (97%), positive predictive value of ninety-three percent (93%) and negative predictive value of sixty-one percent (61%). This cut-off score was designated, being the best compromise between maximum sensitivity and maximum specificity for predicting mortality of arterial switch operation. This is the point closest to one-hundred percent (100%) sensitivity and specificity and therefore is the best cut-off in terms of making the fewest mistakes in predicting mortality of arterial switch operation (Fig.1). Based on the sensitivity and specificity determinations, the following cut-off scores were formulated to be able to apply the clinical scoring index. At a score of four to five (4-5), mortality is unlikely; eight to nine (8-9), probable mortality; and thirteen (13), definite mortality (Table 7).

Table 3. Clinical Pre-operative Variables in D-TGA

VARIABLES	DIED Frequency	%	SURVIVED Frequency	%	P value
INFECTION					
+	12	16	9	11	0.5608
-	26	34	30	39	
ACIDOSIS					
+	1	1	2	3	1.0000
-	37	48	37	48	
SEIZURE					
+	3	4	4	6	1.0000
-	35	45	35	45	
ARRHYTHMIA					
+	2	3	2	3	1.0000
-	36	46	37	48	

Table 4. Post-operative cardiac support in D-TGA

VARIABLES	DIED Frequency	%	SURVIVED Frequency	%	P value
DOPAMINE					
+	36	47	39	50	0.2403
-	2	3	0	0	
DOBUTAMINE					
+	18	23	8	10	0.0244
-	20	26	31	41	
NTG					
+	27	35	35	45	0.0746
-	11	14	4	6	
EPINEPHRINE					
+	27	35	31	41	0.5525
-	11	14	8	10	
MILRINONE					
+	16	21	21	27	0.4221
-	22	29	18	23	
NIPRIDE					
+	10	13	11	14	0.8570
-	28	37	27	36	

Table 5. Odds ratio for three clinical variables

CLINICAL VARIABLES	P- VALUE	ODDS RATIO
SEX	0.0167	4.2125
LV POSTERIOR WALL	0.0458	3.7079
A:P ANNULUS RATIO	0.0059	4.6068

Table 6. Proposed clinical scoring system to predict surgical outcome

CLINICAL VARIABLES	SCORE
Sex	
Male	4
Female	0
LV POST. WALL	
Normal (=/ > 4.5 mm)	0
Abnormal (< 4.5 mm)	4
AORTA: PULMONARY ARTERY RATIO	
Normal (=/>1:1)	0
Abnormal (<1:1)	5
TOTAL	13

Table 7. Sensitivity, specificity and predictive values of clinical scores in predicting mortality in ASO

SCORE	Sensitivity	Specificity	PPV	NPV
13	2.63 %	100 %	100	51.32
9	28.95 %	100 %	91.67	58.46
8	36.84 %	97.44 %	93.33	61.29
5	57.89 %	79.49 %	73.33	65.96
4	78.95 %	53.85 %	62.50	72.41

presence of medical problems in the three types of D-TGA were compared, but none of the several parameters affected the outcome. Procedural variables were also included: duration of procedure, anesthesia and cardiac supports used.

Discussion

Transposition of the great arteries has been recognized for nearly 300 years. Mathew Baillie first described the most common variety of transposition, D-TGA, in 1797. There is atrio-ventricular concordance and ventriculo-arterial discordance. Approximately two-thirds of patients have no major associated abnormalities (simple transposition) and one-third have associated abnormalities (complex transposition). The most common associated abnormalities are ventricular septal defect and pulmonary/subpulmonary stenosis.

Before the 1950s, directions and reports of transposition were directed toward definition and morphologic characterization, as there was no effective therapy.

Surgical therapy for transposition began with palliative procedures in 1950 when Blalock and Hanlon described a method of atrial septectomy,[18] to improve the mixing of systemic and pulmonary venous return at the atrial level.

In 1953, Lillehei and Varco described a partial physiologic correction that consisted of anastomosis of the right pulmonary veins to the right atrium and the inferior vena cava to the left atrium.[19]

Complete repairs were attempted throughout 1950s and 1960s. Early attempts by both Mustard and Bailey were frustrated by the inability to maintain coronary perfusion and adequate oxygen delivery to the myocardium because the coronary circulation was either partially or completely RV dependent. The successful arterial switch procedure done by Jatene in 1975 in infants with TGA-VSD[22] has not been successfully used in older children, because the left ventricle had not been prepared for the systemic pressures it would have to pump against.

Arterial switch operation is the optimal treatment for transposition, so that detailed information about the outcomes and the circumstances in which they are suboptimal becomes important.

Clinical experience with the arterial switch operation suggested that, when this operation is performed in the neonate for D-TGA with intact ventricular septum, surgery should be undertaken within the first two weeks of life. Beyond this time, there is increasing likelihood that the left ventricle will be unable to accommodate the acute increased workload of systemic pressure.

During the past 15 years, the results of ASO have substantially improved. The mortality rate has decreased from approximately 20% in the early 1980s to 3% in the full term infants with D-TGA who are operated on, in the first two weeks of life.[23]

The increased incidence of the male sex in patients with complex cyanotic congenital heart diseases was observed in this study. The three times increased number of males compared with females in this study made the males more susceptible to the poor surgical outcome of D-TGA patients. Thus in the scoring index developed, male patients has an increased risk of mortality. A score of four was assigned to male patients and zero for female patients from the result of the multiple regression analysis.

In contrast to the findings of Blume and Quaegebeur who identified lower birth weight and prematurity as independent risk factors for ASO, our study found otherwise. The presence of atrial septal defect is most desirable in infants with TGA. The frequency of a large ASD occurring naturally in D- TGA is low, as was noted in this study. But when a large ASD is present, infants have good oxygen saturation because of good mixing.

Although an atrial shunt is the best site for intracardiac mixing in these patients with parallel circulation, the presence of VSD in fifty-one percent of our patients is generally accepted as being associated with better survival. This subset of patients is only mildly or moderately cyanotic at birth, and surgical intervention in the first few days or weeks of life is usually not necessary, and the ASO done at a much latter date. This group of patients is responsible for the wide range of age distribution, and why age is not a determinant of the outcome. Although the incremental risk of older age on mortality after an arterial switch operation for simple D-TGA observed by several investigators[24] probably reflects the failure of the left ventricular wall to thicken during the first few weeks of life in patients with simple D-TGA, this finding is refuted by our observation.

The echocardiographic criteria for a good candidate for ASO were strictly followed, and the different echocardiographic parameters for ASO were included in our study. However, of the several parameters, by univariate analysis, pulmonary artery pressure and aorto: pulmonary annulus ratio was identified as important risk factors to the outcome. Pulmonary artery pressure is reflective of the left ventricular pressure, and this may indicate the ability of the left ventricle to handle acute increased workload of systemic pressure after correction. The pulmonary artery pressure as

an ASO parameter has been established and universally accepted, and is confirmed by our findings.

Another important risk factor is the aorto-pulmonary artery annulus ratio. However, because of the small number of subjects of this study, our finding that the aorto-pulmonary artery ratio as a significant risk factor to the surgical outcomecould be verified and validated. On multiple logistic regression analysis, this variable was significantly correlated with the outcome. A score of five was given to those with abnormal A:P annulus ratio and a score of zero for those with normal A:P annulus ratio.

By multiple logistic regression analysis, left ventricular posterior wall thickness was also noted to be contributory to the outcome. Patients with normal left ventricular posterior wall thickness (LVPW) of more than or equal to 0.45 cm has better outcome as compared to those with subnormal LVPW. Likewise, in the scoring index developed, LVPW has a score of four for those with subnormal LVPW while a score of zero was assigned for those with normal LVPW. Same finding was noted in the study done by Yugui et al.[15]

In the 1980's, Norwood and Quaegebeur noted that the presence of patent ductus arteriosus, was a significant risk factor in the surgical outcome. PDA was known to decrease the survival after a balloon atrial septostomy,[25] an incremental risk factor for death after VSD repair,[26] and after atrial switch for D-TGA.[27] Patent ductus arteriosus is the most common associated lesion noted in our patients, but its presence did not affect the outcome. This result indicates an evolution of the development of optimal surgical techniques and minimal human error as well as the methods of care in the current era.

Pre-operative variables such as infection, acidosis, seizure and arrhythmia were noted to be non-contributory to mortality as was noted in other studies.

Several investigators found that prolonged cardiopulmonary bypass time and ischemic time, were important procedural risk factors.[23] Their findings of longer duration of cardiopulmonary bypass time as a risk factor to the ASO outcome is consistent with our findings. In the local study done by Panergo et. al, both bypass time and ischemic time was noted to have significant correlation with the outcome in patients with D-TGA/IVS/PDA28. Arterial Switch Operation patients who survived had an eighty-minute shorter cardiopulmonary bypass time than those who died.

The use of Dobutamine in thirty-four percent of patients as post-operative cardiac support was important in the outcome of the simple TGA group, which was noted to have used this inotrope more (fourteen percent) frequently than the other two groups.

Two important post-operative conditions that we identified which affected the ASO procedure were acidosis and bleeding. Hypoxia and acidosis are detrimental tomyocardial function, and stimulated the carotid and cerebral chemoreceptors, causing hyperventilation and a low PCO_2 in the pulmonary circulation. It can also lead to other metabolic problems like hypoglycemia which is believed to be due to pancreatic islet hypertrophy and hyper- insulinism, as a tendency toward hypothermia.

Hypoglycemia is common in large for gestational age babies and infants of diabetic mothers, and D-TGA babies are common in diabetic mothers. No specific reason however could explain the cause of these clinical conditions, and we believe that it could be multifactorial, from the pre-operative period until the post-operative time.

These high risk patients need appropriate assessment and prompt referral for early evaluation and definitive management for optimum and favorable outcome. Presently, there is no known attempt to come up with a clinical scoring system which could help cardiologists and surgeons assess the risk of mortality in arterial switch operation. It is thus proposed, that this scoring system be used in predicting mortality in arterial switch operation. The scoring system only takes into account sex, left ventricular posterior wall thickness and aorto: pulmonary annulus ratio.

Conclusion

This is a review of seventy-seven patients who underwent arterial switch operation with the aim of coming up with a clinical scoring index to aid cardiologists and surgeons in assessing or predicting the risk for mortality of arterial switch operation.

Pre-operatively, the variables identified as predictors of mortality in arterial switch operation were pulmonary artery pressure and aorto: pulmonary annulus ratio. As to classification, none of the variables affected the outcome. Operative variable that significantly affected the surgical outcome was bypass time. Post-operative variables identified were use of dobutamine, acidosis and bleeding. In D-TGA with IVS, use of dobutamine was significantly correlated with a good outcome. While in D-TGA with VSD, presence of acidosis was significantly correlated with mortality.

In the clinical scoring index developed, the cut off score was at eight, which has 37% sensitivity and 97% specificityfor predicting mortality. At a score of 4-5; sensitivity is at 79%-58% and specificity of 54%-79%, and mortality is probable. At a score of 9-13; sensitivity is at 3%-29% and specificity is 100% and mortality is definite.

Recommendation

It is thus recommended that this research be continued so more subjects may be included and the sample size increased. Other significant variables may be added, which were not

statistically significant in this study, because of the limited number of subjects. An increased number of significant variables may make this scoring index systemmore valid for future guide to our cardiologists and surgeons prior to ASO procedure.

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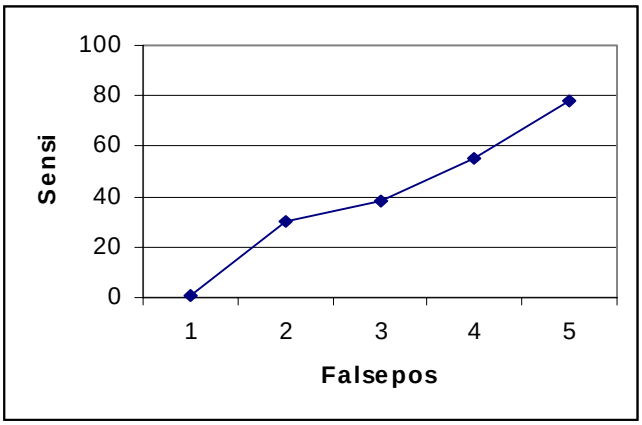

Figure 1.

Appendix 1. Distribution by age

AGE	SURVIVED FREQUENCY	%	DIED FREQUENCY	%
< 21 days	10	13	8	10
> 21 days	29	38	30	39
TOTAL	39	51	38	49
Mean +/- SD	68 +- 97		143 +- 306	
Median	34			43
P value	0.1464			

Appendix 2. Distribution according to outcome

OUTCOME	FREQUENCY	PERCENTAGE (%)
SURVIVED	39	51%
DIED	38	49%
TOTAL	77	100%

Appendix 3. Distribution by D-TGA classification

CLASSIFICATION	SURVIVED		DIED	
	FREQUENCY	%	FREQUENCY	%
TGA w/ IVS	16	21	16	21
TGA w/ VSD	21	27	18	23
TGA w/ LVOTO	2	3	4	5
Total	39	51	38	49

Appendix 4.. Distribution as to associated lesion in D-TGA

LESIONS	DIED		SURVIVED		P value
	Frequency	%	Frequency	%	
PFO					
+	19	25	18	23	0.9127
-	19	25	21	27	
PDA					
+	32	42	31	40	0.8089
-	6	8	8	10	
PR					
+	37	48	38	50	1.0000
-	1	1	1	1	
TR					
+	1	1	0	0	0.4935
-	37	48	39	51	
MR					
+	1	1	0	0	0.4935
-	37	48	39	51	
COA					
+	2	2	0	0	0.2402
-	36	47	39	51	
PS					
+	2	2	3	4	0.6748
-	35	46	37	48	
ASD					
+	1	1	0	0	0.4935
-	37	48	39	51	
DEXTROCARDIA					

Appendix 5. Distribution as to intervention in D-TGA

INTERVENTION	DIED		SURVIVED		P value
	Frequency	%	Frequency	%	
BAS					
+	16	21	14	18	0.7454
-	25	32	22	29	
Use of Dopamine					
+	22	28	23	30	0.8925
-	16	21	16	21	
Use of PGE1					
+	13	18	11	14	0.7469
-	25	32	28	36	
Use of Caverject					
+	10	13	8	10	0.7397
-	28	36	31	41	

Appendix 6. Procedural variables in D-TGA

VARIABLES	MEAN	S.D.	P VALUE
BT (minutes)			
Died	252.11	156.18	0.00311*
Survived	171.56	50.61	
X-CLAMP TIME			
Died	105.61	62.77	0.1189
Survived	85.64	47.40	
LOWEST TEMP.			
Died	25.57	3.75	0.6029
Survived	25.99	3.33	

Appendix 7. Anesthetic used in D-TGA

VARIABLES	DIED		SURVIVED		P value
	Frequency	%	Frequency	%	
ISOFLURANE					
+	27	35	25	32	0.6834
-	11	15	14	18	
SEVOFLURANE					
+	8	10	9	10	0.9516
-	30	40	30	40	
FENTANYL					
+	35	45	39	51	0.1153
-	3	4	0	0	
PAVULON					
+	19	25	20	25	0.9081
-	19	25	19	25	

Appendix 8. Post-operative conditions in D-TGA

VARIABLES	DIED Frequency	%	SURVIVED Frequency	%	P value
SEIZURE					0.3838
+	19	25	18	23	
-	13	17	21	27	
INFECTION					0.0658
+	6	8	16	21	
-	27	36	23	30	
ARRHYTHMIA					0.6395
+	9	12	8	10	
-	23	30	31	40	
PD					0.7459
+	5	6	5	6	
-	27	36	34	44	
ACIDOSIS					0.0001*
+	6	8	0	0	
-	37	48	39	51	
BLEEDING					0.0084*
+	19	25	10	13	
-	13	17	29	38	
HYPOTENSION					0.5147
+	6	8	0	0	
-	9	12	3	4	
MET. ABN.					0.7781
+	6	8	7	9	
-	27	36	32	42	

Original Article

Effect of Medroxyprogesterone Acetate on the Prevention of Postpericardiotomy Adhesions: Experimental Study in an Animal Model

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Pericardial adhesions pose for hazard during reentry. They increase bleeding and prolong the operation time. Several studies regarding the prevention of pericardial adhesions have already been reported using drugs that either promote fibrinolytic activity or modulate the inflammatory response. Others have reported the use of pericardial substitutes such as preserved equine pericardium, silicon rubber and expanded polytetrafluoroethylene as pericardial substitutes. However, these strategies either interfere with hemostasis or are associated with a number of complications such as infection, sterile abscess formation, persistent reactive fever, reactive pericarditis and even severe adhesions.

Preoperative intramuscular administration of Medroxyprogesterone Acetate (MPA) prevents postoperative intraabdominal adhesions in animal models. However, no study has been yet undertaken using medroxyprogesterone acetate in the prevention of post-pericardiotomy adhesions. Histologic similarities between peritoneum and pericardium exist and both mesothelial surfaces respond quite similarly to various mechanical and chemical insults by either reepithelialization or by forming adhesions.

Fourteen adult rabbits were divided into two groups. A controlled surgical trauma was done on the pericardium to induce adhesions by forced air desiccation and abrasion with surgical gauze. Comparable volumes of normal saline solution (control group) and MPA solution (study group) were then instilled in the pericardium of control and study groups respectively. Adhesion scores were analyzed in a necropsy 6 weeks later. The study group showed lesser areas of adhesion (p value 0.001) and the absence of fibrosis and collagen formation on H & E and Trichrome stains (p value 0.02).

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Keywords: medroxyprogesterone acetate; postpericardiotomy syndrome; non-human; pericardial adhesion

Pericardial adhesions pose hazard during surgical reentry, it increase bleeding and prolong the operation time. The incidence of serious cardiac injury during reoperative median sternotomy ranges from 2 - 6%.[1] Dobell and Jain reported a 56% mortality rate associated with injury to aortocoronary bypass graft because of impaired visibility of previous bypass conduits and of the native coronary arteries. Hemorrhages occurred in 88% of reoperative procedures after median sternotomies particularly when the pericardium was left open.[2] Among children with congenital heart disease who underwent initial palliative procedures, repeat sternotomy for subsequent intermediate or definitive procedures were associated with 50% myocardial injury and 8% mortality rate.[3] With increasing cardiac reoperations for congenital heart disease, coronary revascularization and late bioprosthesis failure in valvular heart surgery, injuries due to postpericadiotomy adhesions are becoming even more common.

Numerous studies on the prevention of pericardial adhesions have been reported, but to this date, none has been satisfactory.

Pericardial closure at the time of initial procedure prevents retrosternal adhesion formation but can severely impair the hemodynamics by constricting the myocardium. In a study done by Rao et al, cardiac and stroke work indices were significantly depressed in the early postoperative period when the pericardial sac was closed.[4] Other strategies employ drugs and pericardial substitutes.[5, 6,7,8,9,10] However, the use of drugs that inhibit fibrinolysis interfere with hemostasis and the use of pericardial substitutes results in capsule formation that either obscure anatomy or creates another level of adhesion that is even more difficult to dissect. Other authors have reported the association of heterologous bovine pericardium with infection, sterile abscess formation, persistent reactive fever, reactive pericarditis and severe adhesions.[10]

Preoperative administration of medroxyprogesterone acetate (MPA) has been proven to prevent postoperative intraabdominal adhesions in animal models.[11,12,13,14]

Proposed mechanisms for its beneficial effects on adhesions involve inhibition of fibroblast formation[15] and hormonal regulation of the fibrinolytic system.[16,17] It is,

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however, unclear whether these findings are applicable to pericardial adhesions. No study has been yet undertaken using medroxyprogesterone acetate in the prevention of post-pericardiotomy adhesions.

The pericardium and peritoneum are similar in most respect albeit they invest two different body cavities. Histologically, both are composed of interdigitating mesothelial cells supported by cytoskeletal structural system. Mechanically, both protect organs they invest from external friction and provide a barrier to inflammation from contiguous structures. Both mesothelial surfaces respond quite similarly to various mechanical and chemical insults by reepithelialization or by forming adhesions.

Research Objectives

***General Objective* :**

To evaluate the efficacy of medroxyprogesterone acetate (MPA) in the prevention of postoperative pericardial adhesion formation.

Specific Objectives:

1. To compare the extent of pericardial adhesions observed in the two groups by measuring the area (mm^2) of the retrosternal-epicardial soft tissue interface.
2. To compare the severity of pericardial adhesions observed in the two groups by determining the presence of collagen formation using the trichrome stain.

Materials and Methods

Design

A randomized controlled study to evaluate the efficacy of MPA in reducing post-pericardiotomy adhesion formation comparing it with controls in rabbit model.

Setting

Animal Care Facility and Experimental Laboratory, Philippine Heart Center

Subjects

This study was approved by the Surgical and Experimental Research Committee of the Philippine Heart Center. Fourteen adult New Zealand rabbits weighing 1.5 – 2 kg were divided into 2 groups. All rabbits were acclimatized for a period of two weeks before the experiment and received humane care. Food and water was withheld two hours prior to the procedure. One hour before the sternotomy was made; each rabbit received a prophylactic antibiotic in the form of ampicillin 250mg intravenously via a marginal ear vein. Ketamine (50mg/kg) was administered intramuscular on the right thigh as premedication and midazolam (2mg/kg) intravenously was given as general anesthesia. This was supplemented by either inhalation delivered via a face mask[1]. After anesthesia, the chest was opened through a median sternotomy and a 'controlled surgical trauma' was inflicted on the pericardium of all animals by gauze abrasion. This was followed by forced air desiccation using a compressed filtered air blower for 5 minutes at a flow rate of 2 liters per minute until surfaces were dry and petechial hemorrhages appeared on the pericardium and epicardium. Before chest closure, 1 ml of normal saline solution (Control group) and 1ml of solution containing normal saline + MPA (100mg/kg), (Study group) were instilled in the pericardial cavity. Meticulous hemostasis was affected prior to sternal closure. The sternum then was closed using polyester nonabsorbable (ticron 2-0) interrupted sutures. However, the pericardium was left open to allow the formation of retrosternal epicardial adhesions. Postoperatively, the animals were placed in cages in two's and allowed free access to food and water. Powdered Ampicillin 500 mg were added to each liter of drinking water and given liberally to the animals until 7^{th} postoperative day.

Six weeks later, the rabbits were sacrificed and their hearts were carefully harvested along with the pericardium and the anterior chest wall and fixed in buffered formalin solution. Six sections, 2mm apart, of each heart were stained with hematoxylin and eosin (H & E) and trichrome stains to demonstrate adhesion formation and collagen deposition. Under low power and high power magnification, an independent observer (pathologist) assessed the presence and dimensions of retrosternal-epicardial adhesions. The trichrome stain, which imparts a greenish hue on the collagen, was used to determine the presence of collagen formation.

Statistical Analysis

Statistical software, EPIINFO, was used to analyze variables. Assuming a 5% adhesion-free rate in the saline (control) group and 90% adhesion-free rate in the medroxyprogesterone acetate (study) group, with 95% confidence level and 80% power of test, minimum sample size computed were 7 per group. Differences in the retrosternal adhesion areas between the two groups were determined using the Mann-Whitney test and difference between the results of trichrome staining was analyzed using 2-tailed Fisher exact test with p values <0.05 deemed statistically significant.

Results

All rabbits in the control group (n=7) developedadhesions with adhesion areas ranging from 4.25-5.24 mm^2 with a mean area of 4.684 mm^2. Two rabbits in the study group (2/7) developed adhesion with an area of 0.5mm^2 and 1.7mm^2, respectively. (Table I). Figure 1 shows the pericardial-epicardial adhesions on H & E staining. Comparing their adhesion areas, the placebo group (normal Saline) had

significantly more adhesions compared with the study group (p value=0.001). On trichrome stain, all rabbits, 7/7(100%), in the control group stained positive whereas only two, 2/7(28.57%), in the study group stained positive for the presence of collagen formation (Table 2). This was statistically significant with a p value of 0.02. Figure 2 shows trichrome positive stain for collagen as seen in the control group. Figure 3 shows H & E stain in study group devoid of retrosternal-epicardial adhesions.

Table 1. Comparison of retrosternal adhesions

Adhesion area (mm^2)	Control group (n=7)	Study group (n=7)	p Value
Mean Standard Deviation Range	4.684 mm^2 +0.360 4.25 – 5.24	0.300 mm^2 +0.630 0.5 – 1.7	0.001***

Table 2. Comparison of presence of collagen formation

Collagen formation	Control group (n=7)	Study group (n=7)	*p* Value
Positive	7	2	0.021
Negative	0	5	*
Total	7	7	

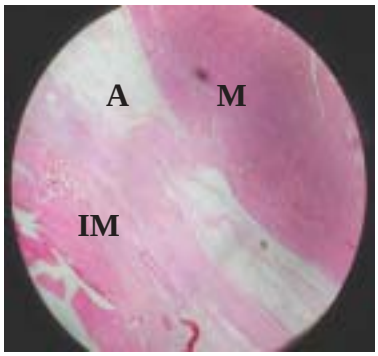

Figure 1. ***Hematoxylin and eosin stain showing epicardial-pericardial adhesion in experimental rabbit model with normal saline as placebo.***
A-adhesion, M- myocardium, IM-intercostal muscle

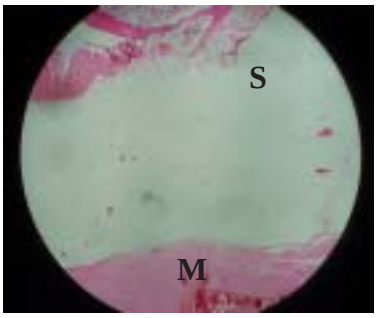

Figure 3. ***Hematoxylin and eosin stain showing the pericardial-myocardial interfaces devoid of adhesions with pericardial instillation of medroxy-progesterone acetate***
S-sternum, M-myocardium

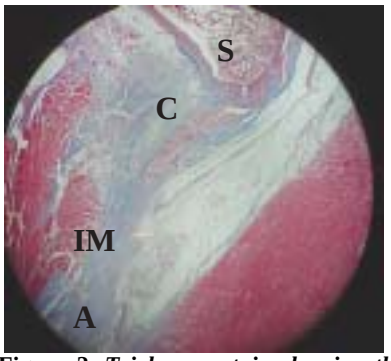

Figure 2. ***Trichrome stain showing the presence of collagen (Bluish-green) between the sternum and myocardium.***
A-adhesion, M-myocardium, IM-intercostal Muscle, C-collagen, S-sternum

Discussion

Presently there are no standardized experimental models for pericardial adhesion. Most experimental studies however, used abrasion and/or warm air desiccation to produce mesothelial injury.[19,20,21] In these studies, time interval between sternotomy and examination for pericardial adhesions varied from 1 week to as long as 10 months. Adhesion rates were 80-100%. Similarly, all animals in the control group of our experiment had dense adhesions after 6 weeks. During this time, resorption of the MPA solution was complete and no interference on gross and microscopic examination was noted.

Recent advancement in molecular biology has led to the identification and better understanding of numerous biologically active molecules that participate in adhesion formation. Among these key molecules are the growth factors, cytokines, proteases and extracellular matrix. The delicate balances of these key molecules are known to regulate inflammation, fibrinolysis, angiogenesis and tissue remodeling.[22] Tissue handling, desiccation, instruments, contact with foreign materials, even sutures and gloves

starches are most commonly implicated in the development of adhesions.[23]

Mesothelial injury leads to the activation of the coagulation mechanism in which varieties of chemical messengers are released bringing about a cascade of events that culminates at tissue repair and/or adhesion formation. Macrophages are activated, enhancing phagocytosis and secretory activity. Polymorphonuclear cells (PMN), through the process migration initiate a fibroproliferative inflammatory reaction.[24] New mesothelial cells are recruited on to the injured area to accomplish reepithelialization. Adhesion formation starts with insolubilization of fibrin polymers and interaction with fibronectin and certain amino acids. Fibrin gel matrix, the progenitor of adhesions, starts to form bands between mesothelial surfaces. Five to seven days following surgical trauma, reepithelialization and
adhesion formation is well in place.[25] Thereon, maturation of adhesions follows with collagen deposition and neovascularization. Fibrin bands ultimately become organized and permanent.[26] Protective in nature and an important part of the normal healing response, surgical adhesion now posts challenges to surgeons during reoperations.

Medroxyprogesterone acetate (MPA) (17α-hydroxy-6-α-methyl progesterone) is a synthetic derivative of naturally occurring progesterone that is used primarily for contraception and treatment of various gynecological conditions. Appropriate doses cause anovulation in the female and suppression of Leydig cell function in the male. Like other steroid hormones, the site of action is within the cell nucleus where binding with progesterone receptors and modification of gene transcription occur. Administered intramuscularly, MPA is released slowly but in a persistent manner. Peak plasma concentration are seen between 4-20 days and circulating levels detected as long as 7-9 months after administration.[27] When instilled in the pericardial cavity, MPA appears as a thin film of white solution over the pericardium.

Androgens like MPA may manifest antiinflammatory effects and corticoid-like activity.[28] Adhesion prevention may be secondary to inhibition of fibroblast emigration and procollagen gene expression through suppression of tumor growth factor (TGF-B) secretion.[29] However it seems that there are mechanisms other than its anti-inflammatory and immunosuppressive actions that are responsible for its beneficial effects on adhesion formation. One such mechanism involves hormonal regulation of the fibrinolytic system. Activation of fibrinolytic enzymes prevents fibrin gel matrix formation but during surgery fibrinolytic activity is reduced due to activation of plasminogen activator inhibitors (PA_1 & PA_2) which are secreted by mesothelial, endothelial and inflammatory cells.[17,30,31,32]

Several hormone replacement therapy (HRT) studies have reported on the effects of steroid hormones on PAI-1.[33,34]

In these studies, PAI levels were reduced by as much as 50% among subjects receiving estrogen and medroxyprogesterone acetate. PAI inhibits both tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA), thus blocking the conversion of plasminogen to plasmin. Conceivably, steroid hormones may prevent adhesion formation by enhancing the clearance of fibrin gel matrix by the fibrinolytic system through its suppressive effects on PAI levels. However, the exact mechanism of action of MPA in the prevention of adhesions, at present, is at best speculative and remains to be elucidated. Potential adverse effects of intrapericardial instillation of MPA include mediastinitis and adverse allergic reactions.

Conclusion and Recommendation

Medroxyprogesterone Acetate, a progestational agent, has potential beneficial effects on the prevention of post-pericardiotomy adhesions compared with placebo. Further studies should be geared towards finding out the exact mechanism of action of its effects and possible clinical application in surgery.

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Case Study

Heterotopic Solid-Pseudopapillary Tumor of the Retroperitoneum

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Solid - pseudopapillary tumor (SPT) of the pancreas is an uncommon but a distinctive neoplasm commonly occurring in young women. It has been reported under various terms such as adenocarcinoma of childhood, cystadenocarcinoma, papillary epithelial neoplasm, and papillary cystic tumor but has been designated as solid-pseudopapillary tumors in the current edition of the WHO classification of tumors of the exocrine pancreas. They are often characterized by its indolent behavior and low malignant potential. Very few cases have mentioned recurrences and distant metastasis. These tumors are often asymptomatic or associated with non-specific abdominal symptoms. About 500 cases have been reported in worldwide literature but very rarely that it has been described outside of the pancreas.[1] Tornoczky et al[1] described 6 cases of extrapancreatic SPT's. Our case is that of a 17 year old female who has undergone exploratory laparotomy due to a gradually enlarging, non-tender abdominal mass diagnosed by CT–scan as hepatic hemangioma. A referral to our institution was done where hepatobiliary radionuclide scan and aortogram, celiac and superior mesenteric angiogram confirmed the initial findings of hepatic hemangioma. Intraoperatively, the mass was seen at the retroperitoneum at the right infrahepatic area, pushing the duodenum and was distinct from the pancreas. Grossly, the mass was a large well encapsulated tumor with a unilocular cyst with trabeculations on cut sections. Microscopic sections show tumor cells arranged in solid sheets and pseudopapillary formations. Immunohistochemical evaluation was done consisting of NSE, Cytokeratin, Vimentin, Alpha-1-antitrypsin, Alpha-1-antichymotrypsin, Alpha-fetopoptein and special stains such as PAS confirming the diagnosis of solid-pseudopapillary tumor.

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Solid-pseudopapillary tumor (SPT) of the pancreas is is recognized as uncommon but a distinct pathologic pathologic entity. Rarely that such entity has been reported outside of the pancreas. Most of the extrapancreatic SPT's that have been reported were seen mostly in the mesocolon, one each in the liver and the omentum.[1]

The origin of the tumor has been disputed with some studies suggesting either an acinar or endocrine cell origin.[2] Though it is characterized by its indolent behavior and is of low malignant potential , there have been few reported cases of local recurrences,[3] and distant metastasis. [2,3]

Macroscopically, it presents as a well encapsulated tumor usually rubbery and with extensive areas of hemorrhage and necrosis. Histologically, the tumor cells are arranged in solid sheets while the pseudopapillary forms have a columnar appearance with palisading arrangement around a central vascular core.[1] Both patterns are characterized by cells with round to oval nuclei with fine chromatin, inconspicuous nucleoli with abundant pale to eosinophilic cytoplasm. Though atypia maybe present it is usually very mild.[4] Mitotic figures[4] are rarely observed but some have reported the presence of multinucleated giant cells.[5] Nuclear grooves and convolutions are typical.The stroma is usually fibrous with hyalinization and is highly vascularized. Clusters of foamy histiocytes are also seen in other areas. Periodic Acid Shiff (PAS) (+) hyaline globules are also seen in the stroma.

Some studies show that inspite extensive sampling most of them failed to see ectopic pancreatic tissue.[5] Some have also reported the presence of ectopic pancreatic tissue providing the only clue to the diagnosis.[1] The diagnosis of SPT's are often distinctive even at a heterotopic site. Histologic diagnosis of SPT's are often straight forward that immunohistochemical evaluation is considered to differentiate this with other entities.

The purpose of this paper is to increase the awareness of this rare tumor known as solid-pseudopapillary tumor especially those seen outside of the pancreas and to differentiate this tumor with the other solid and/or papillary and cystic tumors in the retroperitoneum due to its distinct gross and histologic features as well as it's indolent behavior inspite of the diversity of the cellular components of the tumor.

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Case Summary

A 17 year old female, single was admitted for the first time at a tertiary institution due to a gradually enlarging abdominal mass. Her condition started a year prior to consult as a gradually enlarging abdominal, non-tender, movable mass with no other associated signs and symptoms.

Two months prior to admission, the patient felt that the mass has almost doubled in size and this time was associated with vomiting and diarrhea. She sought consult at a local hospital and CT-Scan was done results of which revealed a hepatic hemangioma. She underwent exploratory laparotomy where a large retroperitoneal mass was seen with an intraoperative diagnosis of hepatic hemangioma. Due to the complex and delicate nature of the mass the surgeon opted not to remove the mass and just close the abdomen. No biopsy sample of the mass was taken. A referral to a Gastroenterologist was done to our institution and hence subsequent admission. A hepatobiliary radionuclide scan revealed a space occupying mass at the infrahepatic area with an impression of a complex cystic mass consistent with a hemangioma. Aortogram, celiac and superior mesenteric angiogram was likewise done revealing a large minimally vascular mass in the right hemiabdomen with the differential diagnoses of an exophytic liver hemangioma or a mass originating from the head of the pancreas.

She underwent another exploratory laparotomy on the 15th hospital day. Intraoperative findings revealed an 18 x 18 cms. cystic, movable mass at the retroperitoneal area located on the right subhepatic area pushing the duodenum anteriorly to the left. Pancreas appears grossly normal and the mass is distinctly separate from the pancreas and the right kidney while the common bile duct is seen directly above the mass .

Grossly, the specimen is described as a well-encapsulated, globular, fluctuant, tan-pink, cystic mass with focal areas of hemorrhage on the surface. It measures 16 x 13 x 9.5 cms. Cut sections reveal a unilocular cyst with trabeculations and contain mostly blood clots and measures 15 cms in diameter (Fig. 1).

Microsections of the mass show tumor cells arranged in pseudopapillary pattern with fine fibrovascular septae (Fig.2) and some in solid patterns (Fig.3). The individual cell appears round with oval, fairly uniform nuclei and fine chromatin. The cytoplasm is clear to eosinophilic. Eosinophilic hyaline globules are noted in some areas (see Fig.4). Also seen are areas with hemorrhage admixed with foamy (see Fig.5) and hemosiderin laden macrophages. The gross and microscopic findings are consistent with solid - pseudopapillary tumor of extrapancreatic location.

Immunohistochemistry consisting of the following stains are requested: Cytokeratin, Vimentin, Neuron Specific Enolase, Alpha fetoprotein, Alpha -1-antitrypsin and Alpha-1- antichymotrypsin and special stains such as PAS. The tumor shows positivity with Neuron specific enolase Alpha-1-antitrypsin , Alpha-1-antichymotrypsin and show focal reaction with Vimentin. The hyaline globules stained positively with PAS. Cytokeratin and Alpha fetoprotein show a negative reaction with the tumor cells. The patient tolerated the procedure well and the rest of the post-operative course was uneventful and was discharged improved on the 20th hospital day. The patient was doing well on her last follow up.

Discussion

Solid-pseudopapillary tumor (SPT) of the pancreas was previously thought of as an unusual carcinoma,[11] or a non-functioning islet cell carcinoma.[12] It was not until the original description of Frantz[7] that it was thought of as a separate and distinct clinical entity. It was reported previously as adenocarcinoma of childhood, cystadenocarcinoma, papillary epithelial neoplasm, papillary cystic tumor, solid and cystic acinar tumor solid and papillary epithelial tumor[5]and Frantz's tumor[7] but has come to finally be known as solid-pseudopapillary tumor according to the current edition of the World Health Organization classification of tumors of the exocrine pancreas.[8]

This classification has recognized SPT as a rare and pathologically distinct entity. SPT's constitute less than 1% [1] of all pancreatic tumors. There are over 500 cases[2,13] of SPT's of the pancreas that has been reported in literature but the occurrence of SPT's in heterotopic site has not been well recognized. We have found only 6 cases[2,4] of extrapancreatic SPT's in our review of literature. (Table 1)

Table 1. Summary of the present and previous published cases of extrapancreatic Solid-pseudopapillary tumor

	Size (cms.)	Age/ Sex	Site	Presence of Heterotopic Pancreas	Symptoms
Case1[11]	8	13/F	Mesocolon	Yes	Pain
Case2[12]	7	17/F	Omentum	Yes	Mass
Case3[13]	6	33/F	Mesocolon	Yes	Mass
Case4[14]	7.5 & 5.5	41/F	Liver	No data	Distention
Case5[15]	8	25/M	Mesocolon	Yes	None
Case6[1]	21	15/F	Mesocolon	Yes	Pain
Present case	16	17/F	Retroperito-neum	No	Mass

SPT is a tumor predominantly occurring in young female patients. The male: female ratio is 1:9.5.[14] The age range is 8 -72 years with a mean age of 27.[14] Cases occurring in the first decade are distinctly unusual. Because of the significant female sex predilection for SPT, many cases have been studied for the expression of estrogen and progesterone receptors. This suggests that these tumors are either dependent on female hormones and or related to the cells of the female genital tract in particular the ovary during embryogenesis but most studies of female hormones in these tumors have failed to demonstrate the presence of such hormones. It would be theorized that the close approximation between the anlage of the genital ridges and the pancreatic anlage during embryogenesis may lead to the attachment of these ovarian tissues into the pancreatic tissue. This could perhaps partially explain its predominance among young females.

The presenting features of SPT are relatively non-specific. Patients may present with symptoms related to compression of adjacent structures which include nausea, vomiting and other intestinal symptoms. Abdominal pain or fullness also occurs. In many cases, there is a palpable upper abdominalmass, which maybe detected incidentally during routine physical examination. This case presented as a gradually enlarging non-tender abdominal mass associated with nausea and vomiting. SPT's are not usually associated with paraneoplastic syndromes inspite of the hormones or enzymes produced by the tumor.

Grossly, SPT's are well encapsulated tumors, rubbery to fluctuant masses and some appears bosselated.[6] The most consistent gross morphological findings are the presence of unilocular to multilocular cysts as well as areas of extensive hemorrhage and necrosis. Cut section often shows multiple or unilocular cysts[4] and some of the cysts may have honeycomb like configuration.[6] This case presents as a well encapsulated fluctuant mass with a unilocular cyst with trabeculations seen on cut sections containing mostly blood clots. Most of the cysts contain extensive areas of hemorrhage and necrosis which makes only the periphery of the tumor suitable for histopathologic sections.[4] The size of most SPT's ranges from 1.5-30 cms, with a mean of 10.5 cms. Our specimen measures 16 x 13 x 9, 5 cms. Smaller SPT's are less likely to show prominent cystic changes are less sharply circumscribed and often appear unencapsulated.

Microscopically, the growth patterns of the tumors are heterogeneous with a combination of solid, pseudopapillary, and/or hemorrhagic pseudocystic structures in varying proportions. The solid and pseudopapillary patterns as well as the cysts and hemorrhage are the result of progressive degenerative changes occurring in a fundamentally solid tumor with a rich vasculature. Admixed with the epithelial components are hyalinized to myxoid connective tissues forming small strands or large areas along thin walled vessels. The cysts are often lined by low cuboidal epithelium which occasionally forms pseudopapillary projections with the cells beginning to fall apart forming a residual rim of cells clustered around a small vessel. Thus, each perivascular cluster represents one pseudopapillae. Cystic cavities are often filled with eosinophilic material which sometimes appears scalloped on the edges. Pseudopapillary structures forming pseudorosettes are almost uniformly seen and sometimes it can be confused with yolk sac tumors of the retroperitoneum. The cells in the solid areas appear as sheets and nests of uniform polygonal epithelioid cells separated by small vessels with variable amounts of perivascular collagen. They often contain cholesterol granulomatas, some foamy macrophages as well as hemosiderin laden macrophages which is also a result of degenerative changes.

PAS (+) hyaline globules are seen in varying sizes and proportions. Both cells from the solid and pseudopapillary areas are characterized by round too val nuclei with fine chromatin and inconspicuous nucleoli with abundant pale eosinophilic cytoplasm. Nuclear grooving and convolutions are typical. Our case showed exactly the same histologic features.

It must also be emphasized that Tornoczky et al [1] was able to demonstrate the presence of compressed pancreatictissues at the periphery of the tumor. In most of the cases of extrapancreatic SPT's, it provides the only clue to thediagnosis. However, one case shows only ductular structures and no definitive pancreatic cells seen. Other unique histologic features as described by Markus Kosmall,[2] include microcystic patterns, large grooved spindle shaped nuclei together with occasional giant cells.

Routine histochemical stains are not particularly revealing in SPT. The hyaline cytoplasmic globules are positive for PAS, but negative for mucin. Numerous immunohistochemical studies have been performed in an attempt to clarify the line of differentiation reflected in SPT's. The neoplastic cells consistently express vimentin which was also true in our case though it was only focally positive. Staining for cytokeratin is inconsistent, with a positive result reported in approximately 35%[14] of cases. When positive, stains for cyto keratin are generally focal and faint while diffuse, intense positivity should suggest an alternative diagnosis. Our case was negative for cytokeratin. Other consistently positive markers include alpha-1-antitrypsin and alpha-1-antichymotrypsin. More than 90% [14] of tumors express positivity usually involving clusters of intensely stained tumor cells. This is also true of our case which shows strong positivity with alpha-1-antitrypsin (AAT) and alpha-1-antichymotrypsin (AACT). Specific markers of acinar differentiation include antibodies against the pancreatic enzymes trypsin, chymotrypsin and lipase which are negative. Staining for neuroendocrine markers is less clear cut. Most cases express diffuse faint positive staining for neuron specific enolase (NSE). Ours also show focal positivity with NSE. Stains for synaptophysin are positive in 10–15% of cases, occasionally in an intense, diffuse pattern. However, all examples of SPT

stained for Chromogranin show negative results. A variety of other markers have also been investigated such as peptide hormones, ductal markers such as CEA, CA 19.9, and B27.3, alpha-fetoprotein, CD 34, inhibin, CD 68, lysozyme and GFAP but unfortunately all of these stains show negative results.

Despite numerous attempts to identify a consistent marker of cell lineage, some authors have concluded that SPT's originate from primitive cells of the pancreas. However, the immunotype of SPT suggests that none of the normal adult pancreatic cell lines (ductal, acinar, or endocrine) is closely mimicked by the cells of SPT. Staining to AAT and AACT have initially been interpreted as evidence of acinar cell differentiation staining but has now been recognized to be non-specific with regard to cell lineage. It is the endocrine cell line that seemed to represent the most likely candidate, given the consistent staining with NSE and occasional positive staining with synaptophysin but the validity of NSE as a neuroendocrine marker is doubtful.[5] However, other immunohistochemical findings in SPT such as positivity for vimentin and AAT are not suggestive of an endocrine differentiation of the tumor and the most specific marker for endocrine differentiation, chromogranin is never expressed. Neuroendocrine differentiation in SPT's has been well described but is generally considered a focal event in certain cases and should be regarded as one possible line of differentiation rather than an evidence of neuroendocrine differentiation. Ultimately, none of the data regarding the cell lineage of SPT's have adequately clarified the unusual nature of this tumor.

The differential diagnoses for these tumors include paragangliomas, yolk sac tumors, as well as atypical serous and mucinous tumors of the retroperitoneum. Paragang-lioma was considered due to the significant histologic similarities of these tumors with SPT's. Among those similarities are the well-defined nests of cuboidal cells with a fibrovascular septae which could resemble the cells of SPT's in the pseudopapillary areas but it must be emphasized that the Paraganglioma cells do not form pseudopapillary patterns. The individual cells in Paraganglioma are also characterized by round with oval, uniform nuclei with moderate to abundant amount of cytoplasm. It is important to emphasize that Paraganglioma cells are often characte- rized by considerable variation in nuclear size and shape with hyperchromatic and atypical nuclei. These features are not characteristic of the cells of SPT's save for some atypia but usually in mild forms. The neuroendocrine nature of the tumor has been clearly defined and always stain positive with NSE, Synapthophysin and Chromogranin A. In contrast, the neuroendocrine nature of SPT's which have not been clearly defined and is not consistently expressed at all times.

Yolk sac tumors in the retroperitoneum can also be considered because of its predilection for young patients. These tumors are often cystic and hemorrhage with necrosis may be seen. The presence of pseudorosettes in pseudopapillary component maybe confused with a Schiller-Duval body as well as the presence of PAS (+) hyaline globules. However, by comparison of the individual cell, cells of Yolk sac tumors are usually more pleiomorphic with hyperchromatic nuclei and atypia. Immunohistochemical studies in Yolk sac tumors are often positive for Alpha fetoprotein which is negative in most of SPT's.

The atypical serious and mucinous tumors are considered because of some structural similarities with SPT's. These tumors are both cystic and may contain abundant secretions. Occasional hemorrhage may also be seen in these tumors but extensive hemorrhage and necrosis are uncommon. Microscopically, serous and mucinous tumors may also show delicate papillary fronds. Most of the immunohistochemical studies used for SPT's do not show positivity with Atypical serous and mucinous tumors such as Alpha-1-antitrypsin, Anti-chymotrypsin, NSE's but the serous and mucinous tumors would express positivity with Cytokeratins.

Imaging modalities such as ultrasonography and CT-scan has greatly improved the differentiation of other cystic masses within the retroperitoneum. Fine needle aspiration biopsy guided by either ultrasound or CT-scan has proven to be ofgood diagnostic reliability as a pre-operative diagnostic modality. On cytology,[6,13,15] the SPT's appear as monolayered sheets of cuboidal epithelium with moderate amounts of nonmucinous cytoplasm with bland nuclear patterns in a hypocellular smear. The course of SPT's is usually favorable. Only 14.7%[1] behaved in a malignant manner and would have metastatic potential and tendencyfor local recurrence in 10% of cases[16] with invasion of nearby structures.[17] There were very fewreported deaths from SPT's even in those cases with malignant behavior. Rupture of a very large intraabdominal cyst resulting in a fatal intraabdominal hemorrhage has been documented.[18] Wide surgical excision is recommended with regular diagnostic imaging evaluation. SPT's should always be considered in a young female with non-specific abdominal and or gastrointestinal manifestations and ancillary studies along with correlation of clinical and radiologic findings are indicated to help differentiate this tumor from other diagnostic entities.

Conclusion

Solid-pseudopapillary tumor of the pancreas is a rare neoplasm and the presence of this in extrapancreatic site remains a curiosity but has been recognized as a distinct clinicopathologic entity. Presented was a case of a 17 year old female with a gradually enlarging mass with non-specific gastrointestinal manifestations such as vomiting and diarrhea.

Imaging modalities such as angiograms and hepato-biliary radionuclide scanning reveal a large cystic mass below the

liver initially diagnosed as hepatic hemangioma. The patient underwent exploratory laparotomy twice and the retroperitoneal mass was diagnosed as heterotopic SPT. Immunohistochemistry evaluation consisting of vimentin, cytokeratin, AFP, NSE, Alpha-1-antitrypsin and Alpha-1-antichymotrypsin and special stains such as PAS confirmed the diagnosis. The diagnosis of SPT's is often straight forward with immunohistochemical evaluation done to differentiate other entities. It has also been said that due to the varied results of immunohistochemistry, SPT's cannot be regarded as a pure neuroendocrine neoplasm.

Although the tumor is considered to be of low malignant potential. Wide surgical excision is always recommended with or without adjuvant treatment coupled with regular imaging evaluation because 14.7% of tumors behave in a malignant fashion with potential to metastasize. It recurs as well as invades other structures. Inspite of these documented cases of metastasis and local recurrence and invasion of nearby structures, the overall prognosis remains to be good with very few documented deaths.

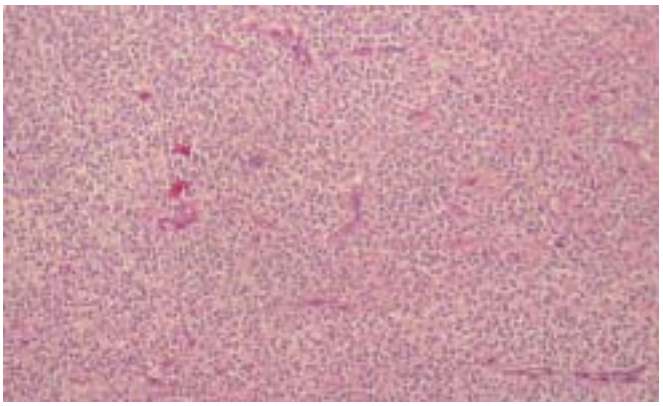

Figure 3. **Microsections showing the solid areas**

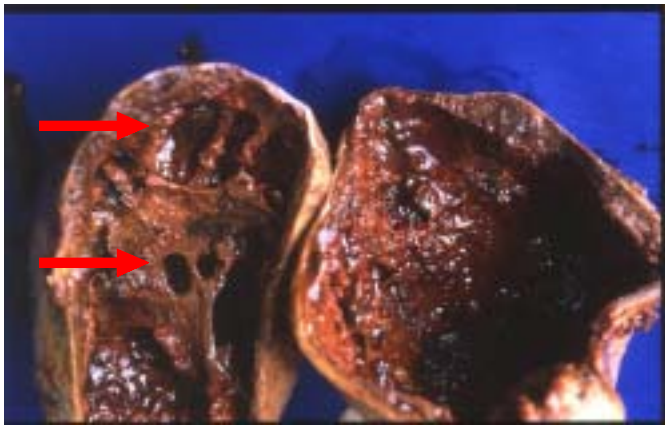

Figure 1. **Gross specimen showing unilocular cyst with**

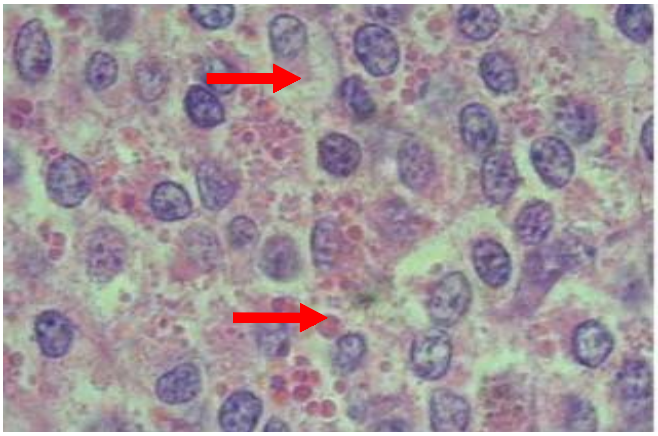

Figure 4. **Microsections show areas with eosinophilic hyaline globules**

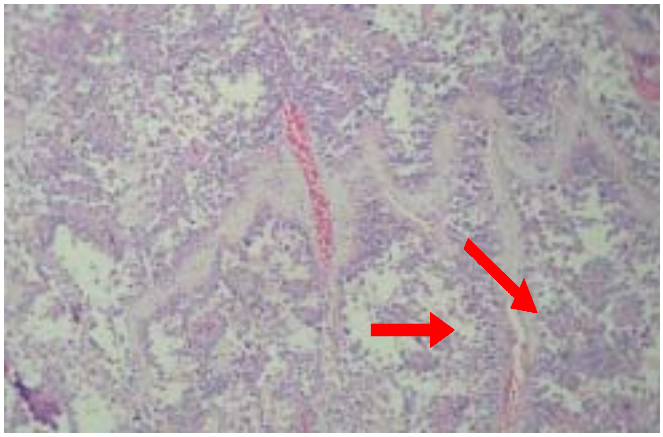

Figure 2. **Microsections showing pseudopapillary areas**

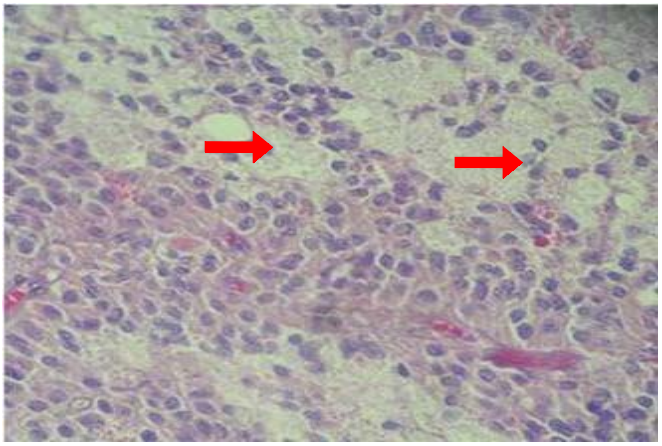

Figure 5. **Microscopic sections showing areas with foamy macrophages**

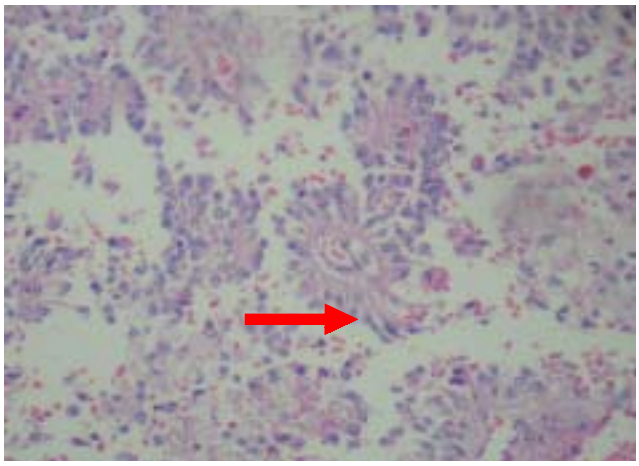

Figure 6. **Areas showing pseudorosette formations**

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Case Report

Primary Systemic Amyloidosis in a 52-year Old Male Presenting with Cardiac Arrhythmia: an autopsy report

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We are presenting with a rare and mysterious case of amyloidosis manifesting as cardiac arrhythmia in a 52 year old male who was admitted at the Philippine Heart Center. The patient succumbed to death on the second hospital day. A partial autopsy was done which revealed amyloid deposits in five different organs, namely the heart, liver, pancreas, kidney and lungs. Variability in tissue distribution and volume of amyloid deposits occur in different individuals and no signs and symptoms are characteristic of this condition. The clinical presentation of the patient is determined by the principal site of amyloid deposition. In this case, symptomatic cardiac amyloidosis has infiltrated and affected the conduction system - mainly sino-atrial (SA) and atrioventricular (AV) nodes of the heart. Hence, impairing ventricular contraction and relaxation, and developing cardiac arrhythmia.

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Keywords: amyloid; arrhythmia; amyloidosis;autopsy; cardiology;

Amyloid is a pathologic proteinaceous substance, deposited between cells in various tissues and organs of the body in a varied array of clinical settings. There are no consistent distinctive patterns of organs or tissue distribution. Amyloidosis may be found as an unsuspected anatomic change, having produced no clinical manifestations, or it may cause death. Kidneys, liver, spleen, lymph nodes, adrenals and thyroid as well as many other tissues are classically involved.

Primary systemic type of amyloidosis most commonly involve the heart. Cardiovascular involvement is in fact the most common cause of morbidity and death. Patient with myocardial deposition can present with congestive heart failure due to restrictive cardiomyopathy, sudden cardiac death and rarely as cardiac arrhythmia. This case of a patient with systemic amyloidosis manifesting as cardiac arrhythmia is presented in the hope that this condition will be understood both by the clinicians and the pathologists despite of its rarity.

Case History

We are presented with a case of a 52-year old Filipino male from Davao City, who was admitted at the Philippine Heart Center for permanent pacemaker insertion. Sixty two days prior to admission, patient presented with recurrent abdominal pain, nausea, vomiting accompanied by weight loss. No consult was done. Thirty five days prior to admission due to recurrent symptoms, consult was done at a private tertiary hospital and magnetic resonance imaging (MRI) of the upper abdomen revealed large pancreatic head suggesting the presence of carcinoma versus lymphoma. Ultrasound of the abdomen also showed the same enlarged pancreatic head with prominent tail.

Twenty one days prior to admission, upper GI series revealed normal findings with hypotonic duodenography and prominent right lobe of the liver. Serum electrolytes and hormonal assays are unremarkable. Short interval follow-up was advised and was treated symptomatically. Eight days prior to admission, esophagogastroduo- denoscopy identified focal pancreatic head enlargement measuring 1.5 to 2 cms. with homogenous echo pattern and was subsequently admitted for exploratory laparotomy of the pancreatic nodule. Cardiac clearance was started on the first hospital day. Abnormal Dobutamine Stress Echocardiography with Stress Induced Ischemia revealed mild hypokinesia of the interventricular septum and antero-apical segment suggested of Coronary Artery Disease. Baseline 2D Echocardiography with doppler study showed concentric left ventricular hypertrophy with normal contractility and systolic function; slightly dilated left atrium; aortic and mitral sclerosis with trivial tricuspid regurgitation.

Total Body Bone Imaging revealed no evidence of metastatic bone disease. However, mild and diffuse hepatic uptake of undetermined etiology was seen suggesting colloid formation as encountered in radiopharmaceuticals, hepatic necrosis, or amyloidosis. On the second hospital day, bibasal pneumonia was noted on chest x-ray. Patient's electrolytes level and coagulation time were monitored in the next five days. One day prior to admission, patient had a hemoglobin level of 10 g/ dl (100 g/ l) and was corrected by transfusion with

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one (1) unit packed red blood cells. However, while receiving blood transfusion, patient complained of dizziness and was bradycardic and hypotensive. Fluid challenge was done. Acute Right Ventricular failure was then confirmed by insertion of Swan Ganz catheter which showed increased right atrial and ventricular pressure with normal wedge pressure. Echocardiography showed junctional bradycardia with a rate of 40-42 per minute. Temporary ventricular pacing was done. Patient also developed oliguria with increasing creatinine levels for which continuous veno- venous hemodialysis was done at bedside. Temporary pacemaker insertion was converted to AV sequential pacing. Patient became hemodynamically stable and was transferred to the Philippine Heart Center for permanent pacemaker insertion.

On admission, patient was conscious and coherent with the following vital signs: BP=100/60, CR=75/min, RR=20/ min. There is an atrial lead on the left internal jugular vein and a ventricular lead on the right internal jugular vein. The rest of the physical examination are essentially normal. Past medical history indicated previous hospitalization in 1999 due to loss of appetite and weight loss with an impression of a pancreatic disease. Patient smoked for at least twenty pack years. No here do familial diseases were elicited.

The Admitting Diagnosis was Right Ventricular Wall Infarct, Pancreatic Nodule, to rule out Carcinoma, Acute Renal failure secondary to Acute Tubular Necrosis, oliguric, Status post temporary pacemaker insertion secondary to junctional bradycardia. Patient was admitted at the Medical Intensive Care Unit.

On the first hospital day, patient underwent permanent pacemaker insertion, and during the procedure, he went into cardiopulmonary arrest. Cardiopulmonary resuscitation was done and was revived. Chest Radiograph revealed pulmonary congestion with edema and left-sided pleural effusion. Ultrafiltration was done. He had several episodes of ventricular tachycardia hence, defibrillation with administration of lidocaine drips were administered. Arterial blood gas revealed metabolic acidosis and was corrected. Patient became hemodynamically unstable and went into coma. On the second hospital day, patient had seizures and went again into cardiopulmonary arrest. Despite heroic measures, patient succumbed to death.

Autopsy Findings

A partial autopsy was done limited to the following organs heart: lungs, liver, pancreas and kidneys. The body was opened with a Y-incision. The pericardial sac is thin and smooth with about 4 cc of clear serous fluid. Two milliliter (2 ml) of blood was aspirated from the heart for blood culture.

Grossly, the heart is moderately enlarged, weighing 420 grams (normal average weight = 300-350 gms.). External examination of the heart reveals mildly opaque epicardium with normal amount of epicardial fat. The coronary arteries show normal origin and course. Serial cross sectioning shows patent lumen without any significant lesions or thrombus. The great vessels at the base of the heart show normal relations. Sectioning of the atria shows mild biatrial dilatation and increased wall thickness of up to 0.4 cms. The atrial endocardium is thickened bilaterally but more prominent on the left side. There are no thrombi in the atrial appendages. Sectioning of the ventricles show mild biventricular dilatation. The left ventricular free wall measures 1.6 cms in thickness and the right ventricular free wall measures 0.6 cms. The interventricular septum measures 1.9 cms. The endocardium is unremarkable without mural thrombosis. The myocardium is homogeneously brown with a firm consistency. No gross evidence of recent or old infarcts is seen. The atrioventricu- lar valves show mild leaflet thickening without vegetations or calcifications noted. The semilunar valves are unremarkable. The approximate valvular circumferences are as follows: Tricuspid valve - 11 cms., Mitral valve - 8.5 cms., Pulmonary valve - 6 cms., Aortic valve - 6.5 cms. Sections of the conduction system, atria and ventricles were taken. Abundant minute nodules ranging from 0.01-0.05 cms in size, were seen resembling sand at the endocardial surface (Fig. 2). Microsections of the heart showed mild myocyte hypertrophy with patchy areas of early ischemic changes as evidenced by margination of polymorphonuclear cells and few extravasated neutrophils in the interstitium. Abundant subendocardial deposits of pink amorphous material are noted in the atria (Fig. 3). Moderate amount of interstitial deposits are also present in the ventricles seen surrounding individual myocytes and associated with myocyte loss and atrophy. Serial cut sections through the conduction system - at the level of the sino atrial and the atrioventricular nodes reveal diffuse infiltration of amyloid deposits. Congo red staining showed positive green birefringence on polarization in microscopy confirming its nature as amyloid (Fig. 5,6). Sections from the right and left coronary and circumflex arteries reveal approximately 40% luminal occlusion with fibrointimal thickening. Thepleural cavities reveal minimal effusion. The right and left lungs weigh 910 gms. The pleural surface is smooth and gray black. The tracheobronchial tree is unremarkable. Dissection of the pulmonary arteries reveals blood clot with an aggregate measurement of 2 x 0.9 x 0.3 cms. at the level of the bifurcation of the artery leading to the right middle lobe and the right lower lobe. The clot however does not completely occlude the vascular lumina (Fig. 7, 8). Microsections of the blood clots taken from the pulmonary artery show numerous red blood cells enmeshed in fibrin. Lines of Zahn are appreciated. Scanty adipose cells with bone marrow elements consistent with bone marrow emboli are seen. Two lymph nodes measuring 2.5 and 2.3 cms. in greatest dimensions from the peribronchial area were harvested. Microsections of the lymph nodes showed dilated sinuses and anthracosis.

Cut sections of the lungs show spongy red brown parenchyma without consolidations or infarcts. The lungs show focal pink deposits of amorphous material along the vascular

walls (Fig. 9) which showed green birefringence in Congo red staining (Fig. 10,11,12). There is focal extravasation of red blood cells within the alveolar spaces but no evidence of infarcts. Sections from the right lower lung lobe show focal bronchialization of alveoli.

The peritoneal cavity contains 200 cc of yellow serous fluid. The stomach, small and large intestines are inspected externally, palpated and are grossly unremarkable.

The pancreas is tan pink, firm and weighs 120 gms. and measures 16 x 5.2 x 3.5 cms. Serial sectioning shows distinct lobulations with unremarkable parenchyma. No nodules or masses noted (Fig. 13). Microsections from the pancreas show no significant histopathologic changes with focal areas of amyloid deposition (Figs. 14, 15).

The liver is gray brown and weighs 2,200 gms. (normal average weight = 1400-1600 gms.). Serial cut sections of the liver shows gray surface with minute micronodulations resembling sand (Fig. 16). Microsections from the liver show diffuse deposition of pink amorphous material along the sinusoids causing compression atrophy of the hepatocytes (Fig. 17). Congo red staining showed positive staining along vessel wall. The gallbladder is dark green and measures 9 x 3.5 x 3.5 cms. On opening, it shows a cavity filled with thick green black fluid.

The right kidney measures 11.8 x 7 x 4.5 cms. and weighs 239 gms. with a cortical thickness of 0.9 cms. The left kidney measures 11.5 x 7.2 x 4 cms. and weighs 241 gms. with a cortical thickness of 0.9 cms. (normal average weight of kidney for age = 150 gms.). There is distinct corticomedullary junction. The pelvocalyceal systems are grossly normal (Fig. 18). Microsections of the both kidneys show normal glomeruli on light microscopy. There is focal neutrophilic infiltration within the tubules. The interstitium show no fibrosis and inflammation. The vessels show minimal amyloid deposits in the subintimal and medial layers as confirmed by Congo red staining. No significant deposits are seen in the glomeruli (Fig. 19).

Discussion

Amyloid deposition appears so insidiously and sometimes mysteriously so that its clinical recognition ultimately depends on morphologic identification of this distinctive substance in appropriate biopsy specimens. With the light microscope and standard tissue stains, amyloid appears as an amorphous, eosinophilic, hyaline, extracellular substance that, with progressive accumulation, encroaches on and produces pressure atrophy of adjacent cells.

To differentiate amyloid from other hyaline deposits such as collagen and fibrin, a variety of histochemical techniques are used. Because glycosaminoglycans are present in amyloid, the Sulfated Alcian Blue stain is a sensitive test useful for screening histologic material.[1] Amyloid imparts a blue green color to tissue deposits. It is able to identify the glycosaminoglycan component of the amyloid deposits. With the Gomori Trichome stain, amyloid tends to be gray blue in contrast to the bright blue of collagen. Material suspicious for amyloid should be confirmed by Congo red staining. Perhaps, the most widely used is the Congo red stain, which under ordinary light imparts a pink or red color to tissue deposits, but far more dramatic and specific is the green birefringence of the stained amyloid when observed by polarizing microscopy. (Figs. 6,12 and 20)

Amyloidosis occurs in two forms; systemic, when involving several organs and localized when involving one organ. Systemic amyloidosis is considered as primary when immunologic dyscracia is seen, though the association is only in 5-10% of cases, and most commonly involved the heart. It is considered secondary when associated with conditions like tuberculosis, bronchitis or osteoarthritis. Primary systemic amyloidosis is usually of the AL (amyloid light chain) type and is a plasma cell disorder characterized by deposition of monoclonal light chains in different organ systems.[2] It is said to be a disorder of protein folding in which normally soluble proteins are deposited as abnormal, insoluble immunoglobulin light chain fragments which produce and polymerize into fibrils that deposit extracellularly,[3] (Fig. 1) eventually disrupting tissue structure and cause dysfunctional disease.

Although about 20 different unrelated proteins can form amyloid fibrils in vivo, all such fibrils share a common cross-beta core structure. Some natural wild type proteins are inherently amyloidogenic, form fibrils and cause amyloidosis in old age or if present for long periods at abnormal high concentration. Other amyloidogenic proteins are acquired or inherited variants, containing amino acid substitutions that render them unstable so that they populate partly unfolded states under physiological conditions, and these intermediates then aggregate in the stable amyloid fold.[4]

Primary amyloidosis frequently involving the heart is most commonly seen in systemic senile amyloidosis. This condition is notably seen during the eight or ninth decade of life among predisposed individual and amyloidosis perse, rarely cause true cardiac dysfunction. However, cardiac amyloidosis causing clinically significant cardiac dysfunction especially in younger patients is a reality but its actual prevalence is not known. Roberts in 1993 reviewed a total of 54 cases in a necropsy report involving cardiac amyloidosis causing cardiac dysfunction.

In cardiac amyloidosis, amyloid fibrils infiltrate the myocardium, impairing ventricular contraction and relaxation. The clinical manifestations of cardiac infiltration in these disorders are protean, though congestive heart failure and arrhythmia are most noted. By electrocardiography, the most common arrhythmia encountered are low voltage QRS complex, atrioventricular and interventricular conduction defects causing varying degrees of heart block.[5] Two cases of cardiac

amyloidosis affecting the conduction system were also reported by Stefani, both of which have succumbed to cardiac arrest. In the first case, evident lesions of the conduction system were revealed by echocardiography and the second, did not exhibit significant echocardiographic abnormalities, with the right atrium and HIS bundle showing slight fibro-amyloid involvement acting as potential forerunner of high-risk arrhythmia.[6]

Another case was reported by Ruckert,[7] which was diagnosed on the basis of heart catheterization and echocardiography. This was a case of a 71-year old woman with congestive heart failure, with a tongue biopsy showingnumerous amyloid fibrils and plasmacytosis in the bone marrow. A monoclonal protein (kappa-light chains) was found in the serum. All these findings indicated a restrictive cardiomyopathy as part of a primary systemic amyloidosis. In other cases, amyloidosis presented as angina pectoris, sudden death,[8] pericardial effusion, and even cardiac tamponade. Our case presented with arrhythmia in the form of junctional bradycardia which is component of a third degree AV block, a typical example of a conduction system defect. The association of the arrhythmia with amyloidosis in this patient is quite strong since the patient is he is just in his fifth decade of life without any apparent history of other cardiac diseases.

At autopsy, heart weight in amyloidosis is usually increased, and the organ is firm and rubbery. Atrial dilatation is common, whereas ventricles are of normal size. The left ventricular septum is occasionally more than 1.3 times as thick as the free wall. Waxy amyloid deposits may be seen in the atrial endocardium (Fig. 2) or heart valves, especially the tricuspid and mitral valves. In some cases, valvular deposits resemble candle grease droppings. Epicardial coronary artery amyloid does occur but less commonly than involvement of intramural coronary arteries. Amyloid deposition within intramyocardial coronary arteries may be associated with focal myocardial infarcts that cause heart failure, angina pectoris or sudden death. Amyloid are also found in the walls of myocardial lymphatics.[9] Involvement of peripheral arteries causing ischemia is occasionally reported.[10]

The kidneys are the organs most commonly functionally impaired by secondary systemic amyloidosis, usually presenting with proteinuria or the nephritic syndrome. Deposition of amyloid in the spleen can occur in either a diffuse or a nodular pattern. In the liver, amyloid is deposited in the space between the sinusoidal lining cells and the hepatocytes. Clinically, it is a cause of hepatomegaly, as seen in the case of our patient. However, there is rarely significant clinical evidence of impaired liver function.

The most important prognostic factor is whether there is cardiac involvement, which is best assessed by echocardiography with Doppler studies. Therapies used include oral melphalan/prednisone and high dose corticosteroids. High-dose chemotheraphy followed by stem cell reconstitution seems to provide the highest reported response rates.[11] Although the response rate is only about 25%, and the prognosis is poor with median survival of about six months. However, a case was reported by Kotha, in which the patient survived for nine years.

The prognosis most likely depended on the period of disease transmission (i.e. negative serum and urine immunoelectrophoresis), which, in turn, depends on response to immunochemotheraphy. It was likewise emphasized that restrictive cardiomyopathy due to light chain deposition may be reversible and relatively have a better prognosis after remission of plasma cell dyscracias.

In a study by Comenzo, high-dose melphalan with autologous blood stem cell transplantation (SCT) can reverse the disease process in selected patients, however, it remains controversial because of the treatment related mortality in patients with cardiac and multisystem organ involvement. Appropriate candidates for stem cell transplantation are patients with one or two involved organs or with early cardiac involvement. Therefore, it is clear that patients with amyloidosis who have advanced amyloid cardiomyopathy or more than two major viscera involved with disease are poor candidates for stem cell tranplantation.

Summary

Despite uncertainty about why amyloid is formed, there are well-characterized associations between particular diseases and the deposition of amyloid. Its recognition requires a high index of suspicion and an understanding of the association between cardiomyopathy, nephrotics syndrome, and hepatomegaly with amyloidosis. Immunofixation of the serum and urine to detect a monoclonal immunoglobulin light chain, the most important screening test for amyloidosis may not be asas helpful if the dysfunction was caught late in the course of the disease. As usual, early detection of the disease is necessary. But, as the disease is caught almost always late in its course, diagnosis is made when manifestations are severe. Almost patients suspected with amyloidosis necessarily requires an invasive process for histologicalconfirmation. Due to the rarity of the disease, it ranks one of the least of the considerations of physician. Amyloidosis still remains to be a subject of current research and therapeutic controversies. It is a subject worth challenging the minds of cardiologists, and pathologists as well.This case is reported in the hope that the disease would be understood, would be diagnosed early while the patient is alive and eventually, would make amyloidosis NOT as a disease of "unresolved mystery."

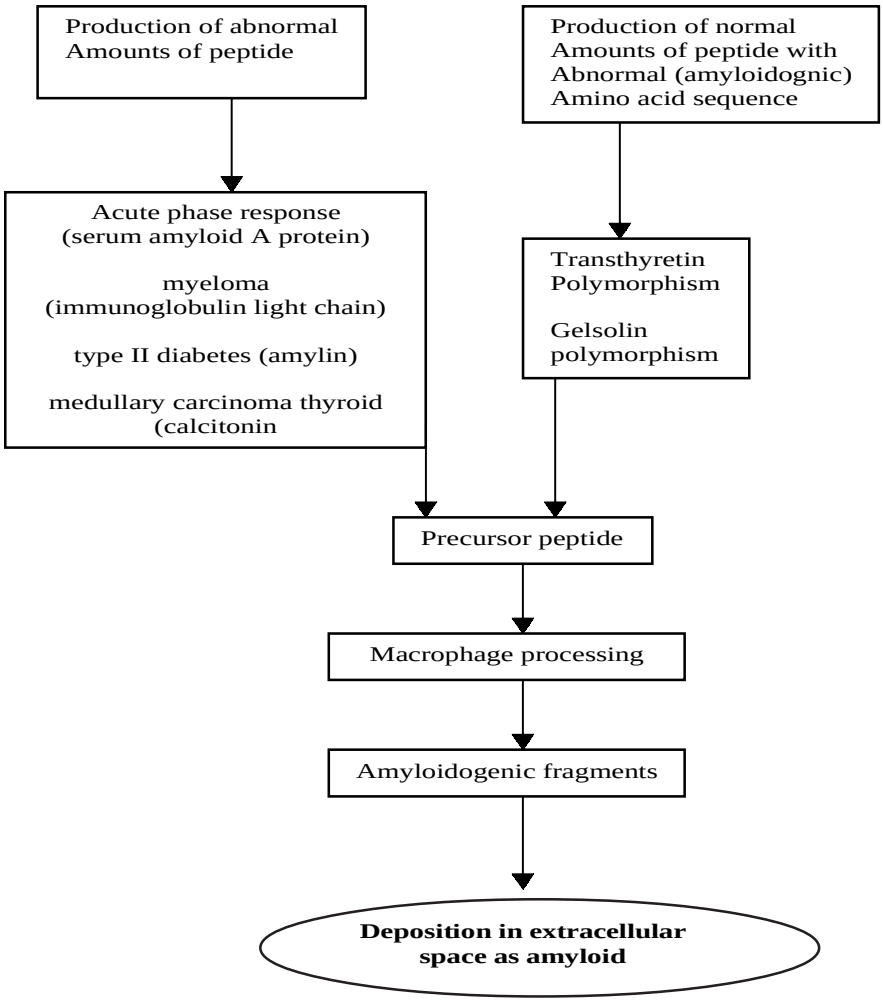

Figure 1. **Amyloidogenesis**

The Heart:

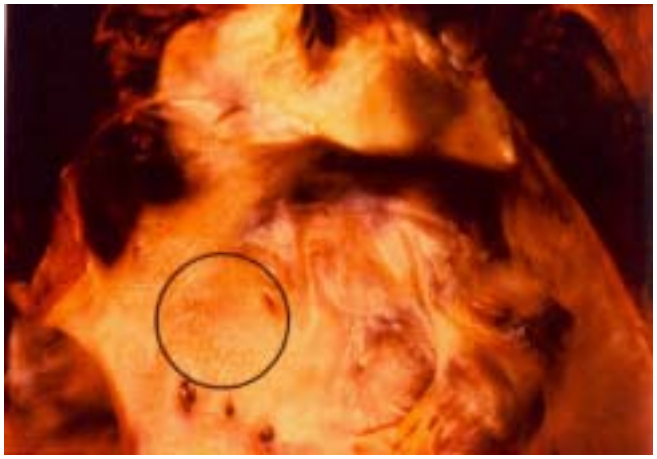

Figure 2. **Amyloid deposits on the surface of the right atrium seen as minute nodules resembling sand-like material (encircled).**

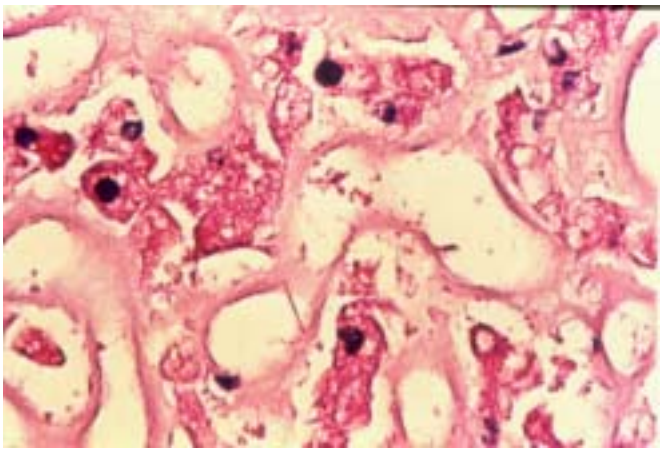

Figure 3. **Microsections of the heart showing interstitial deposition of amyloid as pink, acellular hyaline surrounding & isolating myofibers. (H & E, Non polarizing x 40)**

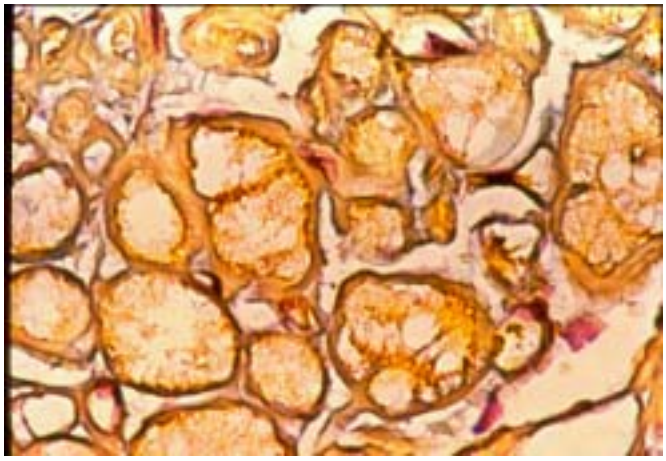

Figure 4. **The heart showing glycogen component of amyloid deposits. (Sulfated Alcian Blue Stain, Nonpolarizing x 40)**

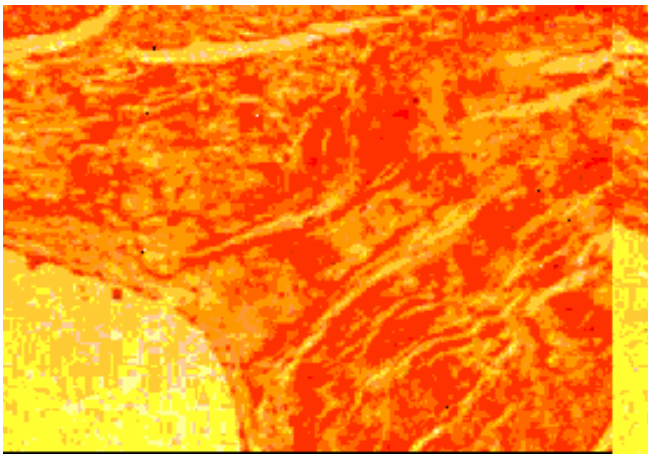

Figure 5. **The heart which show red discoloration of the amyloid deposits.(Congo red stain, Non-polarizing, x 10)**

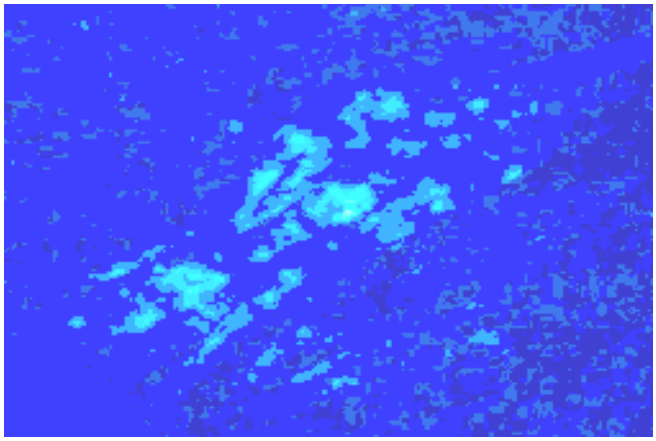

Figure 6. **Similar section showing apple green birefringence on polarizing light microscope. (Congo Red stain, polarizing X 10)**

The Lungs:

Pulmonary Embolism

Figure 7

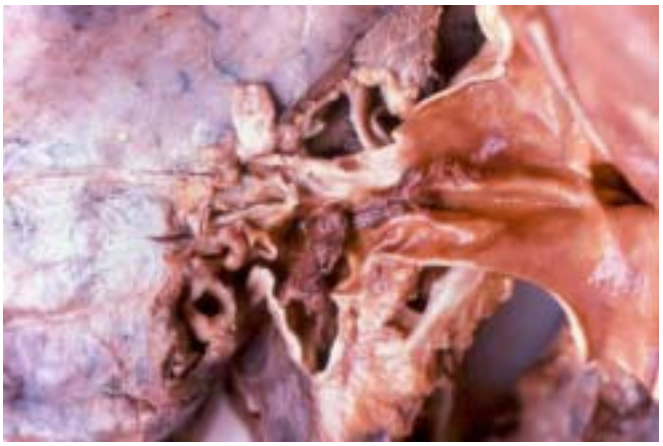

Figure 8

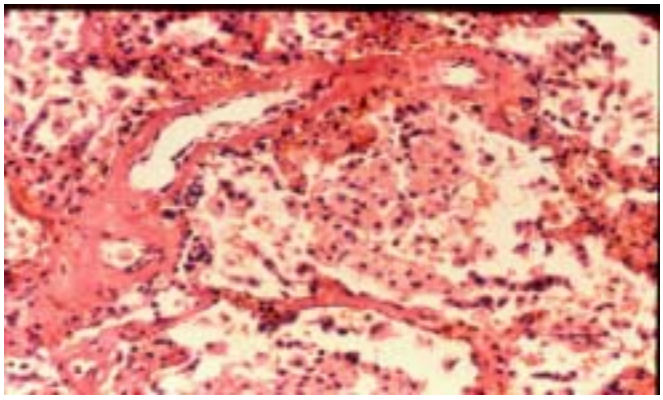

Figure 9. **The lungs partially lined by red amyloid deposits. (Congo Red Stain, Non-polarizing X 40)**

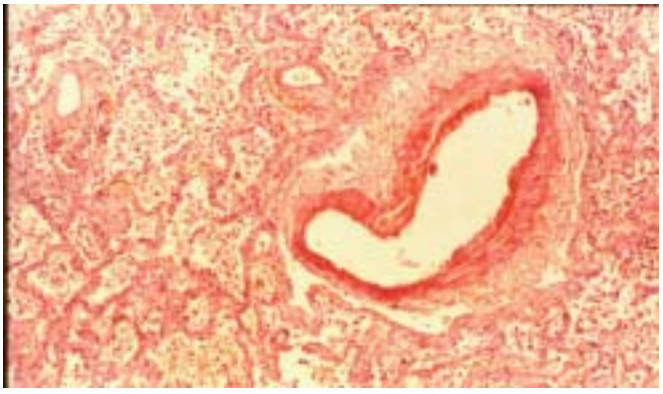

Figure 10. **Section of the lungs revealing pink red amyloid deposits in the vascular wall. (Congo Red Stain, polarizing, x 10)**

Figure 13. **Gross picture of the pancreas.**

The Liver:

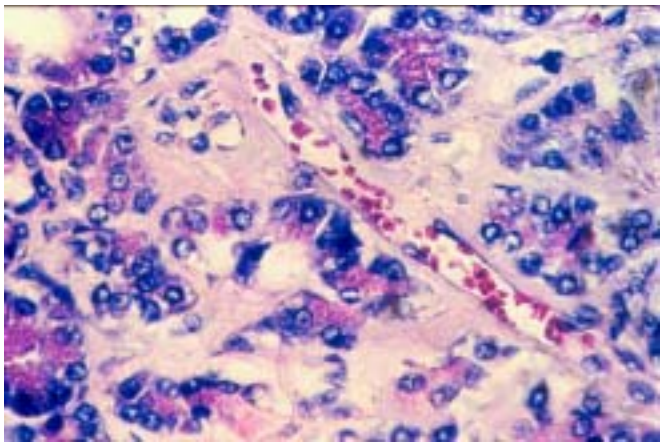

Figure 14. **Sections of the pancreas with amorphous material intervening pancreatic tissue. (H & E x 40)**

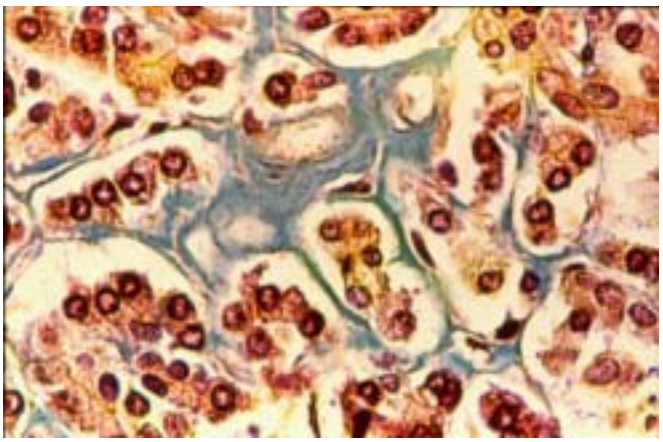

Figure 15. **Section of the pancreas with blue green color of the glycosaminoglycan component of amyloid deposit. (Sulfated Alcian Blue Stain, x 40)**

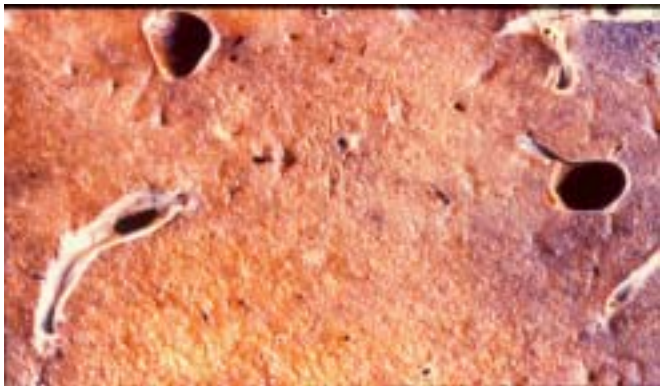

Figure 16. **Close up view of the cut surface of the liver with Amyloidosis disclosing gray surface with numerous micronodulations.**

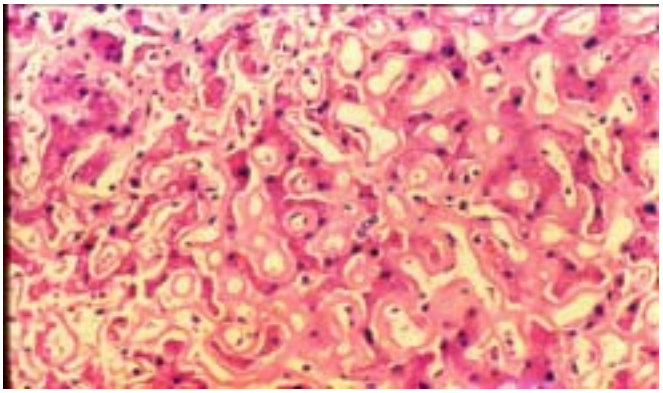

Figure 17. **Amorphous pink hue of amyloid along the sinusoids encircling hepatic tissue. (H & E, x 10)**

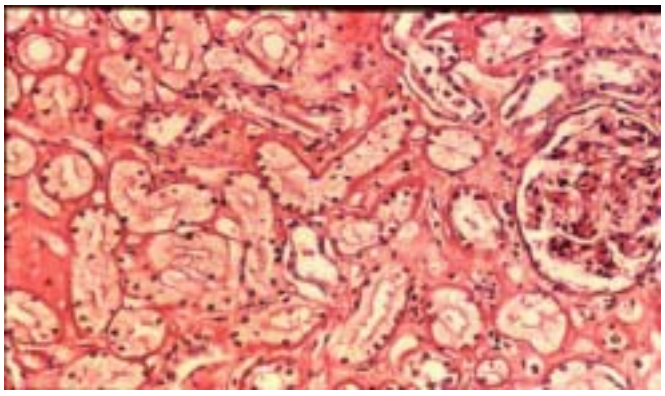

Figure 19. **Microsections of the kidney show amyloid appearing a pink deposits. (Congo red stain, x 10)**

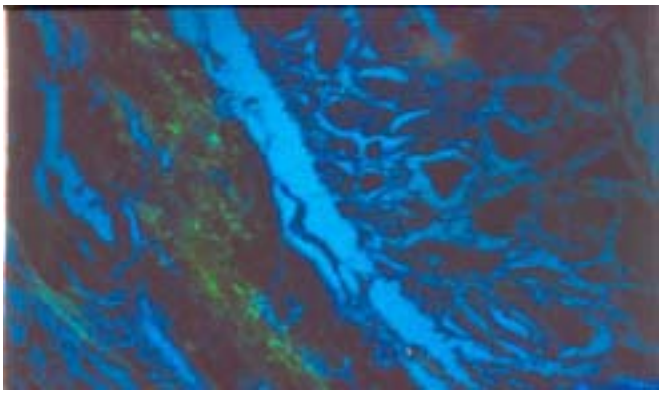

Figure 22. **Using polarizing light microscope, amyloid deposits appear as apple green birefringence. (Congo Red stain, Polarizing, x 40)**

Figure 18. **Gross picture of the kidneys**

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