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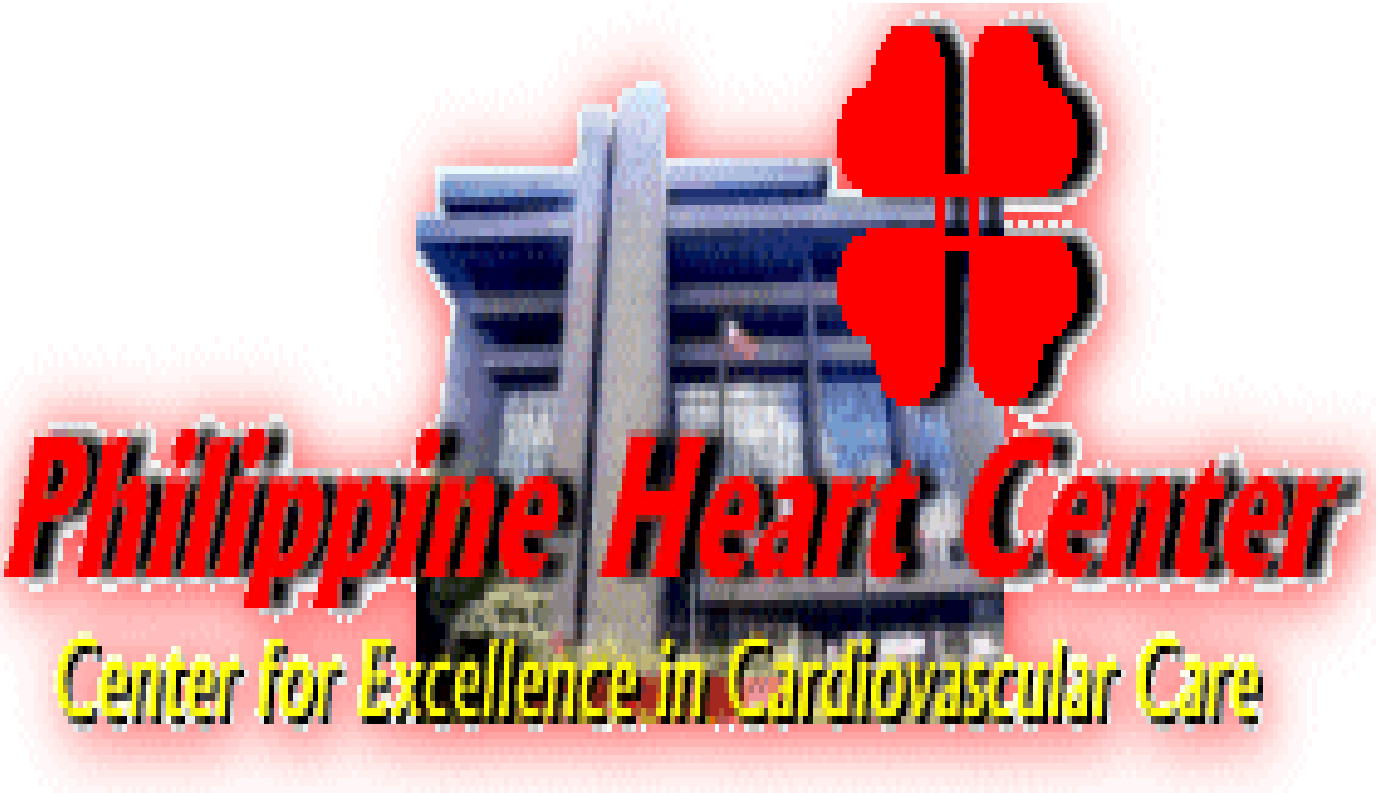

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Original Articles

Original Article

Immediate and Long-term Outcome of Significant Tricuspid Regurgitation After Percutaneous Mitral Balloon Valvotomy

Alexander D. Ang, MD. Ramoncito B. Tria, MD

Moderate and severe tricuspid regurgitation (TR) in patients with severe mitral stenosis may persist after successful percutaneous mitral balloon valvotomy (PMV). Its clinical importance has been well established because its persistence may contribute to a poor outcome after the procedure.

This is a cohort study over a five-year period of cases seen at the Philippine Heart Center. The records of patients with significant TR before successful PMV were reviewed in term of the resolution and its persistence immediately and long after the procedure. Clinical outcome were also analyzed in relation to significant TR in terms of functional impairment, repeated PMV, mitral surgery and death. Factors associated with persistence of TR were also noted. Survival analysis was performed to estimate the event free survival rates while Chi-square, Fisher exact and Mann-Whitney U-test was used to determine association of different variables with outcome.

Seventy-nine patients were included in the study. They were divided into two groups, those with insignificant TR and those with significant TR immediately after successful PMV. Majority of the population were female with mean age of 33 ± 8 and 32 ± 9.5 respectively. Tricuspid regurgitation was resolved to trace or mild in 42 (53%) patients and persisted in 37(47%). On 5 year follow-up TR became insignificant in 15 (41%) patients who initially had moderate to severe TR after PMV, while 22 (59%) continued to have significant TR. Twelve (29%) patients with initially had trace to mild TR after PMV developed significant TR. Patients with moderate to severe TR immediately and after PMV and those who developed significant TR on follow-up had elevated PAP, TVA and RV diameter on the last follow-up. Presence of organic TR was also significantly associated with patients having persistent significant TR. There was a marked reduction of symptoms in almost all of the patients after the procedure, and majority remained remarkably stable on follow-up. However patients with significant TR on follow-up had higher rates of functional impairment compared to those in whom TR resolved to trace or mild. The event free survival rates for trace to mild TR was 80% and 52% for those with moderate to severe TR.

Over all, there was significant improvement in severity of TR in a good number of patients on both short-term and long-term follow-up after successful PMV. More than two thirds of patients were also found to improve clinically with no note of any major cardiac events on 5 year of follow-up.

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Keywords: Tricuspid Valve Insufficiency; Mitral Valve Stenosis

Tricuspid valve regurgitation (TR) of varying degrees is frequently seen in patients with severe mitral stenosis (MS).[1-5] Its clinical importance has been well established because its persistence affects both the short and long-term clinical outcome of patients who undergo mitral valve surgery.[6-8] Although the degree of resolution of significant TR after correction of MS is not always predictable, lesser degrees of TR are likely to resolve after the mitral lesion is corrected but more severe TR tend to persist.[9] Failure to relieve the severity of TR may lead to progressive reight ventricular dysfunction,which can seriously compromise patients outcome after mitral valve operation.[9-10] Therefore, it has been recommended that significant TR be corrected at the time of mitral valve surgery to diminish its adverse effects on the clinical condition of the patient long after the surgery.

Since its introduction by Inoue in 1984, percutaneous mitral balloon valvotomy (PMV) has been accepted as an alternative treatment in selected patients with symptomatic rheumatic MS.[11-16] It has been shown to produce impressive immediate and long-term clinical improvement.[17-22] However, similar to the early surgical technique of closed valvotomy, it has an inherent limitation in correcting the associated tricuspid

Correspondence: *Alexander D. Ang, MD*. Division of Adult Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100

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valve disease.[9,23]

Despite the relatively high prevalence of TR in pre - selected patients undergoing PMV limited information is available at present as to the immediate and long-term outcome of the patients. Hence this study aims to address the above concern.

The objectives of this study are:

1. to assess the resolution of significant TR (moderate to severe TR on color flow Doppler study) during the immediate and long term period after PMV

2. to establish factors which are associated with the persistence of TR after PMV

3. to determine and analyze the association of significant TR in the long term clinical outcome of patient after PMV in terms of death, mitral valve surgery repeated PMV and functional impairment.

The study design is a cohort study, which included all patients aged 18 years old and above, who underwent successful PMV at the Philippine Heart Center (PHC) between January 1989 to December 1998 with significant TR (moderate to severe TR) and had follow-up for ³ 5 years. The following patients were excluded:

1. Patients aged less than 18 years old,

2. Patients with insufficient opening of the mitral valve after PMV define as mitral valve area (MVA) < 1.5 cm^2 after PMV,

3. Patients with insignificant TR (trace to mild TR) prior to PMV,

4. Patients who did not have 2DED study before PMV,

5. Patients who developed complication during PMV and required surgery.

All patients included in the study were divided into 2 groups depending on the severity of TR immediately after PMV. Those with TR resolved to a trace or mild degree on Doppler echocardiogram were classified as group A, and patients with persistent moderate to severe TR were classified as group B. For the 2 groups progression and regression of the TR severity were followed-up in subsequent 2DED studies.

Tricuspid valve regurgitation severity was graded as severe when the ratio of the maximal TR jet area to the right atrial area is equal or more than 40%, moderate when this ratio is equal to or more than 20% but less than 40% and mild if the ratio is less than 20%. The right atrial area will be traced from the same frame as the maximal jet area.[24]

Patients were followed-up for a period of 5 years. The clinical end points of follow-up were death, mitral valve surgery, repeat PMV and functional impairment. Functional status was determined using NYHA classification at baseline prior to intervention as well as on 1st, 3rd, and 5th year of follow-up.

Data was obtained during patient visit to our hospital, by telephone interview or by review of patient's medical records.

Reviewed data was encoded in Database and subjected to statistical analysis using Epi Info and SPSS (Statistical Package for Social Science).

Statistical Analysis:

Data was described in terms of mean, standard deviation, frequency and percent distribution. Event-free survival rate was estimated with the use of survival analysis. Statistical tools such as chi-square, Fisher exact and Mann-Whitney U-test was use to determine association of different variables with outcome.

Based on $\alpha = .05$, with total width of confidence interval of 20% and assumed rate of significant TR of 47% after PMV, sample size computed was greater than or equal to 76.

The records of 387 patients who underwent PMV were reviewed. Two hundred twenty-nine (229) patients had successful PMV, while 75 patients were considered to have insufficient mitral valve opening. In 9 patients, commissurotomy was not performed due to technical difficulty or inability to place or stabilize the balloon across the mitral valve. In 7 patients, the procedure could not be evaluated because of major complications such as development of severe mitral regurgitation in 5 patients, LV wall rupture in 1 patient and cardiac tamponade in another.

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

Of the 229 patients who had successful PMV, 86 patients had significant TR. Seventy-nine patients had at least 5 years of follow-up and the one included in the study.

After PMV TR was decreased to a trace or mild degree immediately on follow-up echocardiography in 42 (53%) out of 79 patients with significant TR and were classified under Group A. There were 37 (47%) patients with persistent moderate to severe TR after PMV and were classified as Group B.

The baseline characteristics of patients in both groups are shown in Table I. For both groups majority of the population were female with mean age of 33 ± 8.06 years for Group A and 32 ± 9.58 years for Group B. Majority of them were in sinus rhythm and most of them were symptomatic The echocardiographic variables measured before and after the procedure are depicted in table II. Majority of patients in both groups had a good valve score (Wilkin score < 8) prior to the procedure, 93% for group A and 89% for group B. The mean mitral valve area significantly improved for the whole population after PMV as well as the mean mitral valve gradient. There was no statistically significant difference between the two groups when it comes to echocardiographic score, mean mitral valve area and gradient before and after the PMV. However patients with moderate to severe TR had a statistically significant higher pulmonary artery pressure (PAP), tricuspid valve annulus (TVA), and RV dimension before and after PMV compared to patients with insignificant TR. The presence of thickened tricuspid valve with restriction of motion and non-coaptation of the leaflets were also significantly higher in Group

B. The other baseline characteristics were not statistically different between the two groups.

Table I: Baseline characteristics of Group A and Group B patients before PMV

	Group A (n=42)	Group B (n=37)
Age	33 ± 8.06	32 ± 9.58
Sex		
Male	9 (21%)	8 (22%)
Female	33 (79%)	29 (78%)
Rhythm		
Sinus	29 (69%)	20 (54%)
AF	13 (31%)	17 (46%)
Functional Classification		
1		
2	27 (64.3%)	21 (6.8%)
3	14 (33.3%)	14 (37.8%)
4	1 (2.4%)	2 (5.4%)

Table II: Preprocedural and Postprocedural Echocardiogaraphic measurements for Group A and Group B.

	Group A	Group B	P value
Wilkin Score			
5	2 (4.8%)	2 (5.4%)	
6	7 (16.7%)	2 (8.1%)	
7	12 (28.6%)	16 (32.4%)	
8	18 (42.8%)	12 (43.2%)	
9	3 (7.1%)	4 (10.9%)	
Pre PMV			
MVA	0.73 ± .14	0.69 ± .18	0.37
MVG	16.71 ± 4.85	16.97 ± 4.56	0.812
TVA	3.16 ± .59	3.52 ± .61	0.016*
RV dimension	3.67 ± .85	4.2 ± .85	0.025*
PAP	61.26 ± 15.7	68.40 ± 15.0	0.043*
Post PMV			
MVA	1.68 ± .21	1.67 ± .23	0.804
MVG	5.55 ± 2.12	5.87 ± 1.94	0.494
TVA	2.96 ± .35	3.40 ± .62	0.007*
RV dimension	3.44 ± .53	3.80 ± .73	0.050*
PAP	48.35 ± 10.70	56.75 ± 13.78	0.003*
Organic TR	7 (16%)	14 (38%)	0.050*

* Statistically significant

On follow-up TR resolved to a trace or mild in 15 (41%) patients of group B after 5 years, while the other 22 (59%) continued to have significant TR. Those patients who continued to have significant TR were noted to have statistically significant higher PAP and RV dimension and presence of organic TR compare to those in which the TR was resolved to trace or mild. The TVA was also higher in those patients with significant TR but the difference did not reach a statistically significant level. (See Table III)

Five year follow-up of group A showed development of significant TR in 12 (29%) patients. These patients belong to a higher age group with atrial fibrillation, with higher PAP and RV dimension. (See Table IV).

Table III: Echocardiographic measurements of Group B on 5 year follow-up

	Insignificant TR n = 15 (41%)	Significant TR n = 22 (59%)	P value
PAP	42 ± 4.7	56 ± 11.3	.0001*
TVA	3.1 ± .62	3.5 ± .71	0.064
RV diameter	3.2 ± .43	3.9 ± 1.1	. 047*

* Statistically significant

Table IV: Echocardiographic measurements of Group A on 5 year follow-up

	Insignificant TR n = 30 (71%)	Significant TR n = 12 (29%)	P value
PAP	42 ± 6.8	55 ± 16.14	.015*
TVA	2.8 ± .33	3.2 ± .61	0.06
RV diameter	3.3 ± .48	3.6 ± .76	.0132*

* Statistically significant

Table V: Group A Percentage of Patients in NYHA functional classes I to IV before PMV and on follow-up.

Functional Class	Pre PMV	1st year	3rd year	5th year
I	34(81%)	35(83.3%)	28(68.3%)	
II	27(64.3%)	8(19%)	6(14.3%)	9(22.0%)
III	14(33.3%)	1(2.4%)	3(7.3%)	
IV	1(2.4%)			1(2.4%)

After PMV, there was a marked reduction of symptoms in most of the patients in both groups. The percent of patients in functional class I and II remained remarkably stable during follow-up as shown in table V and VI. At the time of last follow-up 4 (10%) patients developed functional impairment in group A and 11(30%) patients in group B. The rate of deterioration in terms of functional class was higher in groupB than in group A and it was statistically significant (p= 0.022). One patient underwent repeated PMV on group A and another one underwent MVR in group B because of restenosis. No patient died in both groups. For the whole population, 15(19%)

Table VI: Group B Percentage of Patients in NYHA functional classes I to IV before PMV and on follow-up.

Functional Class	Pre PMV	1st year	3rd year	5th year
I	25(67.6%)	26 (70.3%)	19(52.8%)	
II	21 (56.8%)	12 (32.4%)	9 (24.3%)	6 (16.6%)
III	14 (37.8%)	2 (5.4%)	11 (30.6%)	
IV	2 (5.4%)			

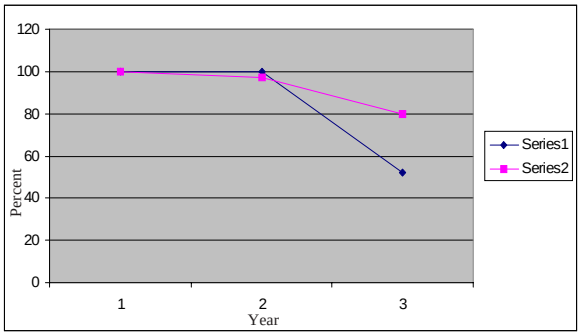

Figure 1 Event free survival rates for Group A and Group B

patients were in functional class III and IV at 5 year follow-up. The 5 year event-free survival rates was 80% and 52% for group A and B respectively. (See Figure 1)

Patients for both groups who developed or continue to have significant TR at 5 year follow-up were 34 patients (43%), and they had a higher rates of functional impairment compared to those patient with insignificant TR and it is statistically significant. *(p=.000).*

Discussion

Our reports involved populations with significant tricuspid regurgitation who underwent successful PMV, majority of which was middle aged female with severe MS, symptom limited in functional class II and III with good valve score. This study provided us information regarding the immediate and long-term outcome of significant TR in patients who underwent successful PMV.

Clinical recognition of the presence, etiology, and severity of TR associated with MS assumed increasing importance because its probable effects on the outcome of PMV. It is believed that persistence of significant TR will seriously compromised the long term clinical condition of the patients who underwent PMV. But despite the high prevalence of significant TR in this set of patients, limited information is still available.

The cornerstone investigation was performed by Sagie et al in 1994. They reported that significant TR is an adverse clinical marker in patients undergoing PMV, with sub-optimal immediate results and poor late outcome. Moreover, they reported that significant TR improved only in 12% of all patients studied regardless of the success of the procedure.[25]

However, in our study, moderate to severe TR was resolved in 53% of patients immediately after successful PMV. The striking difference between the previous report and ours could be attributed to the difference in patient population. Our patients were younger, had a lower prevalence of atrial fibrillation and included only those who had successful PMV. Unlike in the reports of Sagie et al. the mean age of their subjects was 57±15 years, which is much higher that that of the patients in the developing countries where PMV is more frequently performed. Their population also had a higher prevalence of atrial fibrillation and unsuccessful PMV which suggest the possibility that their subjects were a selected group with unfavorable prognostic factor. As reported, atrial fibrillation and suboptimal opening of the mitral valve affect the resolution of significant TR.[9,23]

The study made by Jae-Kwan Song et al reported a 32% decrease of significant TR to trace or mild after PMV. Their report included those patients with unsuccessful mitral valve opening after PMV which probably explain why their reports is lower compare to our results.

On follow-up, our study showed further improvement of significant TR to trace or mild on 41% of patients which initially had moderate to severe TR (group B), this is probably related to late hemodynamic improvement after PMV. Those with persistent significant TR and those with initially insignificant TR (group A) who developed significant TR on follow-up had been noted to have persistent elevated pulmonary artery pressure, wider TVA, and larger RV diameter, which may relate to a subgroup of patients with more advanced mitral, pulmonary vascular and right ventricular disease. Organic TR is also significantly present in those patients with persistent significant TR and more or less plays a compounding role on the outcome of TR after PMV.

Clinical improvement was the rule for patients with sufficient mitral valve opening, as reported by other literature.[13,15,17,18] As seen in our study, most of our patients improved after PMV despite the presence of significant TR in almost half of the patients. Majority remained in functional class I to II over the years. However functional impairment was observed in half of the patients with significant TR on long term 5-year follow-up. The poorer late outcome in this sets of patients despite an initial successful PMV suggest a possible intrinsic contribution of TR in the morbidity of this group. Compared with foreign reports, our study still showed a better clinical outcome.

The event free survival rates defined as freedom from death, mitral valve surgery, repeated PMV, and functional

impairments was 80% for insignificant TR and 52% for those with significant TR. The results are slightly lower than the reports made by Jae-Kwan et al. which reported 100% event free rates for insignificant TR and 94% for significant TR for 3 years. This may be because they only selected patients with functional TR and excluded patients with definite evidence of rheumatic involvement of tricuspid valve. Sagie et al reported event free rates of 68% for insignificant TR and 35% to 58% for significant TR for 4 years. This is much lower than the report of the present study probably due to the difference in the study population as was stated previously.

Conclusion

Immediately following successful PMV, significant TR regressed in almost half of the patients in the study population. Along with it, the pulmonary artery pressure, tricuspid valve annulus and RV diameter also decreased.

Of the subset of patients whose TR persisted following PMV, less than half had regression of TR on 5 year follow-up. However, a certain number of patients in whom TR was reduced to trace or mild immediately following PMV subsequently developed significant TR on further follow-up. All in all, the patient who had significant TR at the end of the 5 year follow-up were found to have higher PAP, TVA and RV diameter. Other features including changes in the tricuspid valve leaflets such as thickening of tricuspid valve leaflets with restriction of motion and noncoaptation were also associated with persistence of significant TR.

General improvement of clinical outcome and freedom from any cardiac events in 5 years was observed in greater than two third of patients with significant TR following successful PMV. The repeat PMV and mitral valve replacement observed in two patients were not found to be associated with the patients TR.

References

1. Sepulveda G, Luks DS. Diagnosis of tricuspid insufficiency. Circ 1955;11:552-559.
2. Braunwald NS, Ross J, Morrow AG. Conservative management of tricuspid regurgitation in-patient's undergoing mitral replacement. Circ 1967;35(1 Suppl):1-63-69.
3. Farid L, Dayem KA, Guindy R. The importance of tricuspid valve structure and function in the surgical treatment of rheumatic mitral and aortic disease. Eur Heart J 1992;13:366-372.
4. Hauck AJ, Freeman DP, Ackerman DM. Surgical pathology of the tricuspid valve: a study of 363 cases spanning 25 years. Mayo Clin Proc 1988;63:851-863.
5. Pluth JR, Ellis FH. Tricuspid insufficiency in patients undergoing mitral valve replacement. J Thorac Cardiovasc Surg 1969;58:484-489.
6. King RM, Scaff HV, Danielson GK. Surgery for tricuspid regurgitation late after mitral valve replacement. Circ 1984; 70 (Suppl): 11 193-197
7. Shafie MZ, Hayat N, Majid OQ. Fate of tricuspid regurgitation after closed valvotomy for mitral stenosis. Chest 1985; 88:870-873.
8. Groves PH, Ikaram S. Ingold U. Tricuspid regurgitation following mitral valve replacement an echocardiographic study. J Heart Valve Dis 1993;2:273-278.
9. Sagie A, Schwammental E, Newell J. Significant tricuspid regurgitation is a marker for adverse outcome in patients undergoing PMBV. J Am Col Cardio 1994;24:696-702.
10. King RM, Schaff HV, Danielson GK. Surgery for tricuspid regurgitation late after mitral valve replacement. Circ 1984; 70 Suppl II;II-193-197.
11. Carroll JD, Feldman T. Percutaneous mitral balloon valvotomy and the new demographic of mitral stenosis. JAMA 1993; 270:1731
12. Inoue K, Owaki T, Nakamura T. Clinical application of Transvenous Mitral Commissurotomy by a New Balloon Catheter. J Thorac Cardiovascular Surg. 1989; 87:394-402.
13. Palacios IF, Tuzco ME, Weyman AE, Nowell JB. Clinical follow-up of patient undergoing percutaneous balloon valvotomy. Circ Feb 1995;91: 671-676.
14. Desideri A, Vanderperren O, Serra A, Barraud P, Petiteclerc R, Lesperance J. Long-term (9-33 months) echocardiographic follow-up after successful percutaneous mitral commissurotomy. Am J Cardio 1992; 69:1602-1606.
15. Palacios IF, Block PC, Wilkins GT, Weyman AE. Follow-up of patients undergoing percutaneous mitral balloon valvotomy:Analysis of factors determining restenosis. Circ 1989; 79:573-576.
16. Palacios I, Block PC, Brandi S. Blanco P. Cesal H, Pulido JI, Munoz S. Percutaneous balloon valvotomy for patients with severe mitral stenosis. Circ 1987;75:778-784.
17. Hernandez R, Banuelos C, Alfonso F, Goiolea J. Long term clinical and echocardiographic follow-up after percutaneous mitral valvuloplasty with Inoue Balloon. Circ 1999;(3)1580-1585.
18. Dean L, Mickel M, Bonan R, Holmes, Jr D, O'Neill W, Palacious I. Four-year follow-up of patients undergoing percutaneous balloon mitral commissurotomy. J Am Coll Cardio 1996;28:1452-1457.
19. Chuan-Rong Chen, Tsung O. Cheng, Ji-Yan Chan, Ying-Ling Zhou, Jia Mei, Tie-Zheng Ma. Long-term results of percutaneous mitral valvuloplasty with Inoue Balloon Catheter. Am JCardio 1992;70:1445-1448.
20. Tuzco M, Block P, Griffin B, Newel J, Palacous I. Immediate and long term outcome of percutaneous mitral valvotomy in patients 65 years old and older. Circ 1992;85:963-971.
21. Reganion J, Azcueta MB, Casas ML, Cantre T. Predictors of outcome after percutaneous mitral balloon valvuloplasty in pediatrics patients (PHC).
22. San Diego Jr P, Pascual A, Pineda R. The therapeutic use of PTMC to alleviate mitral stenosis in-patient with high valve score (PHC).
23. Jae-kwan Song et al. Outcome of significant functional tricuspid regurgitation after percutaneous mitral valvuloplasty. Am Heart J 2003;145:371-376.
24. Lotilla, W, Cayetano J. Outcome of moderate to severe tricuspid associated with dilated tricuspid valve annulus following successful percutaneous transeptal mitral commissurotomy (PHC) .
25. Sagie A, Schwammenthal E. Palacios IF. Significant tricuspid regurgitation does not resolve after percutaneous mitral valvotomy. J Thor Cardiovasc Surg 1994;108:727-735.

Original Article

Estimating the Risk of In-Hospital Mortality after CABG Surgery at Philippine Heart Center: A Comparison of Two Prediction Models

Josephine C. Milo MD, Gerard Vilela MD.

OBJECTIVE: To validate the ACC/AHA guideline of estimating perioperative mortality after CABG surgery and compare with the previously validated PHC Risk Index and determine which reliably predicts mortality among patients at Philippine Heart Center.

DESIGN: Prospective Cohort Study

POPULATION AND SETTING: All patients admitted at Philippine Heart Center from January-December 2003 who underwent CABG.

METHODS: Patients who underwent CABG Surgery were evaluated and scored making use of both the AHA and PHC predicting models: The estimated risk of death was compared with the outcome upon discharge. Validity measures such as Sensitivity, Specificity, and Predictive Values for each model were determined.

RESULTS: Both The ROC curve was used to determine the cutoff score in both Prediction Models. In the AHA Scoring, a total score of 6 was able to predict mortality, however this has a low positive predictive value with a specificity of 87.11% and sensitivity of 45.45%. In the PHC risk index, the cut off score differentiating the patients with poor outcome is 5 with a specificity of 83.97% and 72.73%.

Phil Heart Center J 2004;11:6-12

Keywords: Coronary Arteriosclerosis; Coronary Artery Bypass

Surgical revascularization for coronary artery disease (CAD) is one of the great milestones in medicine. Relief of angina after coronary artery bypass graft (CABG) surgery, improvement in functional capacity, and the realization of survival benefit have attended this procedure since the early stages of development. The ability to accurately predict outcome after cardiac surgery may be particularly useful especially with limited health resources. It is therefore imperative for the clinician and the patient to determine the risk of mortality when considering the decision for CABG.

The Amercian College of Cardiology/ American Heart Association (ACC/AHA) proposed a system of predicting the risk of mortality and morbidity from CABG surgery in the 1999 Practice Guidelines for CABG surgery. This was derived from the experience from the Northern New England Cardiovascular Disease Study Group, which included 7290 patients who underwent CABG surgery between 1996 and 1998. The observed in-hospital mortality in this study was 2.93%.[1]

Locally at Philippine Heart Center, where nearly 300 to 400 cases of CABG are done annually, Go et al. developed a multivariate clinical prediction rule, which allowed calculation of a conditional probability of death. This was derived from a retrospective study of 962 patients who underwent cardiac surgery from 1990-1994 and was tested in a validation set of 124 patients in 1995. It was further validated by Vilela, et al., however retrospectively, in a larger population of 910 patients who underwent CABG from 1996-1999. Both of these studies had reliably predicted the outcome of interest. The in-hospital mortality rate from CABG surgery at PHC was noted to be 6.85%."

It is therefore the purpose of this study to compare 2 different prediction models of estimating the in-hospital mortality from CABG, one derived from a foreign study with one that is derived from a Filipino population, and determine which is reliably applicable to the PHC patients.

Correspondence: Josephine Milo, MD. Division of Adult Cardiology Philippine Heart Center, East Avenue, Quezon City, Philippines 1100

Materials and Methods

A. Study Design: Prospective Cohort Study

B. Study Setting and Time Period:

January 2003 –December 2003 at Philippine Heart Center

C. Study Population

Admitted patients who underwent CABG surgery at Philippine Heart Center

C. Data Collection:

Each patient was evaluated preoperatively as to the risk of mortality after CABG Surgery using both the American Heart

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Association Clinical Guidelines on estimating mortality and the Philippine Heart Center Risk Index for In-Hospital mortality. Variables predictive of mortality in the AHA Clinical Guidelines includes age, female sex, ejection fraction of <40%, priority of the surgery, prior CABG, and comorbid medical problems such as peripheral vascular disease, creatinine of > 2mg/dl, and chronic obstructive pulmonary disease (COPD).[1] Each of these relevant preoperative variables was scored accordingly, and the total score was computed for each patient, which has a corresponding estimation of risk of death. Considered to be important variables predictive of mortality in the PHC Risk Index included age, case category, urgency of CABG, Re-do CABG, NYHA Functional Capacity, Angina Status, use of LIMA, and concomitant surgery either thoracic aneurysmectomy or mitral valve surgery.[2] The risk of death estimated by means of both prediction models were compared with the actual outcome on discharge.

Table 1. ACC/AHA Preoperative Estimation of Risk of Mortality

Patient or Disease Characteristic	Mortality Score
Age 60-69	2
Age 70-79	3
Age e"80	5
Female Sex	1.5
Ejection Fraction<40%	1.5
Urgent Surgery	2
Emergency Surgery	5
Prior CABG	5
PVD	2
Dialysis or Creatininee"2	4
COPD	1.5
Total Score	**Mortality %**
0	0.4
1	0.5
2	0.7
3	0.9
4	1.3
5	1.7
6	2.2
7	3.3
8	3.9
9	6.1
10	7.7
11	10.6
12	13.7
13	17.7
14	>28.3

D. Statistical Analysis

With assumed morality rate of 5% in the PHC study and 2.93% in the AHA study, and á set at 0.05, total width of CI =5%, a population of at least 292 patients was required to have statistical significance. Descriptive analysis using means and standard deviation were computed for the age, ischemic time, bypass time and length of hospital stay. The relationship of nonparametric and nominal variables to mortality in both Prediction Models was determined using the Mann-Whitney U Test and Chi-Square or T- test when appropriate. Receiver Operating Characteristic curve was used to calculate the best cut off score, which would reliably predict the outcome in both models. Validity measures such as sensitivity, specificity, positive and negative predictive values were likewise assessed for each predictive model.

Definitions of Terms:

EF <40% (Left Ventricular Ejection Fraction): The patient's current EF is less than 40%.

Urgent: Medical Factors require patient to stay in hospital to have operation before discharge. The risk of immediate morbidity and death is believed to below.

Emergency: Patient's cardiac disease dictates that surgery should be performed within hours to avoid unnecessary morbidity or death.

PVD (Peripheral Vascular disease): Cerebrovascular disease including prior CVA, prior TIA, prior carotid surgery, carotid stenosis by history or radiographic studies or carotid bruit. Lower extremity disease, including claudication, amputation, prior lower extremity bypass, absent pedal pulses or lower extremity ulcers.

Dialysis or creatinine > 2: Peritoneal or hemodialysis dependent renal failure or creatinine >2 mg/dl.

COPD (Chronic Obstructive Pulmonary Disease): Treated with bronchodilators or steroids.

Service Case Category: refers to those patients who underwent CABG under the PHC's Social Service Program and therefore paid minimal amount for the operation. These cases were handled by surgical fellows in training and supervised by a surgical consultant. In contrast, those categorized under private cases paid the total cost of their hospitalization and had the option to choose the members of the surgical team.

Results

A total of 298 patients with relevant preoperative variables were included and scored utilizing both the AHA Preoperative Estimation of Risk of Mortality and the PHC Risk Index for In-Hospital mortality as shown in Table 1 and 2. Outcome of the CABG surgery was determined upon discharge.

Table 3 shows the demographic profile of patients who

underwent CABG surgery from January-December 2003 at Philippine Heart Center. The population is predominantly male (75.48%) and the mean age is 61.6(±SD 9.15). Majority of the patients (92.28%) are private cases and 7.7% are service cases. Majority (64.76%) are admitted for CABG on an elective basis while 3.02%were done on an emergency basis, 32.2% were urgent procedures. Most of the patient presented with chronic stable angina (59.07%), while 40.93% were admitted due to acute coronary syndrome, 14.77% of which are acute myocardial infarction. Comorbid factors include PVD (15.1%), 4.0% had renal insufficiency, and 4.7% had COPD. There were 10.4% who had preoperative Ejection Fraction of less than 40% nevertheless, 9.4% survived after the surgery while 8.05% have no preoperative data on EF.

Table 2. PHC Risk Index for Mortality after CABG Surgery

Variables	Risk Score
AGE (years)	
>50	0
50-74	1
>75	3
Case Category	
Private	0
Charity	2
Urgency of CABG	
Elective	0
Urgent	1
Emergency	5
Re-do CABG	
No	0
Yes	3
NYHA Functional Class	
I-II	0
III-IV	3
Angina Status	
Chronic Stable Angina	
Unstable Angina	0
Acute Myocardial Infarction	2
LIMA Use	
Yes	0
No	1
TAA	
No	0
Yes	5
Mitral Valve Surgery	
No	0
Yes	2

Total Risk Score	Risk of Death
0-4	Low Risk
5-8	Intermediate Risk
9-12	High Risk
> 12	Ultra High Risk

The in-hospital mortality rate in this study is 3.69%. Among those who were discharged alive, 91.6% were in NYHA Functional Class I-II, 3.36% had concomitant surgery either valve replacement or repair of an aneurysm at the time of CABG. The means for Age, total number of hospital days, Ischemic Time, and Bypass Time were not significantly different among those discharged alive and those who expired. Table 4 and 6 show the frequency distribution of the total AHA and PHC scores of the alive and expired patients, respectively. Table 7 shows the correlation of each of the AHA variables with mortality. Of the 7 variables in the AHA Scoring System, only urgency of CABG had association with the outcome on discharge.

Table 5 shows the association of each variable in the PHC Risk Index for in-hospital mortality with the outcome on discharge. Considered significant predictors of mortality are the case category, urgency of CABG, NYHA Functional Capacity, Angina Status, Use of LIMA, and Concomitant surgery. Only Age variable did not correlate with mortality.

The mean total score obtained from each prediction model correlated significantly with outcome that is, a higher score means greater probability of dying as shown in Table 8. Mean PHC Score of those discharged alive is 2.951±2.608, while those who expired had a mean score of 7.909±3.961. Comparing this with the AHA Prediction Model, the mean score of those discharged alive is 3.193±2.439, while those who expired after CABG the mean score is 5.591±2.548.

Among those discharged alive after CABG surgery, the total risk score correlated with the length of hospital stay as shown in Table 9. Combining both alive and expired patients however, the length of hospital stay did not correlate with the outcome as shown earlier.

The Receiver Operator Characteristic Curve for the AHA Prediction Model is shown in Figure 1 and the corresponding validity measures are shown in Table 10. A total score of 6 provided a specificity of 87.11% and sensitivity of 45.45% in predicting the probability of death. The positive predictive value for a total score of 6 may be low but the negative predictive value is high. Figure 2 shows the ROC curve for the PHC Risk Index, and the corresponding positive and negative predictive values are shown in Table 11. A total risk score of 5 was able to predict mortality with a specificity of 83.97% and sensitivity 72.73%. This has also a low positive predictive value, similar with the AHA Prediction model but the ability of the scoring system to predict those who has the least risk of dying following CABG surgery (negative predictive value) is high.

Table 3. Clinical Profile of CABG Patients

	SURVIVED	EXPIRED	p-value
1. Age Mean ±SD	62 ± 9.25	63 ± 6.11	0.655
2. Sex			
Female	70 (23.5%)	3(1.01%)	0.734
Male	217 (72.8%)	8(2.68%)	
3. Preoperative Ejection Fraction (Mean)			
d"40%	28(9.40%)	3(1.01%)	
>40%	236(79.19%)	7(2.35%)	0.091
No Data	23(7.7%)	1(0.33%)	
4. Case Category			
Private	267(89.6%)	8(2.68%)	0.044*
Service	20(6.7%)	3(1.01%)	
5. Urgency of CABG			
Elective	191(64.1%)	2(0.67%)	0.000***
Urgency	89(29.9%)	7(2.34%)	
Emergency	7(2.34%)	2(0.67%)	
6. Previous/Redo CABG			
No	287(96.3%)	10(3.36%)	NA
Yes	0	0	
7. Comorbid Factors			
PVD	42(14.1%)	3(1.01%)	
Renal	11(3.7%)	1(0.33%)	0.98
COPD	13(4.36%)	1(0.33%	
8. NYHA Functional Capacity			
FC I-II	273(91.6%)	6(2.01%)	0.000***
FC III-IV	14(4.7%)	5(1.68%)	
9. Angina Status			
Chronic Stable Angina	174(58.4%)	20(0.67%)	0.014*
Unstable Angina	73(24.5%)	5(1.68%)	
Acute Myocardial Infarction	40(13.4%)	4(1.345)	
10. Use of LIMA			
Yes	267(89.6%)	8(2.68%)	0.044*
No	20(6.7%)	3(1.01%)	
11. Total Number of Hospital Days Mean±SD	14.76 ± 7.85	14.09 ± 9.19	0.782
12. Ischemic Time (minutes) Mean±SD	90.11±32.52	113.18±59.71	0.231
13. ByPass Time (minutes) Mean±SD	131.19±46.25	191.70±46.17	0.223
14. Concomitant Surgery			
Valve	7(2.35%)	2(0.67%)	0.039*
Aneurysmectomy	0	1(0.33%)	0.037*

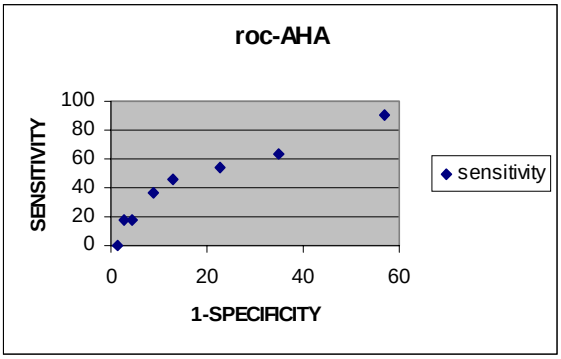

Figure 1. Receiver Operator Curve for Mortality after CABG Surgery Using the AHA

Table 4. Frequency Distribution of the Total AHA Score and Outcome of CABG Surgery.

	Outcome of CABG Surgery		
TOTAL AHA Score	**Alive**	**Expired**	**Total**
0	56	0	56
1.5	16	0	16
2	52	1	53
3	21	0	21
3.5	42	3	45
4	22	1	23
4.5	13	0	13
5	16	0	16
5.5	12	1	13
6.o	3	1	4
6.5	9	0	9
7	9	1	10
7.5	3	1	4
8	2	0	2
8.5	3	0	3
9	1	0	1
9.5	3	2	5
10.5	1	0	1
11	2	0	2
12.5	1	0	1
TOTAL	**287(96.32%)**	**11(3.69%)**	**298**

Table 5. Correlation of the Variables of the AHA Prediction Model with the Outcome of CABG Surgery

Variables	**Alive**	**Expired**	**p-value**
AGE			
<60	122	3	0.9
60-69	93	7	
70-79	68	1	
e”80	4	0	
Sex			
Male	217	8	0.734
Female	70	3	
URGENCY OF CABG			
Elective	190	2	
Urgent	89	7	0.000***
Emergency	7	2	
Previous CABG			
No	287	11	NA
Yes	0	0	
PVD			
Yes	42	3	
No	245	8	0.222
Dialysis or Creatinine of e”2 mg/dl			
No			
Yes	276	10	0.369
	11	1	
COPD			
No	274	10	0.416
Yes	13	1	
	287	11	

***Highly Significant

Table 6. Frequency Distribution of the Total PHC Risk Score and Outcome of CABG Surgery

	Outcome of CABG Surgery		
TOTAL Score	**Survivors**	**Nonsurvivors**	**Total**
0	15	0	15
1	114	1	115
2	19	0	19
3	44	0	44
4	37	1	38
5	12	1	13
6	21	1	22
7	5	1	6
8	7	2	9
9	6	1	7
10	2	0	2
11	2	0	2
12	0	1	1
13	1	1	2
14	1	1	2
15	1	0	1
TOTAL	**287**	**11**	**298**

p-value=0.000*

Table 7. Correlation of the Variables of the PHC Risk Index with the Outcome of CABG Surgery

Variables	**Alive**	**Expired**	**p-value**
AGE			
<50	27	0	0.854
50-74	239	11	
e”75	21	0	
CASE CATEGORY			
Private	267	8	0.044*
Service	20	3	
URGENCY OF CABG			
Elective	191	2	
Urgent	89	7	0.000*
Emergency	7	2	
RE-DO CABG			
No	287	11	NA
Yes	0	0	
NYHA Functional Capacity			
I-II	273	6	0.000*
III-IV	14	5	
Angina Status			
Chronic Stable Angina	174	2	0.004*
Unstable Angina	73	5	
Acute Myocardial Infarction	40	4	
Use of LIMA			
Yes	267	8	0.044*
No	20	3	
Concomitant Repair of TAA			
No	287	10	0.037*
Yes	0	1	
Concomitant Valve Surgery			
No	280	9	0.039*
Yes	7	2	

*** Significant** ***** Highly Significant**

Table 8. Mean Scores of Patients in Both PHC and AHA and Outcome

	N	Mean±SD	p-value
PHC Score			
Alive	287	2.951 ± 2.608	0.000***
Expired	11	7.909 ±3 .961	
AHA Score			
Alive	287	3.193±2.439	0.002***
Expired	11	5.591±2.548	

*** Highly Significant

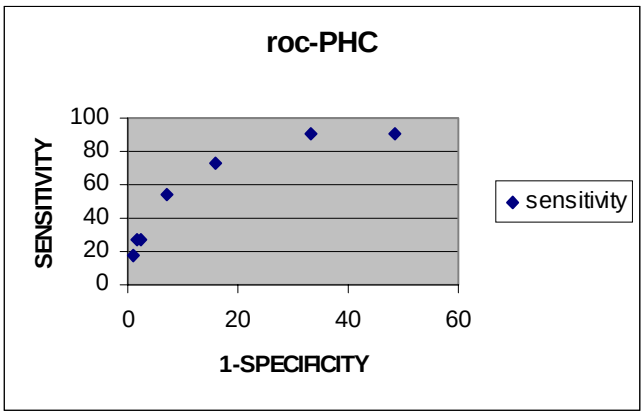

Figure 2. Receiver Operator Curve for Mortality after CABG Surgery Using the PHC Risk Index

Table 9. Correlation of the Length of Hospital Stay with Total Risk Score among Survivors of CABG Surgery

Prediction Model	Correlation Coefficient r	p-value
AHA	0.311	0.000***
PHC	0.321	0.000***

*** Highly Significant

Table 10. Validity Measures of the AHA Prediction Model

Cut-off PointsOf AHA Scores	Sensi-tivity	Speci-ficity	Postitive Predictive Value	Negative Predictive Value
10	0	98.61	0	96.26
9	18.18	97.21	20	96.88
8	18.18	95.47	13.3	96.82
7	36.36	91.29	13.79	97.4
6	45.45	87.11	11.9	97.66
5	54.54	77.35	8.45	97.8
4	63.64	65.16	6.54	97.91
3	90.91	43.21	5.78	99.2

Table 11. Validity Measures of the PHC Risk Index

Cut-off PointsOf PHC Scores	Sensi-tivity	Speci-ficity	Postitive Predictive Value	Negative Predictive Value
12	18.18	99	40	96.93
10	27.27	98.3	37.5	97.24
9	27.27	97.6	30	97.22
7	54.54	93	23.08	98.16
5	72.73	84	14.81	98.77
3	90.91	66.90	9.52	99.48
2	90.91	51.57	6.71	99.33

Discussion

This study has reaffirmed most of the findings in the study initiated by Go, et al. which was further validated by Vilela et.al. Both studies identified 9 variables to be significant predictors of Mortality after CABG Surgery. This study however, noted that age variable did not correlate with mortality. Consistently shown to be predictive of mortality in this study are variables Case category, Urgency of CABG, Angina Status, Use of LIMA, and Concomitant Aneurysmectomy or Valve Surgery. The use of the Left Internal Mammary Artery as a bypass conduit was considered important predictor of survival in the PHC study, which in foreign literature also was shown to have both short-term and long term impact on survival.[4] On the other hand, of the 7-variables in the foreign derived prediction model proposed in the AHA Clinical Guidelines for estimating the risk of death after CABG Surgery, only the urgency of CABG variable was found to be associated with mortality, which has also been included in the PHC Risk Index to be an important predictor. Contrary to foreign studies, which identified the female sex as a predictor of poor outcome after CABG, this study consistently showed no increase in mortality among female patients as earlier observed in the studies of Go and Vilela.

Unlike the AHA Prediction Model and other foreign studies,[1,5] the PHC did not include comorbid conditions like COPD, Renal dysfunction and Peripheral Vascular Disease, which however did not show correlation with mortality among PHC patients in this study. The ROC identified the cut off points that would define risk of death for each prediction model. For the PHC Risk Index, a score of 5 and below are at low risk of dying following CABG surgery. However, due to its low positive predictive value, only about 15% are really at risk given a total score of more than 5. Likewise, for the AHA Prediction Model, a score of 6 and below gives assurance

of a successful outcome after CABG however, has a low positive predictive value. In conclusion, predicting outcome in postoperative cardiac surgery has proved to be an extremely difficult task. Both prediction models can not reliably predict mortality after CABG surgery as high scores are often not associated with poor outcome. However, the PHC Risk index showed a trend having most variables significantly correlated with mortality.

Recommendations

Clinical Prediction Models should be constantly updated with the advent of newer technologies. The ability to normalize the physiology and hemodynamics with pharmacologic and mechanical support postoperatively may in part account for the survival of those patients predicted to have poor outcome**.** The AHA Prediction model primarily predicts outcome based on preoperative variables and has not taken into account events during the operative or immediate postoperative period that can affect outcome. Recent studies have shown that preoperative variables usually have little or no contribution to the final predictive model.[6,7]

The PHC Risk Index having included perioperative variables may be used to guide clinical decisions but caution must be exercised when applying this prediction models. Being assured of a good outcome with low scores may lead to complacency.

References

1. Eagle KA, Guyton RA, Davidoff R, et.al. ACC/AHA Practice Guidelines for Coronary Artery Bypass Graft Surgery. J Am Coll Cardiology 1999;1262-347.
2. Go LR, et. al. Risk Index and Predictor of InHospital Mortality After CABG. A Five Year Retrospective Study Conducted at Philippine Heart Center. PHC J 1998;(5):2-11.
3. Vilele G, et.al. Validation of Risk Index and Predictor of In Hospital Mortality after CABG Surgery at Philippine Heart Center. PHC J 2000;7-10.
4. Braunwald E, et.al. Heart Disease: A Textbook of Cardiovascular Medicine 2001; 6th Edition:34:304.
5. Gupta et.al. Risk and Outcome after CABG. Ann Cardiac Anaesth 2002;(5):156-158.
6. Turner JS, Morgan CJ, et. al. Difficulties in Predicting Outcome in Cardiac Surgery Patients. Crit Care Med 1995;(23):1843-1850.
7. Thompson MJ, Elton RA, et.al. The Edinburgh cardiac Surgery score survival prediction in the long-stay ICU Cardiac Surgical Patient. EUR J Cardiothorac Surg 1995;(9):419-425.

Original Article

ST Segment Elevation in Lead aVR as a Predictor of Left Main Coronary Artery Lesion in Acute Coronary Syndrome

Ronaldo C. Manuel MD, Santos Jose G. Abad MD, Valentin G. Yabes MD.

BACKGROUND: ***The lead aVR is the mostly ignored lead while interpreting a 12-lead ECG but it was found out to be very valuable in the field of clinical electrocardiography. It can be very helpful in ischemic heart disease in diagnosing the site of coronary artery occlusion and size of the area at risk. The purpose of this study is to determine if ST segment elevation in lead aVR can predict critical left main coronary artery (LMCA) stenosis in acute coronary syndrome. And to determine if the ST segment depression in precordial lateral leads (V5 to V6) is an added criterion for LMCA lesion during acute chest pain.***

MATERIALS AND METHODS: ***This is a retrospective, cross sectional study. The correlation between ST segment elevation in lead aVR, ST segment depression in V4 to V6 and infarct related artery (IRA) was examined in 554 patients with acute coronary syndrome. The IRA was defined as the most severe and /or that the lesion with thrombus by coronary angiography.***

RESULTS: ***A total of 554 patients were included in this study. Among this patients, IRA was left main coronary artery (LMCA) in 82 patients, left anterior descending artery (LAD) in 256 patients, left circumflex artery (LCx) in 30 patients, right coronary artery (RCA) in 111 patients and those with three-vessel disease (3VD) in 75 patients. The ST segment elevation in lead aVR was present in 134 patients (24%) among 554 patients. The ST segment elevation in lead aVR was present in 90.2% (74/82) of LMCA, 34.7% (26/75) of 3VD, 10.5% (27/256) of LAD, 6.32% (7/111) of RCA and none from the LCx (p<0.000). The ST segment elevation in lead aVR was specific for LMCA lesion (sensitivity; 90.2%, specificity; 87.3%, positive predictive value; 55.2%, negative predictive value; 98.1%). The ST segment depression in leads V4 to V6 was also present in 150 patients (27%) among 554 patients. The ST segment depression in leads V4 to V6 was present in 94% (77/82) of LMCA, 73% (55/75) of 3VD, 3.7% (11/30) of LCx, 1.9% (5/256) of LAD and 1.8% (2/111) of RCA (p<0.000). The ST segment depression in leads V4 to V6 was specific for LMCA lesion (sensitivity; 93.9%, specificity; 98.1%, positive predictive value; 93.9%, negative predictive value; 98.1%).***

CONCLUSION: ***In acute coronary syndrome, ST segment elevation in lead aVR and ST segment depression in V4 to V6 are present in majority of patients with LMCA lesion and in minority of patients with proximal left descending artery lesion and with three-vessel disease.***

RECOMMENDATION: ***Early aggressive treatment should be done in these particular subsets of patient. Hence coronary angiography with revascularization are needed to save these high-risk patients.***

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Keywords: Coronary Vessels; Electrocardiography; Coronary Angiography

Patients with critical left main coronary artery (LMCA) occlusion are at high risk in develop ing sudden cardiac death. It is important to detect this subset of patient especially in the emergency room and in clinic. Left main coronary artery occlusion is a fatal disease if not properly identified. Early detection, intervention and appropriate treatment are necessary to save this particular subset of patient. High-risk patient with critical stenosis of the left mainstem during acute chest pain had specific electrocardiographic changes. In patients with acute chest pain ST segment in lead aVR can be very helpful in ischemic heart disease in diagnosing the site of coronary artery occlusion and size of the area at risk. It was found out to be highly predictive for critical left main coronary artery lesion. Atie et al[1] noticed that during chest pain all patients had an abnormal ECG, the most frequent pattern being ST segment elevation in leads aVR and V1 and ST segment depression in leads V3, V4 and V5 (with maximal depression in V4).

Yamaji et al [2] noted that ST segment elevation in lead aVR with less ST segment elevation in lead V1 is an important predictor of acute left main coronary artery obstruction. They have shown in their study that lead aVR could be very useful in identifying left main coronary artery (LMCA) obstruction. Ischemia of the basal part of the interventricular septum is the electrocardiographic explanation for the occurrence of ST segment elevation in his lead. In this situation, owing to the dominance of the basal ventricular mass, the ST segment vector

Correspondence: Ronaldo C. Manuel, MD. Division of Adult Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100

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in the frontal plane points in a superior direction, leading to ST segment elevation in leads aVR and aVL and ST depression in the inferior leads.

Gorgels et al[3] concluded that ST segment elevation in lead aVR is highly predictive for left main coronary artery occlusion.

Hori et al[4] also noted that in patient with left main coronary artery obstruction ST segment elevation in lead aVR was very characteristic.

Gorgels et al[5] found out that the most common ECG changes in left main coronary artery disease were ST segment elevation in lead aVR and ST segment depression in leads I, II, V4 to V6.

Nakamori et al[6] concluded in his study that ST segment deviation in lead aVR was the most accurate electrocardiographic predictor of exercise-induced anterior wall ischemia.

Kono et al[8] studied the correlation between ST segment elevation in lead aVR and infarct related artery (IRA) in 841 patients with acute myocardial infarction. And they found out that ST segment elevation in lead aVR was present in 76.7% of left main tract lesion. They concluded that ST segment elevation in lead aVR was specific for left main tract lesion with sensitivity of 76.7% and specificity of 94.7%.

Chi-Keong Ching et al,[9] mentioned that early aggressive treatment is most desirable in high-risk patients with severe left mainstem and triple-vessel disease presenting with unstable angina.

Research Objective

General Objective

To assess the value of 12 lead ECG in identifying significant left main coronary artery (LMCA) lesion in patient with acute coronary syndrome.

Specific Objectives

1. To determine if ST segment elevation in lead aVR is specific for left main coronary artery lesion in acute coronary syndrome.
2. To determine if ST segment elevation in lead aVR is also present in patient with significant RCA, LAD, LCx lesion and three-vessel disease in acute coronary syndrome.
3. To determine if ST segment depression in the precordial lateral leads (V4 to V6) are added criteria for LMCA lesion in acute coronary syndrome.

Research Hypothesis

ST segment elevation in the lead aVR and ST segment depression in the lateral precordial leads (V4 to V6) predict critical left main coronary artery lesion in acute coronary syndrome.

A. Study Design

A cross sectional study will be use to determine the objective.

B. Study Sample, Setting and Time Period

All patient admitted at Philippine Heart Center from January 1, 1998 to December 31, 2003 who were diagnosed to have acute coronary syndrome (ACS) and underwent coronary angiography were included in the study. Admitting resting 12 lead ECG were analyzed with regards to the presence of ST segment elevation in lead aVR, ST segment depression in leads V4 to V6 and compared with each group. They were divided into 5 groups. Patients with LMCA involvement were assigned in group 1 proximal left anterior descending artery stenosis (LAD) in group 2, left circumflex artery stenosis (LCx) in group 3, right coronary artery stenosis (RCA) in group 4, and those with three-vessel disease (3VD) without LMCA involvement in group 5. A total of > 553 patient is needed to achieve the assumed prevalence of ST segment elevation in lead aVR at 5% total width of confidence interval and α= 0.050.

Initially, using 10 randomly selected ECG samples from the five groups will check inter-observer and intra-observer difference. Two observers who were not aware of any angiographic findings then measured measurements.

Definition of Terms

Left main coronary artery obstruction
- >50 % stenosis

Right coronary artery obstruction
- >70 % stenosis

Left anterior descending artery obstruction
- >70 % stenosis obstruction of RCA, LAD, LCX

Left circumflex artery obstruction
- >70 % stenosis

Three-vessel disease
- >70 %

ST segment elevation
- presence of ST segment elevation of >0.05mV measured at 60 ms after J point of the QRS complex.

ST segment depression
- Horizontal or down sloping ST depression >0.5mV below the isoelectric baseline at 80ms from the J point was considered significant

Patients with the following criteria are excluded in the study

1. Patients with recurrent MI.
2. Patients with concomitant pericarditis
3. Patients who previously underwent coronary artery bypass graph.
4. Patients with bundle branch block.
5. Patient with unavailable 12 lead ECG and coronary angiogram result.

C. Statistical Analysis

Data were described as means, standard deviations, frequency and percent distributions. Association of different factors with infarct related artery (IRA) were carried out using analysis of variance for continuous variables and chi-square for dichotomous variables. A $p < 0.050$ was considered significant. To determine the validity of ST elevation in lead aVR and ST depression in lead V4 to V6 in detecting the specific vessel involved, validity measures such as sensitivity, specificity, positive predictive value and negative predictive value were applied to the data.

Abbreviations and Acronyms

LMCA = Left main coronary artery
RCA = Right coronary artery
LAD = Left anterior descending artery
LCx = Left circumflex artery
ECG = Electrocardiogram
ACS = Acute coronary syndrome
UA = Unstable angina
NSTEMI = Non ST elevation myocardial infarction
STEMI = ST elevation myocardial infarction
IRA = Infarct related artery

Results

When evaluating the sample ECGs, the inter-observer and intra-observer differences in lead aVR averaged 0.08+0.07 mV and 0.08+0.07mV respectively. Similarly, the inter-observer and intra-observer differences in the lateral precordial leads (V4 to V6) averaged 0.17+07mV and 0.18+0.07mV respectively. Therefore, intra-observer and inter-observer variations were acceptably small and did not affect the validity of the results.

A total of 554 patients were included in the study. Among this 554 patients IRA was left main coronary artery (LMCA) in 82 patients, left anterior descending artery (LAD) in 256 patients, left circumflex artery (LCx) in 30 patients, right coronary artery (RCA) in 111 patients and three vessel disease (3VD) in 75 patients. Other baseline variables are listed in *Table 1.*

The ST segment elevation in lead aVR was present in 90.2% (74/82) of LMCA, 34.7% (26/75) of 3VD, 10.5% (27/256) of LAD, 6.32% (7/111) of RCA and 0/30 from the LCx ($p<0.000$) see *table 2.* The ST segment elevation in lead aVR was specific for LMCA lesion (sensitivity; 90.2%, specificity; 87.3%, positive predictive value; 55.2%, negative predictive value; 98.1%) see *table 3.* The ST segment depression in leadsV4 to V6 was present in 150 patients (27%) among 554 patients. The ST segment depression in leads V4 to V6 were also present in 94% (77/82) of LMCA, 73% (55/75) of 3VD, 3.7%(11/30) of LCx, 1.9% (5/256) of LAD and 1.8% (2/111) of RCA (*p<0.000)* see *table 4.* The ST segment depression in leads V4 to V6 was specific for LMCA lesion (sensitivity; 93.9%, specificity; 98.1%, positive predictive value; 93.9%, negative predictive value; 98.1%) see *table 5.* Figure 1 shows representative 12-lead ECGs at the hospital admission for one patient from each group and the incidence of ST segment elevation in lead aVR and ST segment depression in leads V4 to V6 were summarized in *figure 2 and figure 3* respectively.

ST segment elevation in lead aVR is highest in group 1 (LMCA) 0.193+0.098 mV in comparison with the other groups which are tabulated in *table 6.*

ST segment depression in leads V4 to V6 was also noted to be higher in group 1 (LMCA) 0.296+0.158 mV in comparison with the other groups *(see table 7).*

Table 1. Baseline characteristics of each study group.

Variable	Group 1 (LMCA)	Group 2 (LAD)	Group 3 (LCx)	Group 4 (RCA)	Group5 (3VD)
Number of Patients	82/554	256/554	30/554	111/554	75/554
Age	61.76+ 11.52	57.18+ 12.13	60.07+ 10.75	55.96+ 11.98	61.93+ 10.12
Male/ Female	61/ 21	200/ 56	27/ 3	4/ 86	10/ 57
Unstable angina	41	6	2	3	27
NSTEMI	41	4	13	0	48
STEMI	0	246	15	108	0

Table 2. Incidence of ST segment elevation in lead aVR.

Variable	Group 1 N=82	Group 2 N=256	Group 3 N=30	Group 4 N=111	Group5 N=75
With ST segment elevation in lead aVR	74	27	0	7	26
Without ST segment elevation in lead aVR	8	229	30	104	49

Table 3. Sensitivity, specificity, positive and negative predictive value (%) of ST Segment elevation in lead aVR

Group	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
1 (LMCA)	90.2	87.3	55.2	98.1
2 (LAD)	10.5	9.8	26.7	3.4
3 (LCx)	0	9.8	0	21.1
4 (RCA)	6.3	9.8	8.6	7.1
5 (3VD)	34.7	9.8	26	14

Table 4. Incidence of ST segment depression in lead V4 to V6.

Variable	Grp 1 N=82	Grp 2 N=256	Grp 3 N=30	Grp 4 N=111	Grp5 N=75
With ST segment depression elevation in leads V4 to V6	77	5	11	2	55
Without ST segment elevation in leads V4 to V6	5	251	19	109	20

Table 5. Sensitivity, specificity, positive and negative predictive value (%) of ST segment depression in lead V4-V6

Group	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
1 (LMCA)	93.9	98.1	93.9	98.1
2 (LAD)	1.9	6.1	6.1	1.9
3 (LCx)	36.7	6.1	12.5	20.8
4 (RCA)	1.8	6.1	2.5	4.4
5 (3VD)	73.3	6.1	41.7	20

Table 6. Summation of ST segment elevation in lead aVR in each group.

Variable	Group 1 (N=74)	Group 2 (N=27)	Group 3 (N=0)	Group 4 (N=7)	Group 5 (N=26)
ST segment elevation in lead aVR (mV)	0.193+ 0.098	0.124+ 0.05	0	0.093+ 0.019	0.11+ 0.041

Table 7. Summation of ST segment depression in lead V4 to V6 in each group.

Variable	Group 1 (N=77)	Group 2 (N=5)	Group 3 (N=11)	Group4 (N=2)	Group 5 (N=55)
ST segment depression in leads V4 to V6 (mV)	0.296+ 0.158	0.147+ 0.087	0.246+ 0.052	0.134+ 0.047	0.241+ 0.090

Discussion

The present study revealed that ST segment elevation in lead aVR was a useful indicator for predicting LMCA lesion in acute coronary syndrome, which requires immediate aggressive treatment.

Total obstruction or severe stenosis with flow delay in the LMCA lesion was demonstrated by the coronary angiography in all patients with LMCA group

The present study found that lead aVR ST segment elevation is present in 90.2% (74/82) of the patients in the LMCA group; this incidence is in good agreement with incidence reported by Yamaji et al, [1] and Kono et al [6] in patients with acute LMCA obstruction. These investigators concluded that lead aVR ST segment elevation in acute LMCA obstruction is the ischemia of the basal part of the interventricular septum [1]. In the LAD group, ST segment elevation was present in 10.5% (27/256) and all of these are located in the proximal region. This result is in good agreement with the incidence reported by Engelen et al [7] in patient with acute LAD obstruction in which the culprit lesion was located proximal to the first major septal branch. These investigators concluded that the lead aVR ST segment elevation in acute proximal LAD occlusion is the result of the transmural ischemia of the basal part of the septum, where the injury's electrical current is directed towards the right shoulder. In 6.32% (7/111) patients in the RCA group with lead aVR ST segment elevation was observed. This suggested that ischemia of the basal part of the septum might be caused by blood flow disturbance in interventricular branches, arising from the well-developed RCA, thus resulting in lead aVR ST segment elevation in these seven patients. Surprisingly, none from the LCx group had a ST elevation in lead aVR. It was previously mentioned from the study of Yamaji et al [2] that LCx obstruction was anatomically unstable to cause ischemia at the basal part of the septum, which has been thought to elevate the ST segment in lead aVR.

ST segment elevation in lead aVR is present in majority of patients with LMCA lesion and in minority of patient with 3VD and proximal LAD lesions. These subsets of patients belong to high-risk group, which if not detected early will put each patient's life into danger.

The occurrence of ST segment depression in LMCA and 3VD has also been observed by other investigators although one vessel CAD, especially left circumflex will mimic this picture. Therefore to differentiate further between LMCA, 3VD and LCx the value of ST segment depression in V4 to V6 was assessed. A highest ST segment depression is highly suggestive for LMCA followed by LCx and 3VD respectively.

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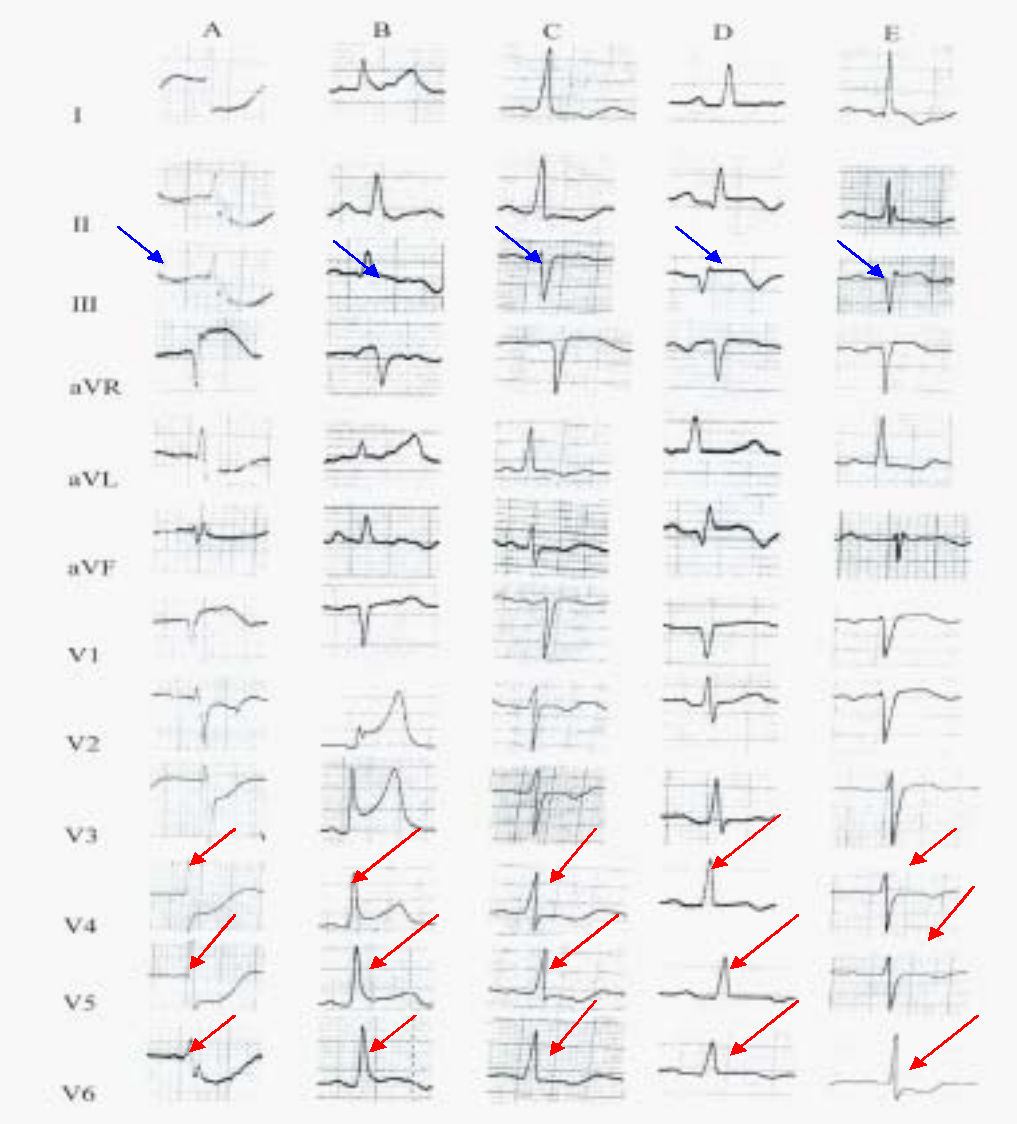

Figure 1. Representative 12-lead electrocardiogram tracings at admission in a patient in (A) the left main coronary artery (LMCA) group, (B) the left anterior descending coronary artery (LAD) group, (C) the left circumflex artery (LCx) group, (D) the right coronary artery (RCA) group and (E) the three-vessel disease without LMCA involvement. In LMCA group, there is marked ST segment elevation in lead aVR with concomitant ST segment depression in leads V4 to V6.

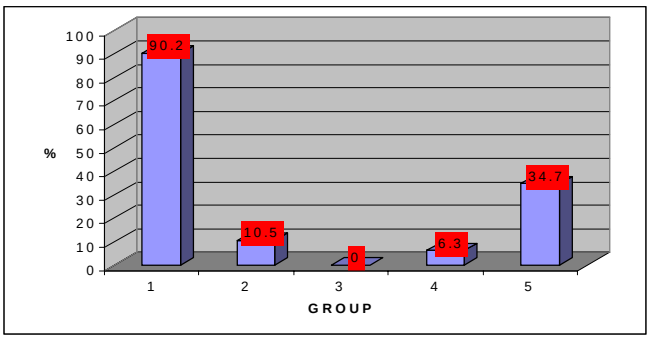

Figure 2. The incidence of ST segment elevation in lead aVR in group 1 (LMCA), group 2 (LAD), group 3 (LCx), group 4 (RCA), and group 5 (3VD)

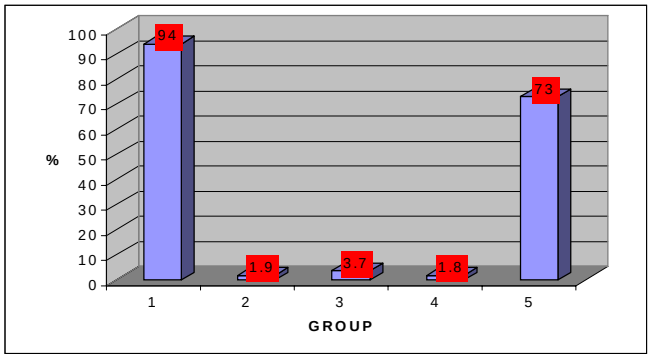

Figure 3. The incidence of ST segment depression in leads V4-V6 in group 1 (LMCA), group 2 (LAD), group 3 (LCx), group 4 (RCA), and group 5 (3VD)

Conclusion

In this present study careful attention should be made in lead aVR. The presence of ST segment elevation is highly sensitive and specific in predicting significant LMCA occlusion in patients with acute coronary syndrome. In addition, the presence of concomitant ST segment depression in leads V4 to V6 in ST segment elevation in lead aVR can be use as an added criterion in the detection of significant LMCA lesion during acute chest pain. This is a retrospective study involving patients diagnosed with acute coronary syndrome and with documented admitting resting 12 lead ECG in whom coronary angiography was performed during the same admission. Ideally, a prospective study should be done to further evaluate the value of these findings.

Finally, it should be emphasized that the described electrocardiographic abnormalities were recorded during chest pain. Therefore, similar electrocardiographic findings recorded without the presence of angina should be interpreted with caution.

References

1. Atie J, Brugada P, Brugada J, Smeets JLRM, Cruz FE, Roukens MP, Gorgels APM, Bar FWHM, Wellens HJJ. Clinical presentation and prognosis of left main coronary artery disease in the 1980's. Eur Heart J 1991; 12:495-502.
2. Yamaji H, Iwasaki K, Kusachi S, et al. Prediction of acute left main coronary obstruction by 12 –lead electrocardiography: ST segment elevation in aVR with less ST-segment elevation in lead V1. J Am Coll Cardiol 2001; 38:1348-54.
3. Gorgels A, Engelen D, Wellens H, Lead aVR, a mostly ignored but very valuable lead in clinical electrocardiography. J Am Coll Cardiol 2001; 38:1355-56.
4. Hori T, Kurosawa T. Yoshida M, Yamazoe M, Aizawa Y, Izumi T. Factors predicting mortality in patients after myocardial infarction caused by left main coronary artery occlusion: significance of ST segment elevation in both aVR and aVL leads. Jpn Heart J 2000 Sep; 41 (5): 571-81.
5. Gorgels AP, Vos MA, Mulleneers R, de Zwaan C, Bar FW, Wellens HJ. Value of the electrocardiogram in diagnosing the number of severely narrowed arteries in rest angina pectoris. Am J Cardiol 1993; 72:999-1003.
6. Hisato Nakamori, Toshiji Iwasaka, et al. Clinical significance of s-t segment elevation in lead avr in anterior myocardial infarction. Cardiology 1995; 86:147-151
7. Kono T, Morita H, Fujiwara A, Kitaura Yayushi. ST elevation in aVR suggests left main tract lesion in acute myocardial infarction. Osaka Medical College, Japan; Osakafu Mishima Critical Care Center, Japan.
8. Engelen DJ, Gorgels AP, Cheriex EC, et al. Value of the electrocardiogram in localizing the occlusion site in the left anterior descending coronary artery in acute myocardial infarction. J Am Coll Cardiol 1999; 34:389-95.
9. Chi-Keong Ching, Li-Fern Hsu, Wee-Siong Teo. Electrocardiographic case: diagnosis of left mainstem disease in unstable angina. Asean Heart Journal 2001; 8 (2): 47-49.

Original Article

Outcomes of Coronary Angioplasty in Patients with Depressed Left Ventricular function

Gerry C. Tan MD, Agapito S. Fortuno Jr., MD.

OBJECTIVE: ***Short term follow up of clinical outcomes following coronary angioplasty in patients with LV dysfunction is not well documented. The aim of this study is to evalutate the six months clinical outcomes in terms of mortality, cardiac events and symptomatology.***

METHODS: ***This is a cohort study which involved patients who underwent first time PTCA from January 1, 2003 to march 31, 2004 who has an available 2DED results with a low ejection fraction prior to the procedure. Eighty-five (85) patients constituted the study population except for the following patients: patient with prior CABG or PCI and patients with valvular heart disease. There baseline clinical characteristics, angiographic and PTCA results as well as 2DED results were noted.***

RESULTS: ***The study sample constituted of 85 patients, 84% were males with a mean age of 60.0 years. Clinical follow up was at least six months following the procedure. Angiographic and procedural success was obtained in 61% of the subjects. There was a total of 21% mortalities with 78% comprises male subjects. Deaths were found to be correlated with ejection fraction with most of reported belong to group 3 with a ejection fraction of less than 30%. However, cardiovascular events and symptoms were found to be not statistically significance.***

CONCLUSION: ***PTCA in patients with significant impairements of LV function is associated with poor outcomes. The investigator recommend more detailed and well documented study in this group of patients to further assessed the outcomes since many limitations were encountered in this study.***

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Keywords: Angioplasty, Transluminal, Percutaneous Coronary;Hypertrophy, Left Ventricular

Heart failure constitutes one of the basic problems of contemporary cardiology. It is most commonly caused by ischemic heart disease which, as an etiologic factor, has a negative impact on prognosis. On the other hand, decreased left ventricular ejection fraction is the most important prognostic factor in patients with ischemic heart disease. Annual mortality among patients with left ventricular ejection fraction of < 35% is 17%, and in a group with left ventricular ejection fraction of < 25%, it reaches 24%.[1] While annual mortality in patients with left ventricular ejection fraction of > 35% does not exceed 6%,[2] trials comparing results of pharmacological and surgical treatment of coronary heart disease showed the advantage of coronary artery bypass grafting over pharmacological treatment in patients with low left ventricular ejection fraction.[3,4] Percutaneous coronary angioplasty in patients with depressed left ventricular ejection fraction is associated with increased acute and late mortality. In contrast to plain percutaneous coronary angioplasty, results of stenting in these patients have not been characterized. The introduction of coronary stents and novel antiplatelet drugs considerably improved the short and long term results of percutaneous coronary angioplasty. These may be especiallyimportant in patients with multivessel disease and those with depressed left ventricular ejection fraction.

Technical advances in the field of interventional cardiology and increased operator experience have resulted in a substantial. Technical advances in the field of interventional cardiology and increased operator experience have resulted in a substantial increase in the volume and complexity of procedures being attempted. Percutaneous transluminal coronary angioplasty is one of these procedure that may be an effective treatment in selected patients with left ventricular dysfunction, but acute and late mortality is higher than in patients with normal left ventricular function.[5] In spite of these, studies in the literature documenting beneficial effects in this subset of populations are very few. Immediate and long term outcomes have been reported and consistently showed procedural complications occurring more frequently than in patients with normal or near normal left ventricular function.[6] A comparison between recent studies in the last decade and earlier reports suggests that hospital outcomes have improved. This may be a result of advances in the management of procedure related complications. Although, the long-term mortality assessed at one year is still high, ranging from 13 to 21% [(7)] Coronary stenting may improve procedural success rate and reduces restenosis rate.[8] However, in contrast to balloon angioplasty, the outcome of patients with left ventricular dysfunction treated by stenting is not well caharacterized.[9] It is also unclear if the adverse

Correspondence: Gerry C. Tan, MD. Division of Adult Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100

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prognostic influence of left ventricular dysfunction undergoing percutaneous transluminal coronary angioplasty in the past persists in the contemporary era.[10, 11]

Objectives :

1. To evaluate the outcomes in terms of mortality, cardiac events and persistence/recurrence of symptoms of patients with low left ventricular ejection fraction six months post percutaneous coronary intervention.
2. To determine the clinical factors associated with mortality, cardiac events and symptomatology.

Study Hypothesis :

Patients with more severe left ventricular dysfunction have higher mortality, cardiac events and symptoms.

Materials and Methods

This is a descriptive cohort study which involved patients admitted at the Philippine Heart Center who underwent first time percutaneous coronary angioplasty with or without stenting from January 1, 2003 to March 31, 2004. The following were the inclusion criteria: Patients who underwent first time percutaneous coronary angioplasty who have echocardiographic findings of left ventricular dysfunction prior to the procedures. The following were the exclusion criteria: Patients who have previous coronary artery bypass or coronary angioplasty and patients with valvular heart disease.

Patients eligible for the study were followed up for a period of about six months. Their medical records, percutaneous coronary intervention results and 2D echocardiographic study results were reviewed for their baseline characteristics. In cases where patients have more than one available echocardiographic results prior to coronary angioplasty, the result' obtained during the echo done immediately prior to the coronary angioplasty was utilized. Data collected from the patients' records include demographic profile such as age and sex. Risk factor profile for coronary artery disease such as hypertension, diabetes mellitus and lipid profile status were also recorded. Percutaneous coronary intervention data collected include number of vessels involved, completeness of revascularization, kind of stent implanted and the presence of complications, if any. The subjects were then grouped into three, based on their left ventricular ejection fraction by 2D echocardiographic results: group I had an ejection fraction of 40-49%, group II had an ejection fraction of 30-39% and group III had an ejection fraction of less than 30. Follow up data for the outcomes were obtained either via medical records, clinic visits or telephone interview. The following data were collected: mortality or death either cardiac or non cardiac, history of myocardial infarction since the last coronary angioplasty, the need for additional revascularization and the presence of symptoms either angina or dyspnea. Summary statistics were presented as frequencies and percentages or a mean +/-SD. Chi square, Fischer exact, Mann Whitney U and Anova tests were used to determine the association of different variables with their outcomes. Six months outcomes of mortality, cardiac events and symptoms were estimated using the Kaplan Meier method. Differences in the clinical outcomes between groups' were compared using paired t-test. P values of less than 0.05 were considered indicative of statistically significant differences between two groups.

Definition of Terms :

Coronary artery disease was classified as one, two, or three vessel disease according to the coronary artery surgery study definition (CASS). Angiographic success was considered complete if successful lesion dilation were accomplished in all lesions attempted. Partial angiographic success or incomplete was defined as successful lesion dilation in more than one vessel but not in all lesions attempted.

Results

The study sample consisted of 85 patients with coronary artery disease for which they underwent coronary angioplasty with or without stenting. Male population accounted for 84% and the remaining 16% were females (figure 1). The patients' ages ranged from 30 to 92 years, with a mean of 60.9 years +/ - SD 1.25 years. For the purpose of subsequent discussions, patients were group into two: those who were at least 60 years of age who comprised the majority of the population at 58% and those who were below this age (figure 2). This arbitrary grouping was made taking into consideration that individuals who were at least sixty years and older were considered to have a higher risk for coronary artery disease. Forty-five percent (45%) of the patients had a left ventricular ejection fraction between 40-49% (Group I), 28% belonged to group II with an ejection fraction between 30-39%, and the remaining 27% belonged to group III with an ejection fraction of less than 30% (figure 3). 33%, 39% and 28% of the populations had one, two and three vessel involvement respectively. Among the mortalities, 33%, 38% and 29% of the subjects had one, two and three vessels involvement, respectively (figure 4). 39% of the patients have an incomplete revascularization and the remaining 61% have a complete revascularization. Clinical characteristics of hypertension, diabetes and dyslipidemia are important risk factors for the development of coronary artery disease. A total of 67% of the subjects have hypertension, 35% have diabetes and 52% were found to have dyslipidemia (figure 6). Results showed no

statistically significant difference in mean age among the different ejection fraction groups' (ANOVA, p=0.54). The differences in ejection fractions between those who were at least 60 years old and those who were younger than 60 years, between males and females and among the number of diseased vessels involved were likewise found to be not statistically significant. (p=.055, p=.06 and p=.90 respectively). The presence or absence of the aforementioned risk factors in the different EF groups' was not statistically significant (HPN p=.27, DM p=.71, lipid p=.98). (O.R. HPN=1.95, DM=.90, lipid=0.38). There was a total of 18 mortalities (21%). 78% of those who died were males in contrast to 22% deaths in females (figure7). However, this difference was not statistically significant (p=.48). 77% of the mortalities were reported in those older than 60 years (p=.09) (figure 8) Of the living 67 patients, 25% experienced a major cardiac event (myocardial infarction, repeat revascularization or CABG) and 67% persisted to have symptoms consisting of chest pains and or dyspnea (figure9). It is surprising to note that 47% of those who had a major cardiac event/s had an ejection fraction between 30-39% and 67% of those still symptomatic despite coronary angioplasty have ejection fractions more than 30% (40% EF=40-49, 27% EF=30-39). However, these were not statistically significant (p=.16 and p=.051).

Mortality was found to be correlated with ejection fraction, with most of the deaths (61%) reported in those with ejection fractions of less than 30 (ANOVA, p=.003; chi2 p=.03). Although 67% of those who died were implanted with a drug eluting stent and 27% received a bare metal stent, no association was found between death and the kind of stent's used. (p=.87). Deaths were also not correlated with the number of diseased vessels involved (p=.99). Although the risk factors HPN, DM and dyslipidemia had odd ratios that showed an increased probability or risk of death, the association was not significant. Hypertension was a co-morbid condition found in 77% of the deceased but this did not reach statistical significance (p=.42). Likewise, 33% of the mortalities had diabetes and dyslipidemia; both were not statistically significant (DM p=.93, dyslipidemia p=.13).

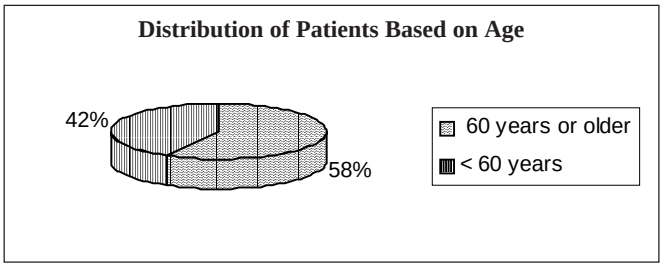

Figure 2: Distribution of Patients Based on Age

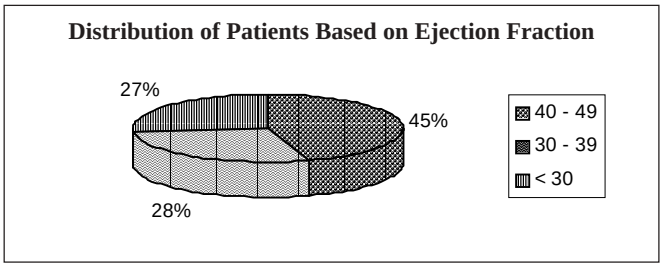

Figure 3: Distribution of Patients Based on Ejection Fraction

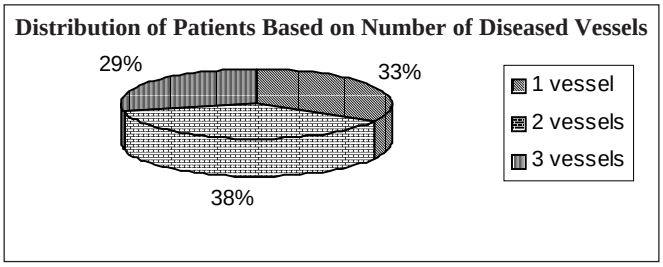

Figure4: Distribution of Patients Based on Number of Diseased Vessels

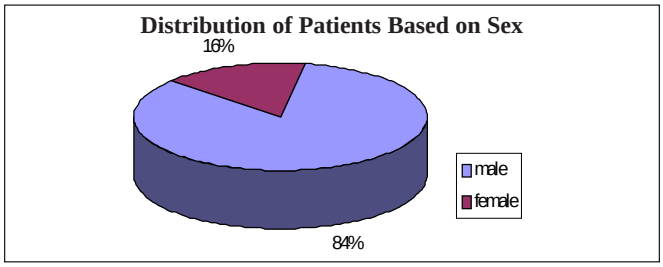

Figure 1 : Distribution of Patients Based on Sex

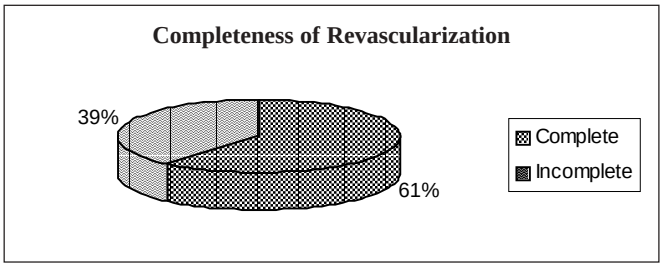

Figure 5:Completeness of Revascularization

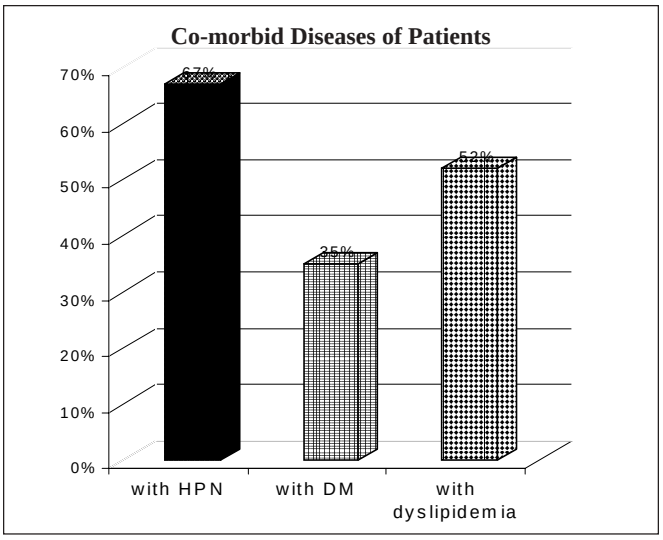

Figure 6 : Co-morbid Diseases of Patients

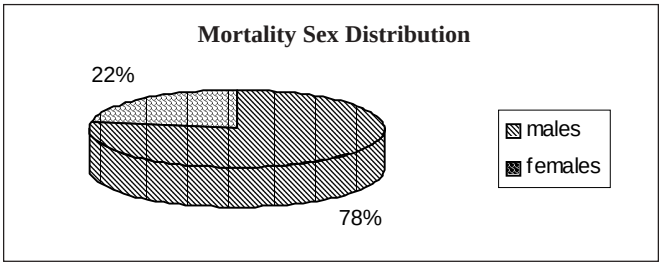

Figure 7 : Mortality Sex Distribution

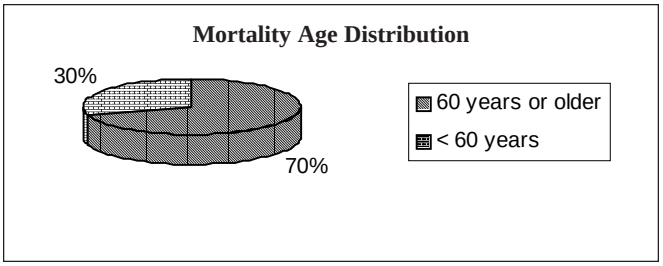

Figure 8: Mortality Age Distribution

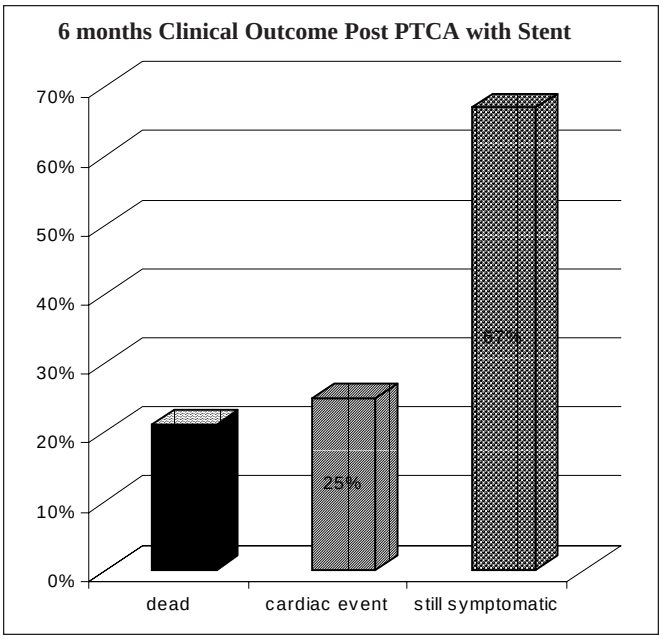

Figure 9 : 6 months Clinical Outcome Post PTCA with Stent

Discussion

When angioplasty was introduced in the late 1970's, it was estimated that only 5-10% of coronary artery disease patients would be acceptable candidates. Absolute contraindications included multivessel disease and severe LV dysfunction. Since then, the application of angioplasty has been extended. Among the constellation of different clinical and anatomic variables, LV function is the most important in predicting the prognosis of coronary artery disease patients.[13] In the CASS study, survival benefit with surgery was observed among patients with low ejection fraction of 35-40%. This was most apparent in patients with ejection fraction less than 26% who had 63% survival with surgery compared to 43% with medical treatment after 7 years follow up. The degree of LV dysfunction is related to the clinical and angiographic extent of coronary artery disease. It was observed that LV function would improve in proportion to the degree of revascularization.[14] This was coupled with the importance of complete revascularization after surgery may suggest a similar effect after coronary angioplasty in coronary artery disease patients with LV dysfunction. Limited published data are available regarding PTCA in patients with LV dysfunction.

In our study, we investigated the six months clinical outcomes of coronary angioplasty in coronary artery disease patients with an ejection fraction of 40-49%, 30-39% and less than 30%. In general, the mortality rate was 21.2%. 25% experienced a major cardiac event other than death and 67% persisted to have symptoms of breathlessness and chest pains.

The most striking finding of this study was the excess mortality in patients with significant LV dysfunction showing that LV dysfunction constitutes an independent marker of poor prognosis on patients with coronary artery disease. Patients with an ejection fraction of less than 30% have an increased risk of death. This is in accordance with several reports that have documented poorer outcomes for patients with LV dysfunction undergoing coronary angioplasty. One year mortality rate in earlier reports of coronary angioplasty in this patient population ranged from 13 to 21%. This association between death and ejection fraction was found to be statistically significant only in patients older than 60 years old (p=.045). Our study also demonstrated an increased incidence of other major cardiac event other than death in the coronary artery disease patients with ejection fraction less than 40%. 71% of those who had a major cardiac events' had an ejection fraction of less than 40%. However this was found to be not statistically significant. This non significance in the association of cardiac events and LV dysfunction is in contrast with the result of the study done by Keelan et al where in they showed that patients with ejection fraction < 40%, had an increase in MI/CABG compared with those with higher ejection fractions. The significance of LV dysfunction in patients who persist to be symptomatic post coronary angioplasty was not demonstrated in our study. The prevalence of symptomatic patients was more in the population with an ejection fraction of more than 40, but this association, was found to be not statistically significant. Since only alive patients were included in the analysis for the association between ejection fraction and cardiac events and the presence of symptoms post PTCA. This could account for the discrepancy in the results when compared with other studies that showed significance of LV dysfunction as a predictor of outcome.

Conclusion

This study demonstrated that the presence of significantly impaired LV function is associated with increased mortality in patients who underwent coronary angioplasty but not associated with the prevalence of other cardiac events like MI, repeat PCI or CABG and persistence of symptoms of dyspnea and angina post coronary angioplasty. Improvements in the safety and effectiveness of PCI have not eliminated this influence. Many questions remain in attempting to optimize the management of these groups of patients.

Limitations

Our study has obvious limitations. Firstly, it is a retrospective non-randomized analysis and is likely to have the bias inherent in this type of study. Secondly, like previous studies the number of patients was small rendering it difficult to make specific conclusions. Thirdly, only the presence of symptoms post PTCA and not improvement in the symptoms was included in the study, decreasing the clinical significance. Fourth, the immediate cause of death, cardiac or otherwise was not ascertained. Fifth, most patients have not had myocardial perfusion studies performed thus making comparative analysis of this data inconclusive. And lastly, the short follow up period of this study. Patients' however were not selected by any criteria apart from depressed LV function. Morever, they were a heterogeneous groups including those with unstable angina and myocardial infarction, those with or without prior myocardial infarction. Some of these baseline characteristics are recognized obstacles to outcomes analysis in percutaneous transluminal coronary revascularization. The investigator' recommend a more detailed and well documented study in this groups of patients to further assessed the outcomes of PTCA and to have a comparative study with other modalities of treatment for coronary artery disease such as CABG and medical therapy.

References

1. Alderman E.L, Fisher MD, Litwin M.S. et al. Results of coronary artery surgery in patients with poor left ventricular function (CASS), Circulation 1993, 68,785-795.
2. Coles JG, Del Campo C, Ahmed S.N. et al: Improved long term survival following myocardial revascularization in patients with severe left ventricular dysfunction. J Thorac. Cardiovasc Surgery, 1981,846-856.
3. Hung J, Kelly D.T, Baird D.K. et al: Aorta Coronary bypass grafting in patients with severe left ventricular dysfunction. J. Thorac. Cardiovasc Surg. 1980, 79, 718-723.
4. CABRI Trial Participants: first year results of CABRI (Coronary angioplasty versus bypass revascularization) Lancet 1995; 346: 1179-84.
5. The (Bypass Angioplasty Revascularization Investigation) BARI Investigators, Comparison of coronary bypass and with angioplasty in patients with multivessel disease. N. Engl J Med 1996; 335:217-25.
6. Stevens T, Kahn JK, Mc Callister BD et al. Safety and efficacy of percutaneous transluminal coronary angioplasty in patients with left ventricular dysfunction. Am J. Cardiol 1991;68:313-9.
7. Kohli R, DiSciascio G, Cowley MJ, et al. Coronary angioplasty in patients with severe left ventricular dysfunction. J Am Coll Cardiol 1990;16:807-11.
8. Lewin RF, Dorros G. et al: Percutaneous transluminal coronary angioplasty in patients with severe left ventricular dysfunction. Cardiol Clin 1989;7:813-25.
9. Maiello L, Colombo A, Gianrossi R, et al: Survival after percutaneous transluminal coronary angioplasty in patients with severe left ventricular dysfunction. Chest 1994; 105:733-40.
10. Holmes DR, Detre KM, Williams DO, et al: Long term outcome of patients with depressed left ventricular function undergoing percutaneous transluminal coronary angioplasty. The NHLBI PTCAA Registry. Circulation 1993;87:21-29.
11. Serota H, Deligonul U, Lee WH, et al. Predictors of cardiac survival after percutaneous transluminal coronary angioplasty in patients with severe left ventricular dysfunction. Am J Cardiol 1991:67:367-72.
12. Gruentzig AR, Senning A, Siegenthaler WE, et al (1979): Nonoperative dilatation of coronary artery stenosis: Percutaneous Transluminal Coronary Angioplasty. N Engl J Med 301:61.
13. Schocken, DD. Arieta MI, Leaverton PA, et al (1992): Prevalence of mortality, rate of congestive heart failure in USA. J Am Coll Cardiol 20:301.
14. Bell MR, Gersh BJ, Schaff HV, et al (1992): Effect of completeness of revascularization on long term outcome on patients with three vessel disease undergoing bypass surgery. A report from the Coronary Artery Surgery Study (CASS) registry. Circulation 86:446.

Original Article

Diagnostic Accuracy of Stress Echocardiography in the Detection of Coronary Artery Disease: Philippine Heart Center Experience 2001-2002

Maria Theresa E. Umali-De Torres MD, Brigida Claro MD, Raul D. Jara MD, Romeo J. Santos, MD

The objective of this study is to determine the accuracy of stress echocardiography using either pharmacologic or exercise stimuli to detect the presence of coronary artery disease. We reviewed the files of 88 patients who underwent stress echocardiography and coronary angiography. DSE was 89% sensitive, 38% specific and 93% accurate in identifying patients with CAD irrespective of the baseline wall motion. The ESE, on the other hand, was 72% sensitive, 77% specific and 84% accurate in detecting CAD. They were both higher than Dobutamine and exercise stress ECG. In conclusion, stress echocardiography is a highly accurate tool for evaluation and identifying patients with CAD.

Phil Heart Center J 2005;11:24-27

Keywords: Adrenocortical Carcinoma; histopathology

A major goal in the management of patients with chest pain is to identify patients with coronary artery disease (CAD) before occurrence of cardiac events such as myocardial infarction or sudden cardiac death. Exercise stress testing is the most commonly used test to prove that myocardial ischemia is present and to determine the extent of coronary artery disease.

Routine stress testing is often inadequate in patients whose pretest probability is low or in patients whose electrocardiogram is difficult to interpret due to conduction disturbances or ST-T abnormalities. To improve the accuracy of exercise testing, exercise electrocardiography has been linked with radionuclide angiographic imaging to assess regional and global left ventricular performance or with myocardial perfusion imaging to identify perfusion defects.

Stress echocardiography, more recently, is being promulgated as a new diagnostic tool for CAD. It is based on the premise that myocardial ischemia causes LV dyssynergy or wall motion abnormalities that can be detected with echocardiographic imaging. Its low cost, non-invasive nature and availability make echocardiography an attractive option as a cardiac imaging modality to combine with exercise or pharmacologic stimuli.

Perhaps its greatest advantage is its versatility. In addition to providing information on the extent of myocardial ischemia, the resting echocardiogram can screen for myocardial, valvular or pericardial disease allowing diagnosis of virtually all forms of cardiac disease many of which can masquerade as ischemic heart disease. Other important advantages include the fact that there is no radiation involve and a short time is required to perform and interpret the test.

Correspondence: **Maria Theresa E. Umali-De Torres MD,** Division of Adult Cardiology Philippine Heart Center, East Avenue, Quezon City, Philippines 1100

As with most technologies, controversies has arisen as to the advisability, practicality and accuracy of this test and specifically its utility as compared with that of the older and more established radionuclide examinations.

The accuracy for detection of angiographically assessed CAD has been reported to vary widely. The mean sensitivity is 81% (67% in single vessel disease and 88% in multivessel disease) and the mean specificity is 85% as reported in the 1997 American College of Cardiology/American Heart Association Guidelines for the clinical application of Echocardiography. This is not surprising if the many factors affecting test sensitivity are taken into account:

1. *Sample Population* – in their desire to validate costly technologies rapidly, investigators often resort to studying populations of convenience, normal volunteers (wellest of the well) and patients with clearly documented disease (sickest of the sick). As with all diagnostic studies, the predictive value of diagnostic procedures is dependent on the prevalence of disease in the population tested being most valuable in the intermediate pretest probability category.
2. *Perceived limited imaging success* – success is possible in most patients and recently, obtaining high quality images has been enhanced by the use of computer based offline analysis system converting the videotape images into high quality continuous loop image sequences.
3. *Experience and expertise of the technician-sonographers and physicians* - both should be well skilled for the test to be accurate. Although echocardiography is operator dependent with substantial interobserver variability, adequate training and use of conservative reading criteria have improve consistency, reproducibility and reliability.

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Exercise echocardiography is performed by obtaining images from multiple echocardiographic views in the resting state and immediately after exercise is completed. The accuracy of the test depends on obtaining images in the shortest amount of time possible usually within 90 seconds. Numerous studies have demonstrated high sensitivity and specificity in detecting coronary artery disease using exercise echocardiography.

Overall Accuracy of Exercise Echocardiography

STUDY	YEAR	PATIENTS	SENSITIVITY (%)	SPECIFICITY (%)
Wann	1979	28	87	100
Maurer	1981	48	86	69
Limacher	1983	73	91	88
Armstrong	1987	23	88	86
Sawada	1989	57	86	86
Mertes	1991	150	87	80
Marwick	1992	150	84	86
Quinones	1992	112	74	81
Hecht	1993	180	84	86
Ryan	1993	309	86	78
Marwick	1995	161	81	80
POOLED DATA		**1,391**	**85**	**84**

In patients unable to exercise, *pharmacologic stress echocardiography* is useful to establish the diagnosis of CAD. Dobutamine closely approaches the hemodynamic changes seen with exercise. It increases myocardial oxygen demand by increasing the heart rate, contractility and blood pressure. Images are obtained at rest and peak and at each change in dobutamine dosing. The accuracy of dobutamine stress echocardiography (DSE) in the detection of CAD has been shown to be similar to stress nuclear imaging. In addition, DSE has been proven useful in evaluating patient who presents for major vascular or non-cardiac surgery. It has also proven of value in the detection of myocardial viability.

Overall Accuracy of Dobutamine Stress Echocardiography

STUDY	YEAR	PATIENTS	SENSITIVITY (%)	SPECIFICITY (%)
Berthe	1986	30	85	88
Sawada	1991	103	89	85
McNeil	1992	80	70	88
Marcovitz	1992	141	96	66
Mazeika	1992	50	78	93
Segar	1992	85	95	82
Marwick	1993	217	72	83
POOLED DATA		706	84	84

Research Objectives:

To evaluate and determine the diagnostic accuracy of stress echocardiography, exercise or pharmacologic, in detecting the presence of coronary artery disease

Materials and Methods

Study Design: a retrospective cross – sectional study

Study Population:

The study population included patients admitted at the Philippine Heart Center for elective coronary angiogram who underwent either exercise or pharmacologic echocardiogram before or during admission from January 2001 to September 2002. The sample population was computed to be 87 with a= 0.5, an assumed sensitivity of 85% and total width of confidence interval of 15%.

Stress Electrocardiography:

The rest 12- lead ECG was performed with the use of conventional chest lead positioning. It was acquired before exercise, at the conclusion of each stage and after stress. Blood pressure and external signs was monitored during exercise testing and the conventional end points for exercise testing was applied.

Exercise Stress Echocardiogram

Baseline 2-D echocardiogram was obtained in patients before exercise using Accuson/Sequoia imaging system. Patients then perform either the Kattus or Neptet protocol on a motor driven treadmill. Immediately after exercise, 2-DE was repeated within 30-90 seconds and recorded continuously.

Dobutamine Infusion Protocol

Dobutamine was administered intravenously beginning at a dose of 5ug/kg/min. Thereafter, the dose was increased to 10, 20, 30 and 40 ug/kg/min every 3 minutes. Infusion was stopped when the dose reached 85% of the age predicted heart rate unless stress test was still negative. In these cases, infusion was continued with addition of 0.25 mg fractions of atropine up to a maximum dose of 2 mg.

Coronary Angiogram:

All patients underwent elective coronary arteriography using Judkins technique. A vessel was considered to have significant obstruction if its diameter was narrowed by 70% with respect with the prestenotic segment. This was done by visual analysis.

Statistical Analysis:

Sensitivity, specificity and diagnostic accuracy in detecting angiographically assessed CAD was calculated according to standard definitions. Kappa test was used to test the agreement of stress echocardiography and coronary angiogram results. The required level of significance is $p<0.05$.

Results

A total of 1,512 patients underwent stress echocardiography using either pharmacologic or exercise stimuli at the Philippine Heart Center Non-Invasive Cardiology Laboratory from January 2001 to September 2002. Only 102 patients subsequently underwent coronary angiogram within

that period. 14 patients were excluded because their files cannot be retrieved for review.

Table 1. Patients Characteristics

Total number of patients	1,512
Sex distribution (%)	
Male	69 (78%)
Female	19 (22%)
Age range	26-78 years old (mean 59.5 years)
Type of Stress Echo	
Dobutamine	57 (65%)
Exercise	31 (35%)

We reviewed the files of eighty-eight patients included in the study who underwent both stress echocardiography and coronary angiography. Sixty-nine (78%) were male and 19(22%) were female. The age of patients range from 26 to 78 years with mean of 59.5. Out of the 88 patients, 57 (65%) underwent dobutamine stress echocardiography (DSE) and 31 (35%) underwent exercise stress echocardiography (ESE). (*Table 1*)

Table 2. Results of Stress Echocardiography

	DSE	ESE	TOTAL
Positive for CAD	45	16	61
Negative for CAD	12	15	27
Total	9	5	14

Quantitative coronary angiography demonstrated significant coronary artery disease (>/= 70% stenosis with respect to the pre-stenotic segment) in 61 patients and no significant disease in 27 patients. (*Table 2*)

Table 3. Results of Dobutamine Stress Echocardiography

DSE	CORONARY ANGIOGRAPHY		
	Positive	Negative	Total
Positive	32	13	45
Negative	4	8	12
Total	36	21	57

Table 4. Results of Dobutamine Stress Electrocardiography

DSE	CORONARY ANGIOGRAPHY		
	Positive	Negative	Total
Positive	16	2	18
Negative	14	14	28
Total	30	16	46

The number of patients with and without coronary artery disease with a positive or negative stress echocardiography and electrocardiography are summarized in *Tables 3 to 7*. Fifty-four patients had significant stenosis by coronary angiograms that were identified by stress echocardiography. Thirty-two patients were identified by DSE (sensitivity of 89%) and thirteen patients by ESE (sensitivity of 72%). Both imaging techniques were more sensitive than Dobutamine stress ECG (sensitivity of 53%) and exercise stress ECG (sensitivity of 54%). In 34 patients with mild or no coronary artery disease, the specificity of DSE and ESE was 38% and 77% respectively.

Table 5. Result of Exercise Stress Echocardiography

ESE	CORONARY ANGIOGRAPHY		
	Positive	Negative	Total
Positive	13	3	16
Negative	5	10	15
Total	18	13	31

Table 5. Result of Exercise Stress Electrocardiography

ESE	CORONARY ANGIOGRAPHY		
	Positive	Negative	Total
Positive	7	2	9
Negative	6	10	16
Total	13	12	25

The overall accuracy of dobutamine stress echocardiography and electrocardiography and exercise stress echocardiography and electrocardiography were computed as 97%, 84%, 65% and 68% respectively. The predictive value of 45 positive dobutamine echocardiography results was 71% while that of exercise stress echo is 81% for the 16 positive exercise stress echo. The respective predictive values of a negative DSE and ESE results were 67% for both (*Table 7*).

Table 6. Result of Combined Dobutamine and Exercise Stress Echocardiography

DSE +ESE	CORONARY ANGIOGRAPHY		
	Positive	Negative	Total
Positive	32 + 13= 45	13 + 3 = 16	61
Negative	4 + 5 = 9	8 + 10 = 18	27
Total	54	34	88

Table 7. Overall accuracy of Stress Echocardiography for the detection of Coronary Artery Disease

	Sensitivity (%)	Specificity (%)	Pos PV (%)	Neg PV (%)	Accuracy (%)
Dobutamine SE	89	38	71	67	93
Exercise SE	72	77	81	67	84
Dobutamine ECG	53	87	59	50	65
Exercise ECG	54	83	78	62	68

Discussion

Several studies have examined the diagnostic accuracy of stress echocardiography using either exercise or pharmacologic stimuli. The overall sensitivity of dobutamine echocardiography for the detection of coronary artery disease in this study is 89% for both with baseline wall motion abnormalities and with none. This correlates with sensitivities of 70 to 96% from previous studies using dobutamine stress echocardiography. Philippine Heart Center is an experienced high volume laboratory with modern equipment thus in this setting adequate images can be obtained in > 85% of patients with suspected coronary artery disease. The ability to obtained diagnostic information has been tremendously enhanced by the use of computer based offline analysis.

False negative results in stress echocardiography may correlate with milder degrees or less extensive coronary artery disease (11% for DSE and 27% for ESE). This is also seen more commonly in women. It may also result from submaximal stress test with premature termination of the test because of side effects or less vigorous stress response as evidence by lower peak HR and HR increment.

In contrast, false positive stress echo findings in this study have no discernable correlate. A possible source will be the presence of left ventricular hypertrophy or left bundle branch block.

On the other hand, the overall specificity of dobutamine stress echocardiography is low at 38% in patients with no significant stenosis and with normal coronary arteries. This result is not consistent with other studies where specificity ranges from 66 to 93%. This might be because not all patients with normal stress echo are referred for cardiac catheterization.

The overall sensitivity of exercise stress echo is 72% and the overall specificity is 77%. Both are comparable with previous studies whose sensitivity ranges from 74 to 91% and specificity ranges from 69 to 100%.

Advantages and Limitaions

Stress echocardiography has several advantages compared with other imaging techniques. Its versatility allows substantially more baseline data evaluating all four cardiac chambers and all four cardiac valves. Dobutamine is well tolerated and not associated with significant side effects. In comparison with ESE, DSE may have higher sensitivity due to higher quality echocardiographic images obtained at each incremental level of stress. This is not feasible with ESE where chest wall and respiratory motion sometimes sometimes makes obtaining consistently high quality images difficult.

Limitation of the study includes interobserver variability and the absence of set reading criteria. A total of 14 echo readers interpreted the stress echocardiographic studies of the patients included in the study. In addition, significant coronary artery obstruction or narrowing of > 70% was diagnosed by visual analysis only.

Conclusion

In our cost conscious climate, assessment of new technology and determination of its optimal utilization are major challenges given today's rapid pace of new modality introduction. Stress echocardiography as a tool for detecting the presence of coronary artery disease is clinically useful and accurate. It is an attractive option further due to ease of access, low cost and non-invasive nature.

References

1. **Armstrong WF**, Exercise Echocardiography: Ready, Willing and Able. JACC 1998; 11: 1359-61.
2. **Picano E, Lattanzi F, Orlandini A, Marini C and L'Abbate A.** Stress Echocardiography and the Human factor: The Importance of Being Expert. JACC 1991; 17: 666-9.
3. **Noel Bairey C, Rozanski A, and Berman D.** Exercise Echocardiography: Ready or Not?. JACC 1998; 11: 1355-8.
4. **Marwick T, Nemec J, Pashkow F, Stewart W, and Salcedo E.** Accuracy and limitations of Exercise Echocardiography in Routine Clinical Setting. JACC 1992; 19: 74-81.
5. **Limancher MC, Quinones MA, Poliner LR, Nelson JG, Winter WL, and Waggoner AD.** Detection of Coronary Artery Disease with Exercise 2DE: Description of a clinically applicable method and comparison with Radionuclide Ventriculography. Circulation 1983; 67: 1211-8.
6. **Hecht HS, DeBond L, Shaw R, et al.** Digital Supine Bicycle Stress Echocardiography: A new technique for evealuating Coronary Artery Disease. JACC 1993; 21: 950-6.
7. **Ryan T, Segar DS, Sawada SG, et al.** Detection of Coronary Artery Disease with upright bicycle Exercise Echocardiography. J Am Soc Echo 1993; 6: 186-97
8. **Marwick T, Anderson T, Williams J, Haluska B, Melin J, Pashkow F, Thomas J.** Exercise Echocardiography is an accurate and cost efficient technique for detection of Coronary Artery Disease in Women. JACC 1995; 26: 335-41.
9. **Berthe C, Pierard LA, Hiernaux M, Trotteur G, Lempereur P, Carlier J , Kulbertus HE.** Predicting the Extent and Location of Coronary Artery Disease in AMI by Echocardiography during Dobutamine infusion. Am J Cardiol 1986; 58: 1167-1172.
10. **Sawada SG, Segar DS, Ryan T, et al.** Echocardiographic detection of CAD during Dobutamine infusion. Circulation 1991; 83: 1605-1614.
11. **McNeil AJ, Fioretti PM, El-Said ME, et al.** Enhanced Sensitivity for detection of Coronary Artery Disease by Addition of Atropine to Dobutamine Stress Echocardiography. Am J Cardiol 1992; 70: 41-46.
12. **Marcovitz PA and Armstrong WF.** Accuracy of Dobutamine Stress Echocardiography in Detecting Coronary Artery Disease. Am J Cardiol 1992; 69: 1269-1273.
13. **Marwick T, D'Hongt A, Baudhuin T, et al.** Optimal use of Dobutamine Stress for the Detection and Evaluation of Coronary Artery Disease: Combination with Echocardiography or Scintigraphy, or Both? JACC 1993; 22: 159-67.
14. **Poldermans D, Arnese M, Fioretti PM, et al.** Improved cardiac Risk Stratification in Major Vascular Surgery with Dobutamine-Atropine Stress Echocardiography. JACC 1995; 26:648-53.

Original Article

Ankle-brachial Index as Predictor of Mortality among Patients Who Underwent Arterial Studies in the Philippine Heart Center

Eleanor Gagalang MD, Ma. Theresa B. Abola MD, Florimond A. Garcia MD, Alex T. Junia MD.

INTRODUCTION: Manu observational and community studies have shown the prognostic value of low ankle-brachial pressure index.

OBJECTIVES: To determine whether a low ankle brachial index is an independent risk factor for all-cause and cardiovascular mortality, paying attention to the confounding effect of other prognostic factors.

Design: Cohort.

Patients/Participants: Consecutive patients referred to the peripheral vascular clinic of the PHC for arterial studies.

Main Outcome Measures: All cause mortality.

Phil Heart Center J 2005;11:28-30

Keywords: Catheterization, Peripheral; Peripheral Vascular Diseases; Carotid Artery Diseases

Peripheral arterial disease (PAD) of the lower extremities is one of the manifestations of systemic atherosclerosis. The risk of disease increases 2-3 fold for every 10 –year increase in age after the age of 40 years. PAD is highly associated with cardiovascular risk factors such as cigarette smoking, diabetes, hyperlipidemia, hypertension and increases in homocysteine levels. Patients with PAD, even in the absence of history of myocardial infarction or ischemic stroke, have approximately the same relative risk of death from cardiovascular causes, as do patients with a history of coronary or cerebrovascular diseases. In patients with PAD, the rate of death is equal from all causes is approximately equal in men and women and is elevated even in asymptomatic patient. With increasing severity of PAD as measured by means of the ankle-brachial index, there is concomitant increased risk of myocardial infarction, ischemic stroke and vascular death. Because of the presence of atherosclerotic risk factors, the systemic nature of atherosclerosis and the risk of ischemic events, patients with PAD should be considered candidates for secondary prevention strategies that include risk factor modification and antiplatelet drug therapy.

The limb manifestation of PAD principally fall into the categories of chronic stable claudication, critical leg ischemia and rarely acute limb ischemia. Patients with critical leg ischemia who have the lowest ankle brachial index values, have an annual mortality of 25 percent.

This study aims to determine the survival rates among patients who underwent arterial studies at the Peripheral Vascular Laboratory of the Philippine Heart Center (PHC).

Correspondence: Eleanor Gagalang MD. Division of Adult Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100

The survival rates among these patients will be plotted depending on the severity of the PAD.[3]

Research Objectives:

General Objective

To determine the survival rates of patients who underwent arterial studies in the Peripheral Vascular Laboratory of the PHC.

Specific Objectives

1. To determine the prevalence rate of PAD among patients who underwent arterial studies in the Peripheral laboratory of the Philippine Heart Center.
2. To determine the atherosclerotic risk factors present in these patients.
3. To determine the clinical manifestations of these patients.
4. To determine the presence of concomitant coronary and cerebrovascular disease among these patients.
5. To determine the survival rates of these patients stratified according to the severity of PAD.

Materials and Methods

a. Research Design

This is a cross-sectional observational study

b. Study Population

All patients 20 years of age or older who underwent arterial studies at the Peripheral Vascular Section of the PHC from January 2002 to December 2004 will be eligible for inclusion in the study. Only the first study will be included.

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c. Sample size

Based on the Mortality rate of 25%, alpha =0.05, total width of confidence interval sample size will be as follows:

Error	N
5%	1152
10%	288
15%	120
20%	72

d. Arterial Studies

1. Ankle-brachial index(ABI)

Systolic blood pressure is measured by using Doppler in each arm and the dorsalis pedis (DP) and posterior tibial (PT) arteries in each ankle. The higher of the two arm pressures is selected, as is the higher of the two pressures in each ankle. The right and the left ankle-brachial index values are determined by dividing the higher ankle pressure in each leg by the higher arm pressure.

2. Arterial Duplex Scan

Arterial duplex scan were performed by duly trained vascular sonographers at the Peripheral Vascular Section of the PHC using either Acuson 128 xp with linear transducer or Logiq.

e. Data Collection

A detailed review of the log of patients who underwent arterial studies from January 2002 to December 31, 2003 will be done by the researcher. A data sheet will be filled up. Its contents will include the demographic and clinical characteristics of the patients.

Contacts with attending physicians and telephone interviews will be undertaken to determine patients' status. Reported deaths will be confirmed from relevant hospital record forms and from conference with the attending physicians.

f. Data Analysis

Parametric data will be reported as mean +/- SD. Standard descriptive and comparative analysis will be undertaken. The death rate will be presented as the number of deaths per 100 patient-years based on the ratio of the number of deaths observed to the total number of patient years of exposure up to death. Survival Curves will be estimated with the use of Kaplan Meier method.

g. Limitations

Different vascular sonographers performed the studies on different patients. The variability between technicians and readers in the conduct of the study cannot be accounted for in this study. In addition data on the clinical and demographic characteristics of the patients will be based on the available data in the patients' charts, telephone interviews and conference with the attending physicians.

h. Definition of terms.

1. Cardiovascular disease
2. Cerebrovascular disease
3. Myocardial Infarction
4. Stroke
5. Coronary Artery Disease
6. Carotid Artery Disease
7. Peripheral Arterial Disease
8. Critical Limb Ischemia
9. Body Mass Index =(Weight in kilograms + Height in centims- 160/100)+ 1

Results

The baseline characteristics of patients included in the study are presented in Table 1.

Table 1.Baseline Characteristics of Patients Who Underwent Arterial Studies

Characteristics	Ankle –Brachial Index		
	0.9-1.4	0.5-0.89	<0.5
Age			
Men %			
BMI, kg/m2			
Smokers, %			
Diabetes Mellitus, %			
Cholesterol, mmol/L			
Triglycerides, mmol/L			
Hypertension, %			
History of CAD, %			
History of CVD, %			
Carotid Artery Disease, %			
Previous Revascularization,%			

The duration of follow up will be reported as mean +/- SD (range) months. The total number of deaths from all causes will be presented and will be stratified according to the ABI levels.

Table 2.Clinical Outcome of Patients Stratified According to ABI Levels

Characteristics	Ankle-Brachial Index Levels		
	0.9-1.4	0.5-0.89	<0.5
All cause mortality			
Death from CV causes			
Non-Fatal MI			
Stroke			
Lower Extremity Revascularizations			
Amputations			

Discussion

Over 20 % of subjects in this study had an ankle-brachial index of </=0.9 at baseline. This is translated as one in five subjects would be identified as at risk should a population of this age be screened for atherosclerosis. Other studies have shown different prevalences. Differences reflect variations in the age structure of the study populations and the techniques of measurement as well as the underlying occurrence of atherosclerotic disease.

A relation between low ABI and subsequent cardiovascular events might have been expected as lower limb disease is known to coexist with coronary and cerebrovascular disease. Previous studies in selected groups of subjects have all shown that a low index is also associated with reduced survival. This study shows that a low index is also associated with an increased risk of subsequent non-fatal cardiovascular events in the general population independent of age, sex and presence of myocardial infarction and diabetes mellitus at baseline.

Follow up of patients for cardiovascular events and mortality is ongoing.

References

1. Criqui MH,Fronek A. Barrett-Connor E, et al. The prevalence of peripheral arterial disease in a defined population. Circ 1985;71:510-15.
2. Hiatt WR,Hoag S, Hamman RF. Effects of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley diabetes study. Circ 1995;91:1472.
3. Newman AB,Siscovick DS, Manolio TA, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study(CHS) Collaborative Research Group. Circ 1993;88:837-45.
4. Criqui MH,Langer RD,Fronek A,et al. Mortality over a period of 10 years in patients with PAD. New England J Med 1992;326:381-6.
5. Mk Kenna M, Wolfson S,Kuller L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. Atherosclerosis 1991;87:119-28.

Original Article

Randomized Control Trial of Buccal Mucosa Administration vs Intramuscular Injection of Midazolam on Infants and Children with Congenital Heart DiseaseUndergoing Diagnostic Procedures

Ma. Rowena C. Sanchez MD, Concepcion Uy-Santos MD, Bernadette Azcueta MD

BACKGROUND: Objectives: To compare the effect of buccal mucosa vs intramuscular administration of Midazalom based on the level of anxiety, sedation, separation, and behavior/induction score; onset of sedation/ anxiolysis (time from administration to first change in sedation/ anxiolysis), length of effective sedation/anxiolysis and side effects/ adverse effect

MATERIALS AND METHODS: Infants and children less than 5 years old, seen at the Philippine Heart Center or congenital heart disease who needs sedation for a diagnostic work-up specifically 2D echo were included in the study. The group was divided into two based on the route of drug administration. Group 1: Midazolam administered via buccal mucosa (Midazolam IV/IM preparation 0.2 mg/kg per dose was administered in between the cheeks and the gums) and Group 2 : Midazolam administered via intramuscular injection (Midazolam IV/IM preparation 0.2 mg/kg per dose was administered intramuscularly).

Study Design: Randomized Control Trial

Computer generated randomized sampling was employed.

RESULTS: Forty-two patients were included in the study, with age ranging from 14.55 + 14.36 mos and 22.95 + 15. 73 mos in Group I and II respectively. After administration of Midazolam, there was no significant difference between the two groups with regards to the onset of sedation and length of effective sedation based on the sedation, separation and behavior scoring. However, based on anxiety score, there was a significant difference between the two groups, with group 1 noted to be less anxious and with more prolonged effect. Drowsiness was the only side effect noted on both groups.

CONCLUSION: IM/IV preparation of Midazolam administered via the buccal mucosa could offer a less painful, safe and equally effective alternative route in achieving sedation and anxiolysis in infants and children with congenital heart disease undergoing diagnostic procedures like 2D-echo.

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Keywords: Mouth Mucosa; Buccal Mucosa; Midazolam; Pediatrics;

Minor diagnostic procedure like 2D Echo may not cause significant pain but rather anxiety not only to the infants and children but also to the parents and physician as well. This procedures could provoke untoward reactions like hypoxic spell in infants and children with cyanotic congenital heart disease. Thus, sedative drugs play a very important role in these special type of patients not only to alleviate pain and anxiety but also to be able to accurately perform a very important diagnostic procedure like 2D-echo.

There are already several available sedative drugs in the market, but the problem lies on its availability, convenience, ease of administration and safety when given in pediatic population.

Benzodiazepines are commonly used for sedation, with midazolam as the most widely used and accepted agent. Midazolam is currently indicated for sedation, anxiolysis, and amnesia preoperatively or during procedures. It has a rapid onset and its relatively short half-life is associated with rapid recovery,[1] thus making it ideal for conscious sedation during diagnostics. It is water soluble that becomes lipid soluble at physiologic pH, allowing it to cross the blood brain barrier. Its route of administration is via IV, rectaI and IM, with IM having the slowest absorption.[2] All of this routes are invasive to the child.

Lately, several studies have been conducted regarding intranasal administration of midazolam[3]. However , it can cause nasal discomfort due to its quantity, pain and potential damage to the nasal mucosa.

It was also reported that some practitioners use midazolam injectable solution often mixed with fruit juices and given orally as premedicant in both adult and children[4]. Another study by Wilson was published regarding oral midazolam at 0.5 mg/kg as a safe and acceptable form of sedation for pediatric dental patients.

Correspondence: Ma.Rowena C. Sanchez, MD. Division of Pediatric Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100

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A study by Kutlu on, " Buccal Midazolam for Treatment of Prolonged Seizure in Children" showed midazolam at 0.3mg/kg per dose had 50% drug efficacy in patients with status epilepticus, and 100% response in patients with convulsion of less 30 min duration. Seizure episode was controlled within 3 minutes. Another study by Marshall on, "Effectiveness of Oral Midazolam as Dental Pre-Operative sedative and Hypnotic" showed an ideal dose of 0.6mg/kg, with sedation occurring with 15 minutes and lasting for about 30 to 40 minutes.

During review of literatures, no local study was published comparing buccal and intramuscular administration of midazolam.

Thus, this study was conducted to determine whether buccal mucosa administration of midazolam is equally effective compared with intramuscular administration of midazolam in achieving sedation and anxiolysis in infants and children undergoing diagnostic procedures. If true, this may open a a less painful but equally effective alternative route in achieving sedation and anxiolysis in infants and children with congenital heart disease undergoing a diagnostic procedure.

Objectives:

To compare the effect of buccal mucosa vs intramuscular administration of Midazalom based on the following:

1. Anxiety, Sedation, Separation and Behavior Score
2. Onset of sedation/ anxiolysis (time from administration to first change in sedation/ anxiolysis)
3. Length of effective sedation/anxiolysis
5. Side effects/Adverse effect

Table 1. Patient scores for Degree of Sedation and Level of Anxiety (Lammers,2002).

Anxiety Score

1. None, playful
2. Little, easily reassured
3. Moderate, not easily reassured
4. Excessive, crying, combative

Sedation Score

1. Asleep
2. Very drowsy, slowly responds to commands or stimulation
3. Drowsy, readily responds to commands or stimulation
4. Awake, calm, quiet
5. Alert and active

Separation Score

1. Easy separation
2. Whimpers but is easily reassured, not clinging to parents
3. Cries and cannot be easily reassured but not clinging to parents
4. Crying and clinging to parents

Behavior/Induction Score

1. Excellent (unafraid, cooperative, accepts procedure readily)
2. Good (Slight fear the procedure, easily reassured)
3. Fair (moderate fear of the procedure, easily reassured)
4. Poor (terrified, crying, combative)

Materials and Methods

A comparative randomized controlled study was conducted in 42 children less than five years old seen at the Philippine Heart Center for congenital heart disease as an out-patient, who needs sedation for a diagnostic work-up specifically 2D echo. They were randomly allocated to receive midazolam IV/IM preparation 0.2mg/kg per dose administered either via buccal mucosa in between the cheeks and the gums (Group I) or administered intramuscularly (Group II). The study protocol was approved by the Medical Ethics Committee of the hospital. A signed consent was obtained from the parents/guardian before any procedures were done.

Degree of anxiety, sedation, separation and induction was scored (Table 1). Scoring was obtained by a blinded observer, initially before the medication was given, and second during the time from first change in sedation, and third during the time when level of sedation was decreasing. The heart rate, respiratory rate, blood pressure and side effects were likewise recorded.

Analysis of data was performed using Mann-Whitney U-test and Wilcoxon Match Pairs. A p value of < 0.05 was considered significant.

Results

Forty-two patients were included in the study, with age ranging from 14.55 + 14.36 mos and 22.95 + 15. 73 mos in Group I and II respectively . Group I have a younger population, thus weigh less compared to group II (Table 2).

Baseline scoring for both groups were comparable except for the separation scoring. Group II were more difficult to separate than group 1 probably because they were older, and are more aware of the unfamiliar faces and places. Thus, subsequent statistical analysis were done based on the magnitude of change.

Table 2. Demographic Characteristics of Patients

Characteristics	Group 1 Mean	SD	Group II Mean	SD	*P* value
Age	14.55	14.37	22.95	15.73	0.078
Weight (Kg)	7.8	3.19	10.36	4.05	**0.028**
Sex	Number	%	Number	%	
Male	9	21	10	23	
Female	13	30	10	23	

P value < 0.05 considered to be significant.

Table 3. Comparison of Response to Treatment

Response	**Group I Mean, SD**	**Group II Mean,SD**	***P* value**
Anxiety Score			
1) Baseline	3.00 +/- 0.62	3.00 +/- 0.32	0.727
2) Onset of sedation	1.27 +/- 0.45	1.65 +/- 0.67	**0.050**
P value (# 1 vs #2)	**0.0001**	**0.0002**	
3) Time of decrease level of sedation	2.32 +/- 0.57	2.65 +/- 0.59	**0.025**
P value (#1 vs # 3)	**0.0026**	**0.0277**	
Sedation Score			
1) Baseline	4.86 +/- 0.35	4.95 +/- 0.22	
2) Onset of sedation	3.14 +/- 1.17	3.25 +/- 0.71	0.347
P value (# 1 vs #2)	**0.0001**	**0.0001**	0.903
3) Time of decrease level of sedation	3.77 +/- 0.87	3.65 +/- 0.93	0.494
P value (#1 vs # 3)	**0.0004**	**0.0015**	
Separation Score			
1) Baseline	2.82+/- 0.50	3.25+/- 0.44	**0.007**
2) Onset of sedation	1.41 +/- 0.59	1.60 +/- 0.60	0.159
P value (# 1 vs #2)	**0.0000**	**0.0001**	
3) Time of decrease level of sedation	0.31 +/- 0.57	0.45 +/- 0.69	0.540
P value (#1 vs # 3)	**0.0382**	**0.0218**	
Behavior Score			
1) Baseline	3.23+/- 0.53	3.10+/- 0.31	0.305
2) Onset of sedation	1.32 +/- 0.57	1.65 +/- 0.75	0.113
P value (# 1 vs #2)	**0.0001**	**0.0003**	
3) Time of decrease level of sedation	2.59 +/- 0.73	2.80 +/- 0.41	0.216
P value (#1 vs # 3)	**0.0051**	**0.0277**	

P value < 0.05 considered to be significant

After administration of midazolam, there was no significant difference between the two groups with regards to the onset of sedation and length of effective sedation based on the sedation, separation and behavior scoring. However, based on anxiety score, there was a significant difference between the two groups, with group 1 noted to be less anxious and with more prolonged effect (Table 3).

Vital signs recorded on both group remained stable throughout the study. Drowsiness was the only side effect noted on both groups.

Conclusion

IM/IV preparation of Midazolam administered via the buccal mucosa could offer a less painful, safe and equally effective alternative route in achieving sedation and anxiolysis in infants and children with congenital heart disease undergoing diagnostic procedures like 2D-echo.

Reference

1. Wilson, K.E, et al. A Randomized, Controlled, Crossover Trial of Midazolam and Nitrous Oxide for Paediatric Dental Sedation. Anaesth 2002;57:860-867.
2. Cuthriell, Alissa M. Pediatr Pharmacoth 2000:6(1). http://hsc.virginia.edu/cmc/pedpharm/ v6n1.htm.
3. Huffman MD, Grace. Reducing Children's Anxiety with Midazolam Nasal Spray. Am Fam Phys 2000.
4. Jie, Zhang, et.al. Oral Mucosal Absorption of Midazolam in Dogs is Strongly pH Dependent. J Pharma Scienc 2002;91(4):980-982 .
5. Kutlu, NO. Buccal Midazolam for Treatment of Prolonged Seizures in Children. Brain Dev 2003;25(4):275-8.
6. Marshall, WR. A Study of the Effectiveness of Oral Midazolam as a Dental Pre-Operative Sedative and Hypnotic. Spec Care Dentist 1999;19(6):259-66.
7. Lammers, CR, MD, et al. Oral Midazolam with an Antacid may Increase the Speed of Onset of Sedation in Children prior to General Anaesthesia. Pediatric Anaesth 2002;12:26-28.
8. Pharmakokinetic Summary if Midazolam. Fall, 1994. **http://www.icomm.ca/shsc/kinetics/midazola.html**

Original Article

Pulmonary Hypertension Secondary to Acyanotic Congenital Heart Disease, the Philippine Heart Center Experience

Herminia Rosario P. Herrera, MD

BACKGROUND: ***Pulmonary arterial hypertension (PAH) is a recognized complication of congenital heart defects with chronic left-to-right shunting, and the status of the pulmonary vascular bed often is the principal determinant of the clinical manifestations, course, and feasibility of surgical treatment as well as in most instances, it is reversible if detected early and the shunt is corrected. In some instances, however, pulmonary hypertension develops very rapidly at the early stages of the disease and precludes any surgical correction.***

This study was conducted to: (1) determine the prevalence of pulmonary arterial hypertension in congenital heart disease specifically with left-to-right shunts; (2) determine if surgery and other medical treatment would improve the pulmonary hypertension; and (3) describe the clinical profile of patients with pulmonary hypertension secondary to congenital heart disease.

. A total of 252 patients aged 2 months to 19 years were included in this study. Most of them (59.5%) were females. The cardiac lesions seen in this study included 22 ASD (8.7%), 99 VSD (39.3%), and 131 PDA (52%). Among these subjects, 30.2% had mild pulmonary hypertension, 51.6% with moderate pulmonary hypertension, and 18.3% with severe pulmonary hypertension as measured by 2D-echocardiography. There were only 37 patients (15%) who underwent cardiac catheterization. Pulmonary artery pressure (PAP) had a mean value of 48.91 + 13.83 mmHg by 2D-echocardiography and 78.84 + 17.88 mmHg by cardiac catheterization. Pulmonary artery pressure decreased after definitive cardiac surgery as seen when PAP was measured by 2D-echocardiography at different periods of time namely: (1) 2 wks to 1 month post-operative, (2) 6 months to 1 year post-operative, and (3) beyond 1 year after surgery. However, no normalization of the PAP was noted. Other medications given were vasodilators, anticoagulants and oxygen.. Of the 252 patients, 163 (65%) had pulmonary function test. Fifty-six percent (92 of 163) showed a restrictive ventilatory defect and 34% (55 of 163) had an obstructive ventilatory defect. Comparing the presence of PAH and lung function, there was no correlation.

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Pulmonary arterial hypertension (PAH) is a recognized complication of congenital heart defects characterized with chronic left-to-right shunting, and the status of the pulmonary vascular bed often is the principal determinant of the clinical manifestations, course, and feasibility of surgical treatment.[2] This, however, can also occur from a variety of pulmonary and non-cardiovascular conditions.

Pulmonary hypertension is defined when the pulmonary artery pressure increases more than 25mmHg at rest or more than 30mmHg with exercise.[2] It is termed hyperkinetic pulmonary hypertension when pulmonary arterial hypertension is secondary to congenital systemic to pulmonary communications with increased blood flow such as ventricular septal defect or patent ductus arteriosus.[9] The other type is pulmonary vascular obstruction or pulmonary venous hypertension caused by disorders of left heart filling such as mitral stenosis, pulmonary venous obstruction or left ventricular failure.[9] Narrowing of any segment of the pulmonary circulation - arteries, arterioles, capillaries, venules, and veins – if sufficient, will cause hypertension.[1]

The risk of acquiring PAH in congenital left-to-right shunts is multifactorial. A significant risk factor for the development of PAH appears to be the size of the shunt and subsequent blood flow. For example, with small- to moderate-size ventricular septal defects, only 3% of patients develop PAH. In contrast, large defects (greater than 1.5cm in diameter), 50% will be affected.[8] The importance of the size of the defect fits well with the hypothesis that the vascular injury results from a mechanical stretch injury to the endothelium and pulmonary vasculature from chronic high pulmonary blood flow. Among patients with atrial septal defects, the incidence of PAH differs. Vogel et al demonstrated that pulmonary arterial pressure and pulmonary vascular resistance was more commonly elevated in patients

Correspondence: **Herminia Rosario P. Herrera,** MD. Divison of Adult Pulmonary and Critical Care Medicine. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100

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with sinus venosus defects than in secundum defects (26% and 9% for sinus venosus defects, versus 16% and 4% in secundum defects for pulmonary arterial pressure and pulmonary vascular resistance, respectively).[8]

Congenital systemic to pulmonary shunts can cause pulmonary hypertension believed to be related to increased blood flow and pressure transmitted to the pulmonary circulation. In most instances, this entity is reversible if detected early and the shunt is corrected. However, pulmonary hypertension may develop very rapidly even at the early stages of the disease and precludes any surgical correction. Some patients present with a remote history of a patent ductus arteriosus that was ligated, or an atrial septal defect that was relatively small with coexisting pulmonary vascular disease. Whether the shunt and the pulmonary hypertension are related or coincidental has been a matter of debate.[8]

The role of cardiac catheterization for diagnosis and treatment of pulmonary hypertension is very important because it can accurately measure pulmonary artery pressure (PAP). The etiology of PAH is diagnosed as left-sided heart failure, if pulmonary capillary wedge pressure (Ppcw) is increased by more than 13 mmHg and pulmonary vascular resistance is increased more than 3 Wood units.[2]

Surgical repair for most children with hyperkinetic PAH is done between 3 to 12 months of age to prevent the development of irreversible pulmonary vascular disease. In contrast, pulmonary hypertension resulting from pulmonary venous hypertension is reversible whenever the left-sided obstructive lesion is corrected.[4] It is also important to determine whether the elevated pulmonary vascular resistance responds favorably to pharmacologic vasodilation.

It is therefore the purpose of this study to give an overview of pulmonary hypertension seen among children with acyanotic congenital heart defect.

Research Objectives:

1) To determine the prevalence of pulmonary arterial hypertension in acyanotic congenital heart disease with left-to-right shunt.
2) To describe the clinical profile of patients with pulmonary hypertension secondary to acyanotic congenital heart disease with left-to-right shunt.
3) To determine if surgery can reverse or decrease the degree of pulmonary hypertension.

Research Hypothesis:

The most common cause of pulmonary vascular lesions is congenital heart disease in the presence of a left-to-right or systemic-to-pulmonary shunt.

Materials and Methods

A. Study Design

This is a cross-sectional retrospective study.

B. Study Sample

Inclusion Criteria:

1. Patients aged <19 y.o. with ventricular septal defect (VSD), atrial septal defect (ASD), and patent ductus arteriosus (PDA).
2. Patients with pulmonary artery pressure of >25mmHg as measured per 2D-echocardiography pre-operatively.
3. Patients who underwent corrective surgery.

Exclusion Criteria:

1. Patients with acyanotic congenital heart disease admitted for medical management only.
2. Patients with pulmonary hypertension secondary to complex heart disease.
3. Patients with Eisenmenger syndrome.

Data Collection

A retrospective review of medical records of 252 pediatric patients (0-19 years old) seen at the in-patient department of the Philippine Heart Center (PHC) from January 2001 to March 2003 was done. Subjects were diagnosed to have atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA) with pulmonary arterial hypertension and subjected to surgery. Diagnosis of the cardiac lesion (ASD, VSD, PDA) was based on history, physical examination and 2D-echocardiography (2DE). The presence of pulmonary arterial hypertension (PAH) was identified and classified through 2D-echocardiography and cardiac catheterization. With 2D-echocardiogram, pulmonary hypertension was considered **mild** if the mean pulmonary arterial pressure (PAP) was between 25-40mmhg by pulmonary acceleration time (PAT); **moderate** if between 40-60 mmhg by PAT; and **severe** if between 60-80 mmhg by PAT. Cardiac catheterization graded pulmonary hypertension as **mild** if the systolic PAP >30-60 or up to 50% of systemic pressure; **moderate** if systolic PAP is 60-80 or 50-75% of systemic pressure; and **severe** if systolic pressure >80 or >75% of systemic pressure. Other data collected and included in the analysis were the chest x-ray findings, arterial blood gas (ABG), pulmonary function tests (PFT), medications, and duration and amount of oxygen given. Post-operative follow-up data (especially PAP by 2D-echocardiography) were also included in the analysis.

Statistical Analysis

A sample size of 296 is needed to assure a 10% width of confidence interval at alpha=0.05. To check if there's any improvement in the pulmonary artery pressure after surgery at different periods of time, a Wilcoxon Matched-Pairs Signed-Ranks Test and student's "t" paired test were done. Spearman Rank Correlation was used to analyze the correlation

of pulmonary function test and the severity of pulmonary hypertension. A p-value of <0.05 was considered statistically significant.

Results

Within the study period , from January 2001 to March 2003, a total of 1360 patients with acyanotic congenital heart disease with left-to-right shunt were admitted. Only 301 patients (22%) had pulmonary arterial hypertension. Excluded form the analysis were 23 patients admitted only for medical management, 7 for cardiac catheterization, 6 with Eisenmenger syndrome and 13 patients whose surgery were deferred due to other medical problems while in the ward. Therefore, only 252 patients were enrolled in this study. Their age ranged from 2 months to 19 years (mean=5.25 + 4.38 y.o.) and most of them were females (n=150 or 59.5%). (Table 1).

Table 1. Demographic characteristics of 252 patients with Acyanotic CHD with PAH seen from January 2001 to March 2003 at PHC

	Mean	SD
Age (years)	5.25	4.38
Sex	**No.**	**%**
Male	102	40.5
Female	150	59.5
TOTAL	252	100

There were 22 ASD (8.7%), 99 VSD (39.3%), and 131 PDA (52%). Among these patients, 76 (30.2%) had mild pulmonary arterial hypertension (PAH), 130 (51.6%) with moderate PAH, and 46 (18.3%) with severe PAH as identified by 2D-echocardiography by pulmonary acceleration time (PAT). However, only 37 patients (15%) underwent cardiac catheterization pre-operatively. Only 1 (2.7%) was identified as mild PAH, 5 (13.5%) as moderate PAH, and 31 (83.9%) as severe PAH. (Table 2). Pulmonary arterial pressure (PAP) had a mean value of 48.91 + 13.83 mmHg by 2D-echocardiography and 78.84 + 17.88 mmHg by cardiac catheterization.

Table 3 shows the assessment of pulmonary hypertension at different periods after surgery as measured by 2D-echocardiography. Only 108 patients had data on PAP, it showed improvement over time, however, PAH by 2DE was only statistically significant at evaluation dates 2 wks to 1 month (p-value=0.000), 6 months to 1 year (p-value=0.008), and >1 yr (p-value=0.001). Subgroup analysis according to classification of pulmonary hypertension using the same evaluation dates showed similar results as to the improvement of PAP as shown in table 4.

Table 2. Clinical Characteristics of 252 patients with Acyanotic CHD with PAH admitted to PHC from January 2001 to March 2003

Characteristics	No.	%
Cardiac lesion		
ASD	22	8.7%
VSD	99	39.3%
PDA	131	52%
Classification of PAP (mmhg) by 2DE by PAT (n=252)		
Mild	76	30.2%
Moderate	130	51.6%
Severe	46	18.3%
Classification of PAP by cardiac catheterization pre-surgery (n=37)		
Mild	1	2.7%
Moderate	5	13.5%
Severe	31	83.8%
	Mean	**SD**
# of hospital days	11.24	7.54
# of intubated days	25.36	36.14
Pre-operative PAP by 2DE (n=252)	48.91	13.83
Pre-operative PAP by cardiac cath (n=37)	78.84	17.88

Table 3. Assessment of Pulmonary Hypertension After Surgery among 108 Patients with follow-up 2DE evaluated at Different Time Periods

Time of Evaluation After Surgery	Mean	SD	p-value
< 24H (n=24)			
Pre-op PAP	60.62	16.69	
Post-op PAP	59.54	11.29	0.714 (NS)
24H - 2 wks (n=76)			
Pre-op PAP	52.21	12.62	
Post-op PAP	50.08	11.05	0.062 (NS)
2 wks – 1 month (n=18)			
Pre-op PAP	65.11	14.62	
Post-op PAP	54.11	10.24	0.000 ***
2 – 4 mos (n=8)			
Pre-op PAP	54.86	11.14	
Post-op PAP	47.00	10.10	0.230 (NS)
4 – 6 mos (n=6)			
Pre-op PAP	62.83	15.96	
Post-op PAP	49.67	8.23	0.086 (NS)
6 mos – 1 yr (n=10)			
Pre-op PAP	65.80	18.47	
Post-op PAP	50.70	11.93	0.008 ***
> 1 yr (n=9)			
Pre-op PAP	62.56	13.57	
Post-op PAP	39.89	3.10	0.001 ***
All cases (n=108)			
Pre-op PAP	54.49	13.93	
Post-op PAP	48.35	10.07	0.000 ***

Table 4. Number of Patients (n=108) with pre-op and post-op classification of PAH based on 2D-echocardiography findings

	Pre-surgery		Post-surgery		p-value
< 24H	No.	%	No.	%	
Mild	4	16.7	2	8.3	
Moderate	4	16.7	12	50.0	
Severe	16	66.7	10	41.7	
TOTAL	24	100%	24	100%	0.3942 (NS)
>24H – 2 wks					
Mild	12	15.8	12	15.8	
Moderate	46	60.5	56	73.7	
Severe	18	23.7	8	10.5	
TOTAL	76	100%	76	100%	0.0926 (NS)
2 wks – 1 month					
Mild	1	5.6	2	11.1	
Moderate	8	44.4	13	72.2	
Severe	9	50.0	3	16.7	
TOTAL	18	100%	18	100%	0.0180 ***
2 to 4 months					
Mild	1	12.5	3	37.5	
Moderate	4	50.0	5	62.5	
Severe	3	37.5	0	0	
TOTAL	8	100%	8	100%	0.1159 (NS)
4 to 6 months					
Mild	0	0	1	16.7	
Moderate	2	33.3	5	83.3	
Severe	4	66.7	0	0	
TOTAL	6	100%	6	100%	0.0431 ***
6 mos – 1 yr					
Mild	1	10.0	1	10	
Moderate	1	10.0	8	80	
Severe	8	80.0	1	10	
TOTAL	10	100%	10	100%	0.0180 ***
> 1 yr					
Mild	0	0	6	66.7	
Moderate	4	44.4	3	33.3	
Severe	5	55.6	0	0	
TOTAL	9	100%	9	100%	0.0117 ***

Pulmonary function test was done in 163 patients (65%). Restrictive ventilatory defect was found in 56% (92 of 163), obstructive ventilatory defect in 34% (55 of 163) and the remaining 10% (16 of 163) had normal PFT. (Table 5) There was no correlation between the severity of pulmonary hypertension and their lung function abnormalities. (Table 6)

The pre-operative radiographic findings of these patients showed either a dilated or prominent main pulmonary artery with increased pulmonary vascular markings. Some, however, had mild pulmonary congestion. Of the 252 subjects, only 234 (93%) had arterial blood gases pre-operatively which showed a pO2 of 93 – 135 mmHg and an O2 saturation of 92 - 100% at room air.

Table 5. Distribution of 163 Patients with Acyanotic CHD with PAH According to PFT and Pulmonary Hypertension

PFT(n=163)	Mild PAH (n=47)	Moderate PAH(n=73)	Severe PAH(n=43)
Normal (n=16)	11	5	0
Restrictive (n=92)			
Mild	3	8	10
Moderate	9	17	6
Severe	5	22	12
Obstructive (n=55)			
Mild	6	9	4
Moderate	11	8	8
Severe	2	4	3

Table 6. Correlation of Patients with PAH with Abnormal PFT

	r_s	P value
Restrictive PFT v.s. PAH	0.030	0.777 (NS)
Obstructive PFT v.s. PAH	0.068	0.624 (NS)

Discussion

Pulmonary arterial hypertension (PAH) is a recognized complication of congenital heart defects characterized by chronic left-to-right shunting. When this occurs, it is called secondary pulmonary hypertension. Acyanotic congenital heart disease with increased pulmonary blood flow commonly leads to the development of pulmonary hypertension and increased vascular reactivity. Included in this study were patients with atrial septal defects (ASD), ventricular septal defects (VSD), and patent ductus arteriosus (PDA). During the study period, 301 or 22% of patients with acyanotic congenital heart disease had pulmonary arterial hypertension. However, only 84% or 252 patients were enrolled and evaluated. In pulmonary hypertension, chest radiographs may disclose evidence of parenchymal lung disease or demonstrate ventricular and pulmonary vascular prominence, degree of cardiomegaly and the increase in pulmonary vascular markings directly related to the magnitude of the left-to-right shunt. The subjects in this study showed either a dilated or prominent main pulmonary artery with increased pulmonary vascular markings.

According to Pornin M et al, pulmonary function test (PFT) may also be done as part of the diagnostic work-up for pre-operative assessment which may show a restrictive lung disease due to reduced lung compliance and reduced lung

volumes. Less frequently, obstructive changes may occur as a result of small airway compression by distended thick pulmonary arteries and encroachment by increased perivascular adventitial tissue. In our study, only 65% of the study population underwent pulmonary function test and it showed that 56% had restrictive ventilatory defect, 55% with obstructive ventilatory defect and the remaining 10% with normal results.

A 2-dimensional and doppler echocardiography can be used to identify the cardiac lesion, estimate the pulmonary artery pressure (PAP) and the magnitude of the shunt. Using the modified Bernoulli equation, the pulmonary hypertension in these subjects was classified into mild, moderate and severe by pulmonary acceleration time (PAT). Most of the subjects had moderate pulmonary hypertension (51.6%) pre-operatively.

The most definitive method to assess the risk of rapidly progressive pulmonary vascular disease is cardiac catheterization. Like 2D-Echocardiography, it assesses the intracardiac shunt and determines the PAP and pulmonary vascular resistance (PVR). This is important since if a patient with elevated pulmonary vascular resistance is being considered for surgery, there is an increased risk of post-operative pulmonary hypertensive crises. In our study, only 37 of 252 subjects (15%) underwent cardiac catheterization and most (84%) have severe pulmonary hypertension. The data on PVR was however not analyzed due to small sample size.

Pulmonary hypertension may be reversible if it is secondary to congenital heart disease resulting from increased blood flow to the lungs. This is still reversible if the shunt is corrected early. However, the vascular obstruction becomes irreversible in severe, long standing cases like Eisenmenger syndrome when damage to the pulmonary vasculature is beyond repair. Approximately one-third of patients with uncorrected congenital heart disease will die from their pulmonary vascular disease. All the 252 subjects in this study underwent surgical correction of their respective cardiac lesions. This included ASD closure for ASD, VSD patch closure for VSD and either PDA ligation and/or clipping or PDA transection for those with PDA. The mean age at which surgery was done in our study is 5.25 + 4.38 years. In a study by Steele et al, the mean age at which surgery was done for ASD showing reversal of PAP to normal was at 1.34 years. This could probably explain why the PAP in our study did not normalize since surgery was done already late in our subjects. The pulmonary artery pressure measured by 2D-echocardiography at different periods of time after surgery showed significant improvement at 2 weeks to 1 month (p-value=0.000), 6 months to 1 year (p-value=0.008) and those measured beyond 1 year (p-value=0.001) post-operatively. Although the PAP did not really reverse to normal, there was a decreasing trend noted from pre-operative value. To check on the reversibility of pulmonary hypertension post-operatively and the optimal time when this is observed, it is to recommended that these patients be followed up until their PAP normalizes.

Conclusion

In conclusion, we have shown that pulmonary hypertension is a recognized complication in congenital heart disease with left-to-right shunt such as atrial septal defect, ventricular septal defect, and patent ductus arteriosus. The pulmonary hypertension improves over time, not totally reversing to normal after cardiac surgery.

References

1. Moss and Adam's Heart Diseases in Infants, Children & Adolescents, 16th ed. Lippincot Williams & Wilkins 2001.
2. David G. Nichols, MD et al. Critical Heart Disease in Infants and Children. Mosby-Year Book, Inc. 1995.
3. Chernick and Boat. Kendig's Disorders of the Respiratory Tract in Children. W.B. Saunders Company 1998.
4. Pornin M, Morin D, Guize L. Diagnosis, course and prognosis of pulmonary arterial hypertension. Ann Cardiol Angeil (paris) 1994 Oct; 43 (8): 479-85.
5. Caceres Espejo J, Santos de Soto J, Gavilan Camacho JL, Cabello Lauro R, et al. Doppler echocardiographic evaluation of pulmonary hypertension in children. Rev Esp Cardiology 1995 Feb; 48 (2): 122-7
6. Salzer-Muhar U, Schlemmer M, Proll E, Salzer HR, Winner M. Doppler echocardiographic evaluation of pressure in the pulmonary artery in children with congenital heat defects.
7. Alt B, Shikes RH. Pulmonary hypertension in congenital heart diseases: irreversible vascular changes in young infants. Pediatr Pathol 1983 Oct-Dec; 1 (4): 423-34.
8. John Granton, MD, Marlene Rabinovitch, MD. Cardiology Clinics. W.B. Saunders Company, Aug 2002. Volume 20, No. 3
9. Steele P, Fuster V, Cohen M, et al. Isolated atrial septal defect with pulmonary vascular obstructive disease-long term follow-up and prediction of outcome after surgical correction. Circulation 1987;76:1037-42

Original Article

Scintigraphic Parameters for Determination of Left Ventricular Cavity Dilatation on SPECT Myocardial Perfusion Scintigraphy

Raymund Augustus O. Conlu MD, Jerry M. Obaldo MD.

BACKGROUND: ***The ability to identify patients with severe coronary artery disease by analysis of perfusion defects alone is limited. The presence of both a perfusion abnormality and an enlarged scintigraphic LV cavity size was found to be more predictive of late cardiac events than either scintigraphic variable alone. LV cavity dilatation is a secondary indicator of LV dysfunction and indicates significant CAD.***

OBJECTIVE: ***This study aims to establish and validate different scintigraphic parameters for LV cavity dilatation as well as cut-off values of these parameters that could be most predictive of LV cavity dilatation using the echocardiogram as gold standard.***

MATERIALS AND METHODS: ***Patients referred for either stress or dipyridamole thallium scintigraphy at the Philippine Heart Center, 30 to 80 years of age, diagnosed with CAD, from August 2003 to August 2004. Different scintigraphic parameters used included measurement of LV cavity size in 3 orthogonal planes (LV cavity area using the short axis at the mid-LV level and distance between inner borders of the myocardium at the mid-LV level using both vertical and horizontal axes) and inferential or indirect signs of LV cavity enlargement such as absolute number of short axis slices on the scintigram, increased lung-to-heart thallium ratio and presence of significant right ventricular uptake (hypertrophy). Comparison of mean values of the different parameters were done using independent t-test. Different cut-off points were established and validation of these different parameters and cut-off values were computed.***

RESULTS: ***A total of 100 patients, who had CAD or were CAD suspects, were included in the study. The best cut-off value for LV cavity dilatation (LV cavity area) on short axis was > 5 sq. cm with 100% sensitivity and 94% specificity. Vertical and horizontal axes measurements best correlated with 2-D echo at cut-off value of > 2.5 cm for both axes with 100% sensitivity, 94% specificity and 95% sensitivity, 96% specificity, respectively. A cut-off point of > 15 for the absolute number of short axis slices on the scintigram was noted with 85% sensitivity and 86% specificity. For abnormal lung-to-heart thallium ratio, sensitivity and specificity were 69% and 100% respectively. Prominent right ventricular uptake, suggestive of hypertrophy, was 52% sensitive and 100% specific for LV cavity enlargement.***

CONCLUSION: ***This simple method for measurement of LV cavity size obtained from SPECT and the different inferential scintigraphic signs for LV cavity dilatation may provide important adjunct to SPECT myocardial perfusion study in identification of patients with extensive CAD and could further risk-stratify patients as to likelihood for future cardiac events.***

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Keywords: Tomography, Emission-Computed, Single-Photon; Myocardial Reperfusion

After initial determination of the presence or absence of myocardial perfusion defects on the scintigram, a complete study includes assessment of size, location, severity and vascular distribution of the defects. The ability to identify patients with severe coronary artery disease (CAD) by analysis of perfusion defects alone is limited [1]. The presence of thallium perfusion defects and scintigraphic LV cavity dilatation were found to be more predictive of late cardiac events than either scintigraphic variable alone. Left ventricular (LV) dilatation, more significantly transient ischemic dilatation, is a secondary indicator of left ventricular dysfunction and indicates significant CAD. Stress-induced or Dipyridamole-induced LV cavity dilatation is detected by comparing post-stress images with the delayed 4-hourredistribution/rest images. Weiss A T et al concluded that an abnormal transient ischemic LV dilatation ratio had a sensitivity of 60% and a specificity of 95% for identifying patients with multivessel critical stenosis and thus, extensive CAD [2]. In another study by Chouraqui P. et al, an abnormal transient ischemic dilation ratio of equal to or greater than 1.12 was a specific marker of multivessel disease and critical CAD [3]. Georg Emlein et al demonstrated that a measurement of LV cavity size can provide risk stratification for late cardiac events on dipyridamole-thallium scintigraphy [4]. Fixed LV cavity dilatation on the other hand implies increased cavity dimensions to equal degree on both sets of images and indicates pre-existing cavity enlargement. In either case, LV cavity

Correspondence: Raymund Augustus O. Conlu MD. Division of Cardiovascular Surgery. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100

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dilatation has negative prognostic implications. Heupler et al rationalized that increased LV cavity size, not wall thickness (hypertrophy), potentiates ischemia. They postulated that oxygen demand increases as LV cavity size increases at a given pressure, thus ischemia is potentiated in diseased coronary beds [6]. White et al likewise demonstrated end-systolic volume to be the strongest correlate of mortality after infarction. and that the deleterious effects of ventricular dilatation were independent of the extent of CAD. LV cavity size therefore, is an important predictor of post-infarction mortality[7].

In practice however, assessment of LV cavity size is highly subjective. Prior studies only demonstrated the prognostic utility of scintigraphic LV cavity size assessment but did not establish absolute measure of true LV cavity size. This study was undertaken to establish specific parameters for LV cavity dilatation as well as cut-off values of these different parameters that could be predictive of LV cavity dilatation. Validation of these parameters using the echocardiogram as gold standard was done. Furthermore, this study aimed to predict the prognostic utility of this tool in clinical situations.

Research Objective

1. To establish specific scintigraphic criteria for LV cavity dilatation.
2. To determine the sensitivity and specificity of each scintigraphic parameter using the echocardiogram as gold standard.

Materials and Methods

Study design: Cross-sectional prospective study

Study sample: Patients referred for stress-thallium or dipyridamole-thallium scintigraphy at the Philippine Heart Center, male or female, 30 to 80 years old.

Inclusion Criteria:

Patients with CAD or CAD suspects with echocardiogram and SPECT myocardial perfusion scan obtained within 30-day interval

Exclusion Criteria:

1. Presence of congenital heart disease and other non-coronary causes of LV enlargement such as rheumatic heart disease and non-ischemic cardiomyopathy
2. Presence of pulmonary hypertension and chronic lung changes like COPD
3. Myocardial revascularization before SPECT thallium study
4. Poor thallium images as well as non-diagnostic thallium SPECT data

Study setting and time period: Patients referred for SPECT thallium at the Nuclear Medicine Department of Philippine Heart Center from August 2003 to August 2004.

Scintigraphic parameters used:

1. Measurement of LV cavity area (π x [diameter/2]^2). A short-axis slice at the mid-LV level was used. The diameter of the LV cavity was measured as the distance between the inner borders of the myocardium (assuming that the area iscircular in shape) using pixel-calibrated count profile software on the Pegasys computer.
2. Distance (cm) between inner borders of the myocardium at mid- LV level using the vertical axis on the computer screen using the same software as above.
3. Distance (cm) between inner borders of the myocardium at mid-LV level in the horizontal axis on the computer screen using the same software.
4. Absolute number of short-axis slices on the scintigram.
5. Presence of significant right ventricular (RV) uptake or hypertrophy (RVH).
6. Presence of increased lung-to-heart thallium activity ratio (L-H ratio)

Echocardiographic Criterion

Left ventricular dimensions were measured by the M-mode echocardiography using the criteria established by the committee on M-mode Standardization of the American Society of Echocardiography.

Description of data collection and statistical analysis:

SPECT acquisition. SPECT myocardial perfusion scintigraphy was performed using thallium-201 either after treadmill or dipyridamole infusion (as requested by the attending physician) and after 4-hour redistribution. Delayed 24-hour redistribution imaging was done when necessary. Images were acquired using a low energy all-purpose (LEAP) collimator with the heart at the center of the field of view and using a circular orbit starting from the 45 degree right anterior oblique projection and ending at the 45 degree left posterior oblique projection. Each of the 32 projections was acquired employing a 64 x 64 matrix at 40 seconds per image. Data were processed in the ADAC Pegasys computer. From the transaxial slices, the long axis of the LV was identified and the images generated in 3 orthogonal planes (short-axis from apex to base, vertical axis, horizontal axis).

Measurement of LV cavity size. A short axis slice at the mid-LV level was determined. The diameter of the LV cavity was measured as the distance between the inner borders of the myocardium (assuming that the area is circular in shape) using the pixel-calibrated count profile software on the Pegasys computer screen. The LV cavity area was then computed using the formula (p x [diameter/2]^2). For both vertical and horizontal axes, the distance (cm) between the inner borders of the myocardium at the mid-LV level were measured on the computer screen using the same software. Other scintigraphic parameters used whether directly related to or are inferential

signs of LV dilatation were likewise assessed. The absolute number of short axis slices on the scintigram was determined after re-orientation of the transverse and sagittal slices during computer processing of data. The presence of significant uptake in the right ventricle was likewise noted that indicates hypertrophy secondary to increased left sided pressure. Lung-to-heart thallium activity ratio was assessed by placing regions of interest in the hottest area in the anterior free wall of myocardium and left upper lung area. Results were tallied and correlated with echocardiographic LV cavity measurements.

Statistical analysis. From the data gathered, sensitivity and specificity, positive and negative predictive values as well as p-value of each parameter were obtained. A p-value of less than 0.05 was considered significant. Comparison of mean values of different parameters were carried out using independent t-test (table 2). Different cut-off points were established for each parameter. The sensitivity, specificity, positive and negative predictive values of these different cut-off values were computed (table 1) and receiver operating characteristic (ROC) curves were constructed to determine the best cut-off points (figures 1 to 4). Data were presented as mean, standard deviation, frequency and percent distribution.

Results

LV cavity size on short-axis, vertical and horizontal axes. There were a total of 100 patients, 68 males and 32 females, enrolled in the study. The best cut-off point for LV cavity dilatation (LV cavity area) on short axis was > 5 sq. cm, with a sensitivity of 100% and specificity of 94%. Measurements for LV cavity dilatation using the vertical and horizontal axes best correlated with 2-D echo at cut-off value of > 2.5 cm for both axes (100 % sensitivity, 94% specificity and 95% sensitivity, 96% specificity, respectively).

Transient cavity dilatation versus fixed cavity size. Transient LV cavity dilatation refers to apparent increase in LV cavity size after stress, relative to the resting images. Fixed LV cavity dilatation on the other hand implies increased cavity dimensions to equal degree in both sets of images and indicates pre-existing cavity enlargement. In either case, LV cavity dilatation has negative prognostic implications. There is strong correlation between LV stress dilatation and presence of multivessel CAD (often with stenosis > 90%). Cardiac death and non-fatal myocardial infarction rates are significantly higher in patients with transient dilatation.[10] Pre-existing (fixed) LV cavity dilatation likewise has poor prognostic implication. Data in the literature support the concept that LV dilatation predisposes the myocardium to ischemia. Following the law of Laplace, which states that ventricular wall stress is proportional to LV radius and systolic pressure, myocardial oxygen demand increases as LV cavity size increases at a given pressure, and ischemia may be potentiated. Straus[11]measured oxygen consumption in patients with different types of heart disease and found out that consumption was highest in patients with dilated LV cavities and lowest in patients with small ventricular volumes. Furthermore, Heupler et al suggested that the likelihood of a thallium perfusion defect in a patient with CAD is augmented by increased LV mass and that this effect is primarily caused by increased LV cavity dimension, rather than increased wall thickness. The relation between LV cavity size and perfusion defect was confirmed when LV end-diastolic volume was averaged in patients with and without defects. This volume was significantly larger in the population with defects than in those without perfusion abnormality.[6] Increased LV cavity size potentiates ischemia only in diseased coronaries but not in normal coronary beds. Alternatively, development of LV cavity dilatation due to ischemia could also explain the relation between LV cavity size and thallium perfusion defects. Progressive LV dilatation may result from increased LV wall stress secondary to intermittent ischemia.

Absolute number of short axis slices on the scintigram. A left ventricular cavity measurement could also be obtained using SPECT by determining the number of short axis slices encompassing the left ventricular chamber. A cut-off value of > 15 (no. of short axis slices) was noted, with a sensitivity of 85%, specificity of 86% and positive predictive value of 85%.

Lung-to-heart thallium ratio. Increased pulmonary activity is an indicator of increased LV end-diastolic pressure or LV dysfunction. In general, in an adequately stressed patient, pulmonary activity should be less than 50%. Increased lung activity is seen in patients with exercise-induced LV dysfunction and may be the only evidence of 3-vessel coronary artery disease. It is perhaps the most important prognostic indicator for likelihood of future cardiac events (positive predictive value of 70%). An abnormal lung-to heart thallium ratio, as an inferential or indirect sign for LV cavity dilatation (secondary to LV dysfunction/global ischemia) has sensitivity of 69%, specificity and positive predictive value of 100% in predicting cavity enlargement.

Right ventricular activity. RV activity can be seen during stress but faintly at rest. Significant RV activity, especially at rest, is associated with RV pressure overload (hypertrophy), volume overload or both, and is most commonly secondary to left sided failure. As an inferential or indirect sign for LV enlargement and failure, it has sensitivity of 52% and specificity of 100% in predicting LV cavity dilatation.

Study limitations and recommendations. While this study is able to generate absolute measure of LV cavity size and cut-off values (correlating best with the echocardiogram) for chamber size that would imply poor prognosis, these cut-off values for LV cavity dimensions may not be applicable to other gamma camera software and analog image formatters. These SPECT data could also be further refined by using gated Technetium-99m Sestamibi for better resolution and

reduction of image blurring caused by motion.

A scoring system using the different scintigraphic parameters for LV cavity dilatation may also be done for higher overall accuracy in assessing LV cavity enlargement.

Conclusion

LV cavity dilatation (transient or fixed) influences long-term prognosis in CAD patients. This study suggests that this simple method for measurement of LV cavity size and the different inferential scintigraphic parameters for LV cavity dilatation may provide important adjunct to SPECT myocardial perfusion study in the assessment of patients with extensive CAD and could further risk-stratify patients as to likelihood for future cardiac events.

Table 1 Sensitivity, specificity, positive and negative predictive values, accuracy of different cut-off values

LV cavity area (cm^2)	Sensitivity	Specificity	pos pred	Neg pred	accuracy
> 2.0	100%	25%	55%	100%	61%
> 3.0	100%	48%	64%	100%	73%
> 4.0	100%	84%	86%	100%	92%
> 5.0	100%	94%	94%	100%	97%
> 6.0	98%	96%	96%	98%	97%
> 7.0	88%	96%	95%	89%	92%
>10.0	77%	96%	95%	82%	87%
>15.0	58%	98%	96%	72%	79%
No. of short axis slices					
13	96%	23%	53%	86%	58%
14	88%	62%	68%	84%	74%
15	85%	86%	85%	87%	86%
16	79%	98%	97%	84%	89%
17	54%	100%	100%	70%	78%
Vertical distance (cm)					
> 1.5	100%	13%	52%	100%	55%
> 2.0	100%	52%	66%	100%	75%
> 2.5	100%	94%	94%	100%	97%
> 3.0	88%	96%	95%	89%	92%
> 3.5	77%	96%	95%	81%	87%
> 4.0	71%	96%	94%	78%	84%
> 4.5	56%	98%	96%	71%	78%
> 5.0	33%	100%	100%	62%	68%
> 5.5	21%	100%	100%	58%	62%
Horizontal distance (cm)					
> 1.5	100%	27%	56%	100%	62%
> 2.0	100%	65%	73%	100%	82%
> 2.5	96%	96%	96%	96%	96%
> 3.0	81%	96%	95%	85%	89%
> 4.0	67%	98%	97%	76%	83%
> 4.5	52%	100%	100%	69%	77%
> 5.0	29%	100%	100%	60%	66%
L-H ratio					
> 0.5	69%	100%	100%	78%	85%
RVH (+)	52%	100%	100%	69%	77%

Table 2 Comparison of mean values of different parameters

	Positive mean	2D Echo SD	Negative mean	SD	p-value t-test	
LV cavity area (cm2)	3.32	2.52	17.02	8.34	0.000	***
Vertical axis (cm)	1.97	0.60	4.51	1.15	0.000	***
Horizontal axis (cm)	1.84	0.59	4.33	1.09	0.000	***
No. of short axis						

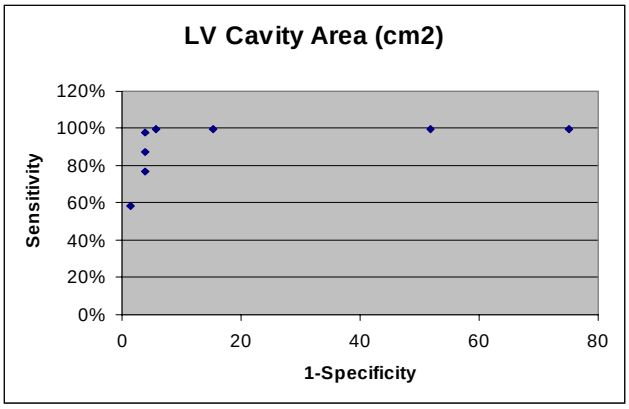

Figure 1 ROC Curve of LV cavity area showing best cut-off value

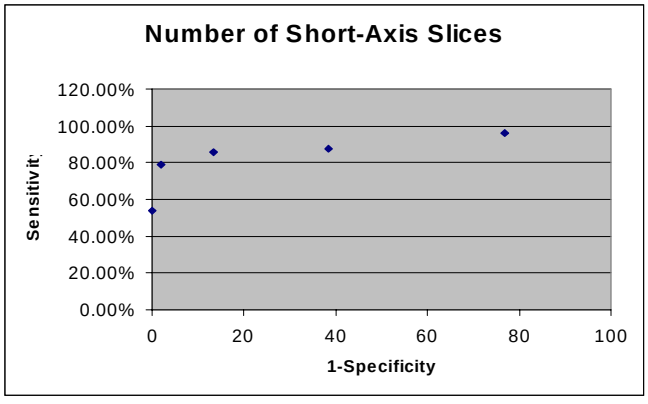

Figure 2 Number of short axis slices showing best cut-off point

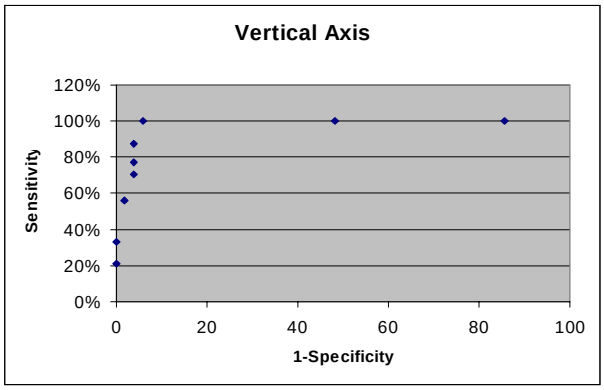

Figure 3 ROC curve of distance of inner borders of myocardium at mid-LV level in the vertical axis showing best cut-off value

References

1. Romanens M, Gradel C., Saner H, Pfisterer M. Comparison of 99m Tc-sestamibi lung/heart ratio, transient ischaemic dilatation and perfusion defect size for identification of severe and extensive coronary artery disease. Eur J Nucl Med 2001 Jul;28(7):907-10.
2. Weiss AT, Berman DS, Lew AS, Nielsen J, Potkin B, Swan HJ, Waxman A, Maddahi J. Transient ischemic dilatation of the left ventricle on stress thallium-201 scintigraphy: a marker of severe and extensive coronary artery disease. J Am Coll Cardiol 1987 Apr;9(4):752-9.
3. Chouraqui P, Rodrigues EA, Berman DS, Maddahi J. Significance of dipyridamole-induced transient dilation of the left ventricle during thallium-201 scintigraphy in suspected coronary artery disease. Am J Cardiol 1990 Sep 15;66(7):689-94.
4. Georg Emlein, Bernard Villegas, Seth Dahlberg, Jeffrey Leppo MD. Left ventricular cavity size determined by preoperative dipyridamole thallium scintigraphy as a predictor of late cardiac events in vascular surgery patients. Am Heart J 1996;131(5).
5. Marco Mazzanti, Guido Germano, Hosen Kiat, Paul B. Kavanagh, Erick Alexanderson, John D. Friedman, Rory Hachamovitch, Kenneth F. Van Train and Daniel S. Berman. Identification of Severe and Extensive Coronary Artery
6. Disease by Automatic Measurement of Transient Ischemic Dilatation of the Left Ventricle in Dual-Isotope Myocardial Perfusion SPECT. J Am Coll Cardiol 1996;27(7):1612-1620.
7. Heupler, Stephen MD; Lauer, Michael MD; Williams, M. John MD; Shan, Kesavan MD; Marwick, Thomas H. MD. Increased left ventricular cavity size, not wall thickness, potentiates myocardial ischemia. Am Heart J 1997;133(6): 691-697.
8. White HD, Norris RM, Brown MA, et al. Left ventricular end systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 1987;76:44-51.
9. Iskandrian AS, Heo J, Nguyen T, Lyons E, Paugh E. Left ventricular dilatation and pulmonary thallium uptake after single photon emission computer tomography using thallium-201 during adenosine-induced coronary hyperemia. Am J Cardiol 1990;66(10):807-11.
10. Krawczynska EG, Weintraub WS et al. Left ventricular dilatation and multivessel coronary artery disease on thallium-201 SPECT are important prognostic indicators in patients with large defects in the left ascending distributions. Am J Cardiol 1994;74(12):1233-9.
11. McLaughlin MG, Danias PG. Transient ischemic dilatation: a powerful diagnostic and prognostic finding of stress myocardial perfusion imaging. J Nucl Cardiol 2002;9:663-667.
12. Straues B. Myocardial oxygen consumption in chronic heart disease: role of wall stress, hypertrophy and coronary reserve. Am J Cardiol 1979;730-40.

Case Report

Childhood In Childhood Interventricular Septal Lipoma

Donaldson M. Gadingan MD, Marissa Orillaza MD, Leonisa Sagun MD, Bernadette R. Asuncion, MD

We report a rare case of an 8-year-old girl with history of dizziness and shortness of breath who was referred to our institution due to an echocardiographic finding of a right ventricular mass arising from the interventricular septum. Rhabdomyoma was the primary consideration. A repeat 2-D echocardiography revealed a mass at the right ventricular body with the stalk attached to the distal third of the ventricular septum. The mass was excised with a histopathologic diagnosis of lipoma.

The patient recovered well and is currently asymptomatic.

Cardiac lipomas are very rare benign neoplasms occurring anywhere in the heart with unclear etiology. Diagnosis is based on the histologic findings with clinical correlation and ancillary non-invasive procedures. The treatment of choice is surgical resection and patients generally have a good outcome after resection.

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Keywords: cardiac lipoma, interventricular septum

Primary cardiac tumors are rare and account for 5% to 10% of all neoplasias of the heart and pericardium with an incidence in autopsies ranging from 0.0001% to 0.05%. Approximately 75% of the primary cardiac neoplasms are benign, 30%-50% being myxomas and the remaining being lipomas, papillary fibroelastomas, and rhabdomyomas. The remaining 25% are malignant and the more common are rhabdomyosarcomas and angiosarcomas.[1]

In the pediatric age group, rhabdomyoma is the most common followed by fibroma, teratoma, hamartoma, and lipoma.[2]

Cardiac tumors may invade the endocardium, myocardium, pericardium, and the emergence of great vessels.[3] In a survey by Odim et al at the UCLA School of Medicine on 29 primary cardiac tumors of both adults and children from 1979 to 1999, 22 were located in the atria and 5 in the ventricles.[4]

The signs and symptoms of cardiac tumors depend mostly on their location causing valvar dysfunction or cardiac compression hindering cardiac filling and emptying. Cardiac lipomas occur in any part of the heart and signs and symptoms may vary depending on the location of the tumor. Lipomas of the right atrium, interatrial septum, and the right ventricle may predispose to development of arrhythmias. Lipomas that involve the epicardium or the myocardium may remain asymptomatic during a prolonged time and may reach very large dimensions.[3]

Correspondence: **Donaldson M. Gadingan** MD. Division of Biological and Clinical Laboratory Philippine Heart Center, East Avenue, Quezon City, Philippines 1100

We report a rare case of a right ventricular lipoma arising from the interventricular septum. Review of literature has documented only 6 cases of lipoma of the interventricular septum.[5]

Case History

An eight-year-old girl was referred to our center because of occasional episodes of dizziness and shortness of breath since a year before admission. Diagnostic work-up including chest x-ray and electrocardiogram done that time yielded unremarkable findings. Two weeks prior to admission, there was recurrence of dizziness. The patient was then brought to a local hospital and underwent a 2-D echocardiographic exam. A homogenous pedunculated mass at the right ventricular cavity attached to the apical septum measuring 3.7-4 cm^2 was noted with primary impression of rhabdomyoma. Trivial tricuspid and pulmonic regurgitation with no obstruction to ventricular inflow and outflow and good gross contractility was noted. The patient was then referred to our institution for further management and work-up. Birth and past medical histories were unremarkable. The only morbid antecedent reported was intestinal amoebiasis two years earlier. On physical examination, the patient was in good condition with the following vital signs: BP=100/60, CR=84/min, RR=24/min, T=36.3°C, height=130.5 cm, weight=28 kg. Cardiovascular examination revealed normal and regular cardiac rate and rhythm, no murmurs, and full pulses. The rest of the physical

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examination findings were essentially normal. Further work-up done which included CBC, PTPA, serum creatinine, chest x-ray, and ECG showed unremarkable results. A repeat 2-D echocardiographic examination revealed the following: situs solitus, atrio-ventricular and ventriculo-arterial concordance, intact interatrial and interventricular septae, normal chamber sizes, right ventricular mass at the right ventricular body with the stalk attached to the distal third of the ventricular septum measuring 5.82 mm-7.53 mm (figure 1), no atrioventricular valve insufficiency, normal pulmonary artery pressure, good LV ejection fraction of 96%, left-sided aortic arch, no PDA, and no coarctation of aorta noted. The patient was referred to surgical service for co-management. She then underwent resection of the mass on the 2nd hospital day. Gross examination of the excised mass showed a tan-white to tan-yellow roughly ovoid rubbery tissue measuring 2 x 1.8 x 1.0 cm (figure 2). Cut section showed a tan-yellow, solid cut surface (figure 3). Histologically, the tumor is composed of mature adipose cells with entrapped cardiomyocytes. No lipoblasts were seen (figures 4 and 5). A diagnosis of lipoma was made. The patient had no post-operative complications. A repeat 2-D echocardiography done four days post surgery showed good left ventricular ejection fraction (64%), good right ventricular function of (62%), normal chamber sizes and pulmonary artery pressure by PAT, mild tricuspid regurgitation jet of 17 mmHg, trivial pulmonary regurgitation, and no pericardial effusion. The patient was discharged improved after 6 hospital days (4 days post-surgery) and has been asymptomatic on regular follow-up.

Discussion

Cardiac lipomas are very rare benign neoplasms accounting for 8.4% of primary cardiac tumors occurring anywhere in the heart.[6,7] Based on the Philippine Heart Center Cardiac Tumor Registry from 1975 to 2005, this is the second case of cardiac lipoma encountered and the first case in the pediatric age group (Table 1).[8] Approximately 50% of the tumors have a subendocardial origin, 25% intramyocardial, and the remaining 25% of pericardial origin.[5] Lipomas are typically found in adult patients but can affect all ages with no sexual predilection. [4,6]

Grossly, they appear as circumscribed, spherical, or elliptical masses of homogenous fat.[6] From the histological point of view, cardiac lipomas are true neoplasms composed of mature adipose tissue and sometimes with entrapped myocytes.[9] They may be encapsulated although it may be focally absent or attenuated. They may also undergo fat necrosis and calcification. [5,6]

No report of malignancy or metastasis exists. Some authors have attempted to classify the neoplasm according to invasion of surrounding tissues: myolipoma when the cells infiltrate the myocardium, fibrolipoma when connective tissue is present, and lipoma if it is composed of pure fat with free support reticulum.[5]

The etiology of lipoma is unclear but some authors suspect a congenital origin in which new tissues of the same type are formed from the existing tissue in a particular organ. Others postulate a heterotopia of mesodermal embryonic cells which may differentiate as lipocytes and cause lipomas in the mediastinum, pericardium, and interatrial septum.[5] Basson et al conducted a cytogenetic study on adipose growth of the human heart. They have identified a unique chromosomal translocation that mediates cardiac lipoma invasion into the myocardium. His team is now exploring the role of that genomic region in lipoma formation in families with multiple lipomatosis syndromes.[10]

The definitive diagnosis of lipoma is its histopathologic findings with clinical association and other ancillary non-invasive methods such as chest radiograph, echocardiography, computerized tomography, and nuclear magnetic resonance. In the six reported cases of interventricular septal lipoma, two patients presented with systolic murmur.[11,12] One patient had dyspnea[13] and another manifested with chest pain and syncope.[14] One patient had left hemiplegia due to right temporo-parietal infarction and lipoma of the septum was considered as the cause of the systemic and pulmonary emboli.[15] Only one patient was asymptomatic.[16] Most of the reported cases occur in adults (Table 2).

The most frequent radiographic abnormality in patients with cardiac lipoma is cardiomegaly.[6] 2-D-echocardiography remains the mainstay of tumor detection and has contributed to the increase in the number of diagnosed cardiac tumors especially in asymptomatic patients. Its disadvantage is its limited sensitivity in differentiating tissue characteristics. CT scan has great specificity for identifying and locating the tumor aside from delineating its shape, dimension, and density. It is useful in making a tissue-specific diagnosis based on the findings of fat attenuation. Lipomas appear as predominantly homogenous masses on CT scanning.[5,6] Nuclear magnetic resonance is highly sensitive and highly specific. It provides direct visualization of the tumor in different planes.[2,17] It is also useful in diagnosing extracardiac tumors that compress cavities simulating intracardiac mass and low-density mediastinal cysts.[5]

Cardiac lipomas are treated with surgical resection, and patients generally have a good outcome after resection.[6] The first successful resection of an epicardial lipoma was performed by Maurer et al in 1954.[5] And it was Bradford and his team in 1980 who first described and successfully removed an intraventricular lipoma.[3]

The problem with benign cardiac tumors does not reside on its histological characteristics but on its intracavitary component especially if there is extension to the cardiac cavities causing alteration of cardiac output, insufficiency, peripheral embolism, and rhythm and conduction disorders.

Thus, surgery is mandatory after determination of diagnosis.[3]

Other cardiac tumors with fat differentiation are liposarcoma and lipomatous hypertrophy. Cardiac liposarcomas are most often found on the epicardial surface. Just like their extracardiac counterparts, they are composed of mature fat cells with variable number of spindled cells with hyperchromatic nuclei and multivacuolated lipoblasts. Lipomatous hypertrophy on the other hand almost always occurs in the atrial septum. This tumor is composed of mature and brown fat with myocytes which are distributed throughout the tumor.[9,18]

Summary

In the case, our patient presented with dizziness and shortness of breath . We cannot entirely conclude that the symptoms are due to blood flow obstruction caused by the tumor because the heart's physiologic status was normal on echocardiography. The tumor was first considered as rhabdomyoma probably because our patient is a child and rhabdomyoma is the most common primary tumor in their age group. The mass was excised and diagnosed as lipoma. Our patient has been asymptomatic on regular follow-up.

Lipomas of the interventricular septum are very rare with only 6 cases reported. Our patient is the first case of cardiac lipoma in the pediatric age group encountered at our center.

Definitive diagnosis is the histologic finding of mature adipose cells with no lipoblasts. Clinical correlation and ancillary non-invasive procedures such as radiography, echocardiography, CT scan, and MRI are of big help in detection of the tumor.

Lipomas are treated with surgical resection. Surgery is highly indicated especially if there is tumoral extension into the cardiac cavities. Generally, the prognosis is good after surgery.

Conclusion

We report a rare case of lipoma arising from the interventricular septum in an 8-year-old child who presented with dizziness and shortness of breath. 2-D echocardiography demonstrated its presence and definite diagnosis was confirmed by histopatologic examination. Surgical resection of the tumor offered a favorable prognosis.

References

1. BurkeA, VirmainR. Atlas of Tumor Pathology. Tumors of the Heart and Great Vessels. Washington D.C.: Armed Forces Institute of Pathology, 1996:231. Copyright Ó 2002 by Lippincott, Williams, and Wilkins. GatesJ, HartnellG, et al. Cardiac Tumors. Emedicine. 2003
2. GatesJ, HartnellG, et al. Cardiac Tumors. Emedicine. 2003
3. FernandesPM, BatagelloCA, et al. Left ventricular lipoma, Case Report. Arquivos Brasileiros de Cardiologia. 2004; 82: 188-90.
4. OdimJ, ReehalV, et al. Surgical Pathology of Cardiac Tumors, Two Decades at an Urban Institution. Cardiovascular Pathology. 2003; 5: 267-70.
5. SilveiraWL, NeryMW, et al. Lipoma of the Right Atrium, Case Report. Arquivos Brasileiros de Cardiologia. 2001; 77: 365-8.
6. Department of Radiology, National Naval Medical Center, Bethesda, Md, Department of Radiologic Pathology and Cardiovascular Pathology, et al. Primary Cardiac Neoplasms. 2000
7. CohnLH, EdmundsLH, eds. Cardiac Surgery in the Adult. New York: McGraw-Hill, 2003:13731400.
8. Philippine Heart Center Cardiac Tumor Registry. 1975-2004.
9. SilverMD, GotleibAI, Schoen, FJ. Cardiovascular Pathology, 3rd Edition. Philadelphia: Churchill Livingstone. 2001: 588-9.
10. BassonCT, et al. Genetic Regulation of Cardiac Tumorigenesis and Cardiac Cell Proliferation. Weill Medical College of Cornell University. 2003
11. HayaseS, YanoY, et al. Kyobu Geka. 1991; 44(13): 1151-4.
12. KamiyaH, OhnoM, et al. American Heart Journal. 1990; 119(5): 1215-7
13. SrinivasBK, GopalakrishnanM, et al. Asian Cardiovascular and Thoracic Annals. 2002; 10(1): 64-5.
14. BeniniA, GabaldoS, et al. G Italian Cardiology. 1991; 21(10):1135-6.
15. ZamirD, PelledB, et al. Harefuah. 1995; 129(5-6): 179-81.
16. KatoY, MurataH, et al. Japanese Journal of Thoracic and Cardiovascular Surgery. 1998; 46(10): 1057-60.
17. WeiselTH, EnzweilerlCN, et al. Electron Beam CT in the diagnosis of Recurrent Cardiac Lipoma. American Journal of Radiology. 2001; 176: 1066-68.
18. WeissS, GoldblumJ, et al. Soft Tissue Tumors, 4th Edition. Missouri: Mosby. 2001: 648-9.

Table 1. Cardiac Tumor Registry of Philippine Heart Center from 1976-2005

HISTOLOGIC TYPE	NUMBER OF CASES
1. MYXOMA	204
2. RHABDOMYOMA	3
3. UNDIFFERENTIATED SARCOMA	3
4. METASTATIC CARCINOMA	3
5. MALIGNANT FIBROUS HISTIOCYTOMA	2
6. MYXOSARCOMA	2
7. ANGIOSARCOMA	1
8. ATYPICAL MESOTHELIAL PROLIFERATION	1
9. BENIGN VASCULAR MALFORMATION	1
10. FIBROLIPOMA	1
11. HAMARTOMA	1
12. LIPOMA	1
13. LIPOSARCOMA, WELL-DIFFERENTIATED	1
14. NON-HODGKIN'S LYMPHOMA	1
15. PAPILLARY FIBROELASTOMA	1
16. RHABDOMYOSARCOMA	1
17. SMALL ROUND BLUE CELL TUMOR	1
18. UNDIFFERENTIATED CARCINOMA	1

Table 2. Published cases of interventricular septal lipoma.

AUTHOR	YEAR	AGE	SEX	LOCATION	SYMPTOM	OUTCOME AFTER RESECTION
SrinivasBK, et al	2002	36	F	Interventricular septum	Dyspnea	Asymptomatic
KatoY, et al	1998	60	M	Ventricular septum	Asymptomatic	Uneventful
ZamirD, et al	1995	46	F	Apical septum	Left hemiplegia	(?)
BeniniA, et al	1991	(?)	(?)	Interventricular septum	Chest pain, syncope	Uneventful
HayaseS, et al	1991	45	M	Ventricular septum	Systolic murmur	Uneventful
KamiyaH, et al	1990	45	M	Interventricular septum	Systolic murmur	Uneventful

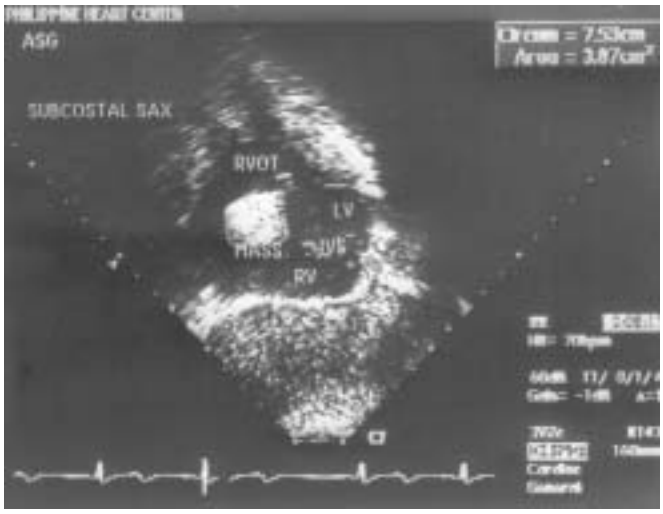

FIGURE 1. Transthoracic 2-D-echocardiogram four-chamber view showing a mass at the right ventricular body with the stalk attached to the distal third of the ventricular septum.

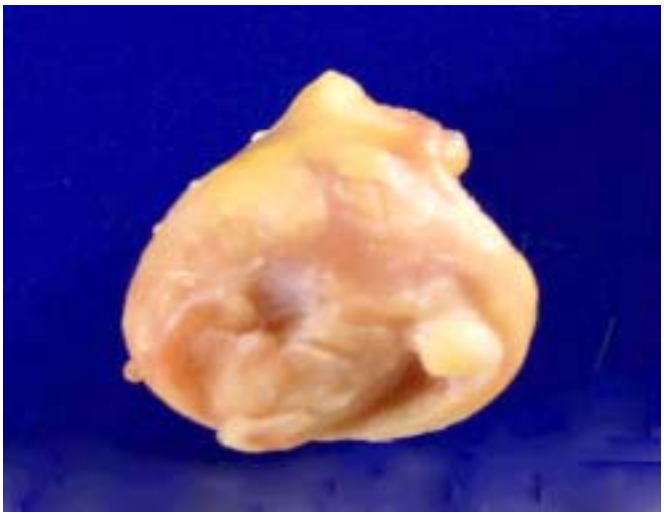

FIGURE 2. Gross. A tan-yellow roughly ovoid rubbery tissue measuring 2 x 1.8 x 1.0 cm.

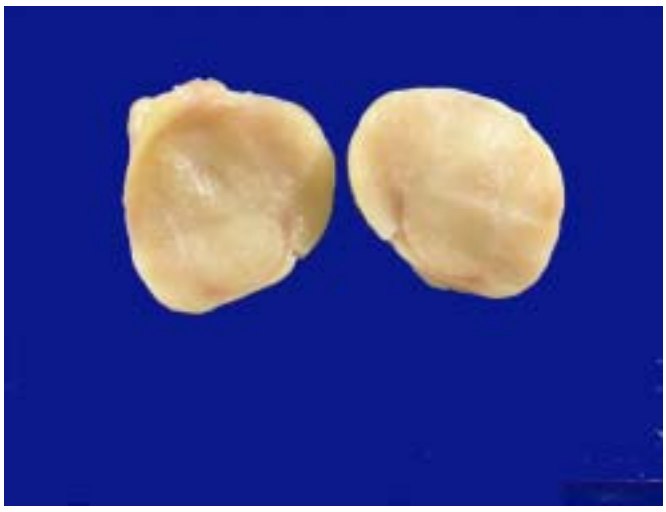

FIGURE 3. Gross. Cut section of the specimen showing a tan-yellow cut surface. No necrosis and hemorrhage are noted.

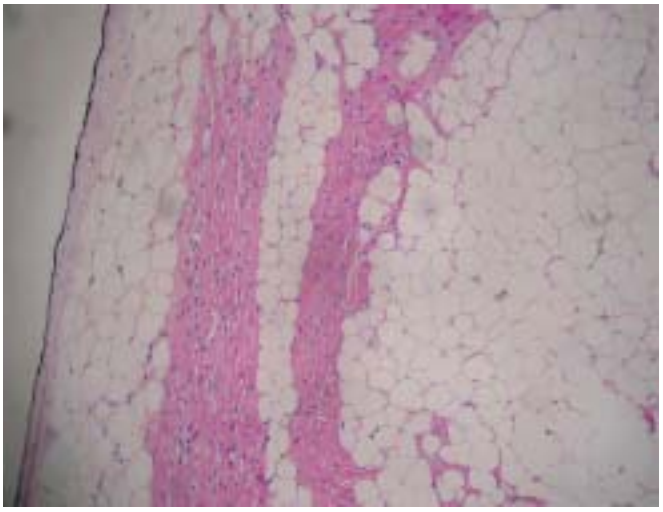

FIGURE 4. Photomicrograph of the tumor composed of mature adipose cells with entrapped myocytes. No lipoblasts are seen. (X100).

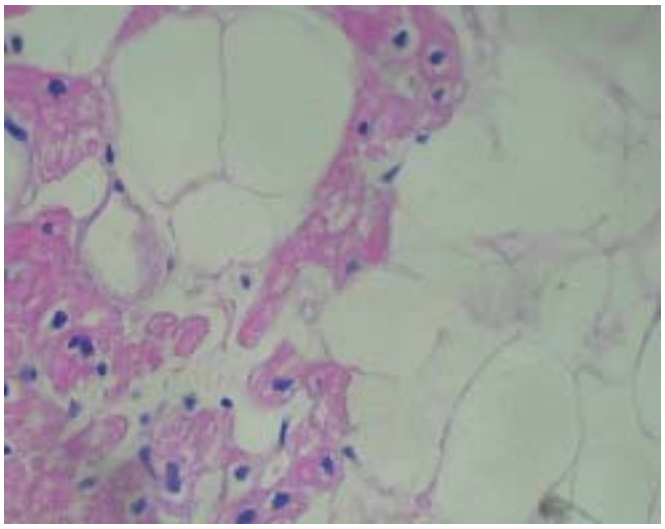

FIGURE 5. Photomicrograph of the tumor showing entrapped myocytes amongst mature adipose cells. No mature brown fat cells are seen. (X400).

Case Report

Adrenal Incidentaloma in a 50 year old male: a case report

Laarnie N. Cale MD, Marissa Orillaza MD, Leonisa Sagun MD, Bernadette R. Asuncion, MD

Adrenocortical carcinoma (ACC) is a rare neoplasm, usually considered to be one of the most morbid and lethal human tumors due to delayed diagnosis and presence of significant micrometastasis. Incidentalomas detected by diagnostic imaging techniques imposes a great challenge to modern medicine nowadays with regards to proper approach to management.

We report a case of a right adrenal mass detected incidentally in an asymptomatic 50 year old Filipino male by ultrasound of abdomen. A CT scan guided fine needle aspiration biopsy was done and adrenal neoplasm was entertained. Vimentin immunoreactivity was noted. Hormonal evaluation was unremarkable. Right adrenalectomy was done and the histopathologic findings revealed features of ACC. Patient expired after a year with recurrence and metastasis despite of chemotherapy and radiotherapy.

Phil Heart Center J 2005;11:49-55

Keywords: Adrenocortical Carcinoma; histopathology;

Clinically inapparent adrenal masses are incidentally detected after imaging studies conducted for reasons other than the evaluation of the adrenal gland, that have been frequently referred to as adrenal incidentalomas.[1] Despite the rarity of primary endocrine cancers of the adrenal, adrenal masses are one of the most prevalent of all human tumors[2], a bad impact on health outcomes with its reputation of difficult treatment and poor prognosis. As we approach the modern diagnostic era, the management of clinically inapparent adrenal mass is becoming an important aspect of health care, with much higher incidence detected through imaging technology, management of incidentaloma remains a challenge to the modern medicine.

The objective of this paper is to present a case of adrenocortical carcinoma (ACC) in a 50 year old Filipino male as incidentaloma and diagnosed through CT scan-guided FNAB, confirmed by immunostain and histopathologic examination with impact on patient management.

Case History

A 50 year old male came for regular annual medical examination at this institution with chronic problem of atherosclerotic heart disease (ASHD), non-insulin dependent diabetes mellitus (NIDDM), hyperlipidemia and colonic diverticulum. An ultrasound of liver, gallbladder and prostate showed normal sized liver with fatty infiltration, grade II prostatic enlargement with concretions and incidental finding of a well-defined lobulated solid mass lesion in the right suprarenal area likely adrenal in origin measuring 7.2 x 8.3 x 6.7 cm (Figure 1A). The patient is asymptomatic so the suprarenal mass was ignored. Patient had CT scan of the whole abdomen a year after the initial finding and adrenal neoplasm was considered (Figure 1B). Suspicious nodular density at the left presacral area was also noted that may represent lymphadenopathy. The patient was admitted and CT scan guided biopsy was done revealing adrenocortical tumor favoring carcinoma (Figure 2A and 2B). Immunostains showed strong positive reaction to vimentin (Figure 3) and negative reaction to cytokeratin. Patient was then referred to surgery for possible surgical resection of the tumor. Blood chemistries, hematologic profiles, total body scan hormonal evaluation were unremarkable. Right adrenelectomy, with 11th rib resection on the right showed adrenal mass markedly enlarged measuring 10 x 6 cm with areas of necrosis seen in the cortex and medulla. Final histopathologic findings showed adrenocortical carcinoma (Figure 4) using the Weiss criteria (Table 1).[3] The referral to oncology service showed stage II disease (T2N0M0). Chemotherapy was started using cisplatin with good response. The patient was discharged improved after 23 hospital days and was advised to come back for succesive chemoradiotherapies.After 3 cycles of chemotherapy and 22 sessions of radiotherapy, patient came for admission due to fever and chills. He was anorexic and had significant weight loss. Magnetic resonance imaging revealed multiple soft tissue mass in the liver, right suprarenal region and right paravertebral space. There was a filling defect in the inferior vena cava indicative of tumor thrombus. A small hepatic cyst in

Correspondence: **Laarnie N. Cale** MD. Division of Biological and Clinical Laboratory Philippine Heart Center, East Avenue, Quezon City, Philippines 1100

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the segment II was also noted. Chest x-ray done and a pneumonia was considered with subsegmental atelectasis. Hematologic work-up showed decreased white blood cells and elevated acid phosphatase and alkaline phosphatase. Proteinuria and glucosuria were also noted. Immunotherapy was initiated and the patient was discharged improved. Patient was on regular follow-up with his oncologist and eventually expired after one year.

Discussion

Adrenal incidentalomas, as often referred to us, are adrenal masses detected through imaging for nonadrenal disease and were first described about 20 years ago.[3] The prevalence of adrenal incidentalomas approaches 3% in middle age and increase to as much as 10% in the elderly.[2]

Adrenal gland has become frequent target of needle biopsies nowadays with the availability of sensitive imaging techniques and better localization. In this case, the physician opted for fine needle aspiration biopsy being less a invasive procedure to confirm the consideration of adrenal neoplasm. Needle biopsy, currently, is the only non-surgical means of obtaining a diagnosis in patients with adrenal mass.[4]

In the study of FNA by Wadih et al[5] and Mansmann et al.,[1] fine-needle aspiration is a sensitive (81-100%) and highly specific (83-100%) procedure for the evaluation of primary and metastatic malignancies involving the adrenal gland although Mansmann mentioned that in many literatures reviewed, the test performance for FNA to diagnose adrenal masses either did not clearly define the reference standard or, in part, used FNA as both test under investigation and reference standard.

Specimen from FNA imposes problem of accurate diagnosis since scanty amount is submitted for cytologic study. Cytomorphologic features are not so specific to define a benign from malignant tumor. Carcinoma exhibit a wide range of differentiation, from tumors that are so well-differentiated as to be almost impossible to distinguish from adenoma to totally undifferentiated neoplasms composed of giant cells with abundant acidophilic cytoplasm and bizarre hyperchromatic nuclei, and sometimes multiple.[6]

In FNA biopsy samples, cortical carcinoma generally contain single cells and poorly cohesive cell clusters in a necrotic background. There were no cytologic differences between normal adrenal and adrenocortical nodules. There may be considerable nuclear atypia and mitotic activity but some may appear deceptively bland. Large nuclei with prominent nucleoli were observed predominantly in adrenocortical neoplasms. The cytoplasm varies from vacuolated to densely eosinophilic and a few spindle cells may be evident.[7]

Most of the time, with the help of clinical findings and imaging studies, diagnosis by FNAB may be outright for considering the neoplasm, but there are instances that adenomas, which are more common, could not be ruled out. Then the specimen may be submitted for immunostaining and the positivity to vimentin and negative reaction to cytokeratin strongly suggest ACC.

When the mass is finally submitted for histopathology, different diagnostic consideration are encountered. If the mass is not clearly defined and the possibilty of other primary tumor is entertained, the following differential diagnoses should be considered: (1) between adrenocortical adenoma and carcinoma; (2) between adrenocortical carcinoma and renal cell carcinoma (RCC); (3) between adrenocortical and adreno-medullary tumors.

In adrenal adenomas, the mass tend to be smaller, more homogenous, and lacking hemorrhage and necrosis. Specifically, lesions under 50 grams are generally cured by excision, even if exceptions occur. Microscopically, mitotic activity and venous invasion correlate best with recurrence or metastasis. Immunohistochemically, adrenal cortical adenomas show a greater expression of low-molecular-weight keratins and a lesser expression of vimentin than adrenal cortical carcinomas. Therefore an adrenocortical tumor that is strongly positive for vimentin and negative or weakly positive for keratin is likely to be carcinoma.[6]

Just like in this case, adrenal cortical carcinomas, on the other hand, are rare tumors with incidence of about 1-2 cases per million population. They account for approximately 0.02% of all malignancies. Cortical carcinomas are large tumors weighing more than 100 grams in adults, most often, tumor weight is in excess of 750 grams.[8] A combined evaluation of clinical features, size or weight, microscopic appearance, and immunohistochemical/genetic data is necessary for distinction between adenomas and carcinomas though this may be impossible at the practical level.

Another important differential diagnosis is between adrenocortical carcinoma and RCC, which can invade the adrenal gland directly or metastasize to it, either ipsilaterally or contralaterally. The presence of cells in sheets with central, thin-walled vascular core (endocrine vascular pattern); monomorphic cell population; eccentric nuclei; focal dramatic anisonucleosis; and focal spindling with crushing were prominent and significant features of ACC in contrast to RCC, which showed mainly an acinar pattern with only a focal endocrine pattern, well-defined cytoplasmic angles and projections, and cytoplasmic vacuolations; pleomorphism, if present was gradual and seen uniformly in all the cells.[9]

To date, the immunohistochemical distinction of ACC from RCC is based on a panel of antibodies. Strong positivity for cytokeratin, EMA, CD10 and Lewis blood group isoantigen favors renal cell carcinoma whereas positivity for inhibin, A103, Melan-A (Mart-1), and synaptophysin favors ACC.[6]

The differentiation between adrenocortical and adrenomedullary component is quite difficult in hematoxylin

and eosin level. In the study of Fetch et.al., ACC and benign adrenocortical cells were immunoreactive with the a-inhibin antibody, showing diffuse cytoplasmic and granular staining pattern. The staining intensity and number of immunoreactive cells vary within each sample, with the cases of ACC having the greatest proportion of immunoreactive cells and the strongest intensity.[10] ACC should be favored in the presence of inhibin, Melan-A and calretinin positivity, whereas adrenomedullary tumors is more likely if chromogranin reactivity is present; synaptophysin is of no help since it stains both tumor types.[6,8]

ACC staging is determined primarily by the size of the primary tumor, the degree of local invasion and whether it has spread to regional lymph nodes or distant sites. Proper staging should include computed tomography of the abdomen. MRI may add specificity to CT evaluation of an adrenal mass. It can also often clearly demonstrate any evidence of extracapsular tumor invasion, extension into the vena cava, or metastases. The most common sites of metastatic involvement are liver (60%), regional lymph nodes (40%), lungs (40%), peritoneal and pleural surfaces, and bone.[1,6,8] Patency of surrounding vessels can often be demonstrated with gadolinium-enhanced sequences or flip-angle techniques. Vena caval contrast studies and angiography may provide additional staging information and allow for more complete preoperative assessment.[11] The patient in this case had follow up of the tumor status post chemotherapy and radiotherapy and MRI clearly shows recurrence and metastasis of the carcinoma in the liver, which is the most common metastatic site, and tumor thrombosis in the vena cava.

Review of published data from 608 patients revealed the following stage distribution at diagnosis : 3% stage I, 29% stage II, 20% stage III, and 49% stage IV.[12] Stages are defined by TNM classification (Table 2). In this particular case, the patient was diagnosed with stage 2 of the disease. He underwent complete surgical removal of the tumor. The score of more than 4 using Weiss criteria[13,14] (Table 1) suggest that the patient has the possibility of recurrence and metastasis. MRI done after few months of the surgical resection indeed showed tumor recurrence, liver metastasis and tumor thormbosis.

Due to rarity of the disease, there is no clinical trial supporting the effectiveness of chemotherapy and radiotherapy in adrenocortical carcinoma, in which early radical surgery is the only curative approach.[1,6,8,15,16,17,18] Despite the aggresiveness of the treatment, in which he had chemoradiotherapies, the patient expired. This carcinoma has the reputation of short survival with mean of 14-18 months after the diagnosis.

Summary

We presented a case of a 50 year old male who was diagnosed with adrenal incidentaloma and underwent CT scan guided needle biopsy with consideration of adrenal neoplasm. Vimentin showed strong immunoreactivity. Histopathologic study of the mass resected confirmed the diagnosis of adrenocortical carcinoma. Further follow up by imaging study showed metastasis to liver and tumor thrombosis to vena cava. Chemotherapy and radiotherapy offered palliative effect but patient expired in spite of the aggresive approach. ACC has the reputation of poor prognosis if diagnosed in its late stage.

Conclusion

Adrenal incidentalomas are evaluated further for the detection of adrenal carcinomas. ACC, being one of the rarest, lack study of effective therapy in the later stages and the overall benefit of detection is small. The availability of imaging studies is of valuable interest in early diagnosis. Cytology and immunostains are tools for less invasive approach to diagnosis. Radical surgery is the most effective treatment if done in early stage and palliative support offer little importance. Early and accurate diagnosis is important in the management since this affects the prognosis of the disease.

References

1. Mansmann G, Lau J, Balk E, Rothberg M, Miyachi Y, Bornstein S. The Clinically Inapparent Adrenal Mass: Update in Diagnosis and Management. Endocrine Reviews. 25(2):309-340, 2004
2. Kloss RT, Gross MD, Francis IR, Korobkin M, Shapiro B. Incidentally discovered adrenal masses. Endocrine Review 16:460-484, 1995.
3. Geelhoed GW, Druy EM. Management of the adrenal "incidnetaloma." Surgery 92:866-874. 1982.
4. Dhawan SB, Aggarwal R, Mohan H, Bawa AS. Adrenocortical carcinoma: diagnosis by fine needle aspiration cytology. Indian Journal of Pathology and Microbiology: 47(1): 44-5, 2004
5. Wadih GE, Nance KV, Silverman JF. Fine-needle aspiration cytology of the adrenal gland. Fifty biopsies in 48 patients. Archives of Pathology and Laboratory Medicine: 116(8):841-6, 1992.
6. Juan Rosai. Rosai and Ackermann's Surgical Pathology. 9th edition. 2004; volume 1. Mosby Elsevier Inc. USA. pp1115-1126.
7. Sasano H, Shizawa S, Nagura H. Adrenocortical cytopathology. American Journal of Clinical Pathology. 104 (2): 161-6. 1995.
8. Sternberg S. Diagnostic Surgical Pathology. 3rd edition. 1999. Lippincott, Williams and Wilkins. Philadelphia. pp600-605.
9. Sharma S, Singh R, Verma K. Cytomorphology of adrenocortical carcinoma and comparison with renal carcinoma. Acta Cytology: 41(2):385-2, 1997.
10. Fetsch PA, Powers CN, Zakowski MF, Abati A. Anti-alpha-inhibin: marker of choice for the consistent distinction between adrenocortical carcinoma and renal cell carcinoma in the fine-needle aspiration. Cancer: 87(3): 168-72, 1999.
11. Brown ED, Semelka RC. Magnetic resonance imaging of the adrenal gland and kidney. Topics in Magnetic Resonance Imaging. 7(2): 90-101,1995.
12. Wooten MD, King DK: Adrenal cortical carcinoma: epidemiology and treatment with mitotane and a review of the literature. Cancer 72(11): 3145-3155, 1993.
13. Weiss,LM. Comparative histologic study if 43 metastasizing and nonmetastasizing adrenocortical tumors. American Journal of Surgical Pathology. 8: 163-169, 1984.

14. Weiss LM, Medeiros Lj, Vickery Jr AL. Pathologic features of prognostic significance in adrenocortical carcinoma. American Journal of Surgical Pathology. 13:202-206, 1989
15. Langer P, Bartsch D, Moebius E, Rothmund M, Nies C. Adrenocortical Carcinoma—our experience with 11 cases. Langenback Archives of Surgery. 385(6):393-7, 2000.
16. Causeret S, Monneuse O, Mabrut JY, Berger N, Peix JL. Adrenocortical carcinoma:prognostic factors for local recurrence and indications for reoperation. A report on a series of 22 series. Annals of Chir. 127(5):370-7, 2002.
17. Aiba M, Fujibayashi M. Histopathological diagnosis and prognostic factors in adrenocortical carcinoma. Endocrine Pathology. 16(1): 13-22, 2005.
18. Shoh Ch, Mladenovski V, et al. Diagnosis and Surgical treatment of adrenocortical carcinoma. A review of literature and report of two cases. Khirurgiia (Sofiia). 56(2):45-9, 2000.

Meta Analysis

The Role of Antibiotics in Coronary Artery Disease: A Meta-Analysis

Mario Victor M. Villardo, M.D.

BACKGROUND : ***Coronary artery disease (CAD) is a leading cause of mortality and morbidity worldwide. Recent studies showed that atherosclerosis is an inflammatory disease; that an infection that may cause the disease is plausible. Chlamydia pneumoniae, being an infectious agent, has been linked to be an activator of inflammation and thus may lead to atherosclerosis giving rise to coronary artery disease. This study hopes to discuss the potential role of antibiotic treatment to patients with known CAD in reducing mortality and morbidity.***

Objectives: To determine the effectiveness of administering antibiotics vs placebo in reducing cardiac events, mortality and morbidity among patients with coronary artery disease.

Search strategy: The English language randomized controlled trials were reviewed via a search in Medline, Ovid, and Proquest databases, published and reported from year 1980's up to present with the key words "antibiotics," "coronary artery disease," and "acute coronary artery disease." Likewise, cross reference was also done by doing searches on the relevant topics in the reference list of the mentioned articles.

Selection criteria: Randomized, double blinded, placebo-controlled trials on antibiotics for coronary artery disease.

Data collection : Two investigators independently assesses the selected articles for review. Odds ratio and ARR at 95% confidence interval were determined using the Review Manager.

RESULTS: Ten studies were reviewed to determine the number of patients randomized, mean follow up and end points. End points of interest like death, myocardial infarction (MI), unstable angina (UA), and stroke were included in the primary and secondary end points. The study among post-MI patients had no impact on reduction in primary end points with OR of 0.92; 95% CI, .81-1.04; ARR of 1% at a p – value of 0.18. It likewise did not have impact on reduction in the primary end points among patients with chronic/stable coronary artery disease with OR 1; 95% CI, 0.88-1.12; ARR at 0%; p value of 0.94. In acute ACS, the study did not show any reduction on primary end point (OR 0.88; 95% CI, 0.75-1.03; p value 0.11) as well as on secondary end point (OR 0.96; 95% CI, 0.72-1.28; p value 0.77).

CONCLUSIONS: This meta-analysis demonstrates that, based on evidence available, antichlamydial antibiotic therapy does not significantly improve major clinical outcomes in patients with CAD and at present cannot be recommended.

Phil Heart Center J 2005;11:53-62

Keywords: Coronary Arteriosclerosis; Pharmaceutical Preparations

Despite the use of pharmaceutical therapy against known risk factors and changes in lifestyle and behavior, cardiovascular disease remains a leading cause of death worldwide.[1] Apart from well-known risk factors such as elevated and modified low-density protein cholesterol, free radicals, hypertension, diabetes mellitus, genetic alterations, and hyperhomocysteinemia, infections caused by various microorganisms were also considered potential causes of atherosclerosis. For example, *CMV, helicobacter pylori*, and *Chlamydia pneumoniae* have been linked to the pathogenesis of atherosclerosis.[2] All these risk factors can cause endothelial injury and dysfunction, which in many studies is considered the first step in the pathogenesis of atherosclerosis.

Recently, further understanding at the molecular level revealed that atherosclerosis is an inflammatory disease; thus, an infection being linked to CAD is biologically plausible. [3] The infectious hypothesis of atherosclerosis was postulated during the latter part of the 19th century: Gilbert and Leon described fatty sclerotic change in an arterial wall of a rabbit after slight mechanical injury couple with injection of pathogenic bacteria. [4] The association of *C pneumoniae* with CAD was first noted in 1988 by Saikku et al in Finland.[5] Since then, a large body of research has shown that *C pneumonia* is associated seroepidemiologically with CAD . Small trials with antibiotics with surrogate markers as end point have also been done to study *C pneumoniae.*[6, 7, 8]

Considerable interest was generated in the possible causative role of *Chlamydia pneumoniae* in coronary artery disease (CAD) by the publication of a small pilot study in London of antibiotic treatment of CAD that reduced coronaryevents. [9] Since then, several trials have emerged analyzing the effect of treating patients with CAD and its associate complications with antibiotics that have activity against *C pneumoniae*; but results were conflicting.

Correspondence: **Mario Victor M. Villardo, MD.** Adult Cardiology Division, Philippine Heart Center, East Avenue, Quezon City, Philippines 1100

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End Points and Definitions

End point definitions were those used in the individual trials. *All-cause mortality* was death from any cause (cardiac or noncardiac). *Myocardial infarction* (MI) was defined as elevation of serum markers of myocardial injury along with electrocardiographic changes. *Unstable angina* (UA) was defined as a change in typical anginal pattern including increases in anginal frequency, intensity, or duration, with or without electrocardiographic changes, requiring hospitalization. These 3 end points were extracted from each trial. Event rates at the end of the follow-up period for each study were used for the analysis.

Rationale for Antibiotics and their mechanisms.

Four classes of antibiotics have activity against C. pneumoniae: quinolones, macrolides, tetracyclines, and antituberculars .

Macrolide antibiotics have several anti-inflammatory effects. They affect migration of inflammatory cells and production of proinflammatory mediators, cytokines, and superoxide by activated leucocytes.[10] By subduing inflammation, these antibiotics may stabilize atheromatous plaque, which may in part explain some benefits noted in the trials involving patients with ACS.

One crucial issue is whether antibiotics are bactericidal in all tissues. In one study, neither azithromycin nor rifampin inhibited *C pneumoniae* growth within monocytes. Thus, circulating monocytes carrying *C pneumoni*ae with reduced antimicrobial susceptibility could initiate reinfection or promote atherosclerosis by the release of proinflammatory mediators. [11] In contrast, actively replicating *C pneumoniae* in coronary endothelial cells and smooth muscle cells can be eliminated with quinolones (ofloxacin, levofloxacin, trovafloxacin, and moxifloxacin), macrolides (erythromycin, azithromycin, and roxithromycin), and antituberculars (rifapentine and rifampin; rifampin was the most effective drug over all). [10]

In acute coronary syndromes, macrophages elaborate metalloproteinase enzymes (eg collagenase, stromelysin, and gelatinase), which may digest structural components of the fibrous cap and predispose to plaque rupture. Tetracycline antibiotics have been shown to inhibit collagenase activity in vivo and vitro. Macrolides may possess similar qualities.[12]

Objectives : General Objectives

To determine the effectiveness of antibiotics in reducing cardiac events, mortality and morbidity among patients with coronary artery disease.

Specific Objectives

1. To determine the effectiveness of antibiotics in the reduction of primary end point among post MI patients.
2. To determine the effectiveness of antibiotics in the reduction of primary end point among patients with chronic/stable CAD.
3. To determine the effectiveness in the reduction of primary and secondary end point among patients with acute coronary syndrome.

Criteria for considering studies for this review

Types of studies: Randomized Controlled Trial

Types of participants: Patients with coronary artery disease

Types of interventions: Administration of antibiotics versus placebo

Types of outcome measures: Reduction in primary and secondary end points.

Search strategy

The English language randomized controlled trials were reviewed via a search in Medline, Ovid, and Proquest databases, published and reported from year 1980's up to present with the key words "antibiotics," "coronary artery disease," and "acute coronary artery disease." Likewise, cross reference was also done by doing searches on the relevant topics in the reference list of the mentioned articles.

Selection criteria

Randomized, double blinded, placebo-controlled trials on antibiotics for coronary artery disease.

Methods of the review

CAT form for treatment was utilized for the review of each article. Quality scale for meta-analytic review was also followed. Criteria for the validity included allocation concealment and intention to treat.

The Review Manager was used in computing for odds ratio. Confidence interval was calculated at 95% with a p value of less than 0.05 considered as statistically significant.

Results

Main results

There were thirteen studies identified in this study. Ten randomized trials published from 1990 to 2005 that met the criteria were retrieved and enrolled in this study which included 19,133 participants; of these, 9, 570 were assigned to the treatment group. Majority of the trials involved macrolide particularly Clarithromycin, Azithromycin, and Roxithromycin. Only one trial (Prove It) involved Gatifloxacin, a fluroquinolone. Different dosages were utilized in the retrieved studies. All were given in oral preparation.

1. Post MI

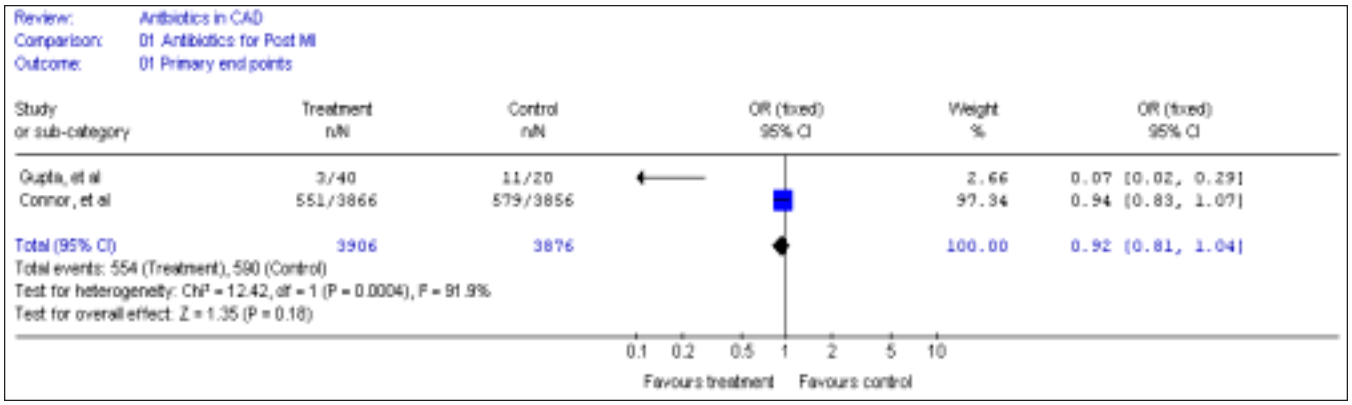

Figure 1 : Antibiotics in CAD (Post MI)

Description of studies

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	OUTCOMEMEASURES	ALLOCATIO]N CONCEALMENT
1.ACADEMIC (Anderson, et al)	RCT	150 for AZT; 152 for placebo	500 mg/day for 3 days then 500/week for 3 months	Primary composite end point (death, MI, UA, revascularization)	B
2.PROVE IT (Cannon, et al)	RCT	2076 for Gatifloxacin; 2086 for placebo	In the gatifloxacin grp, subjects receive 400 mg daily during 2 weeks ffd by 10 day course every month for the duration of the study (2 years – mean duration)	Primary composite end point (death, MI, UA, revascularization, stroke)	B
3.AZACS (Cercek, et al)	RCT	716 for AZT; 723 for placebo	500 mg on 1st day ffd by 250 mg daily for 4 days	Primary end point (Death, MI, revascularization) Secondary end points (UA)	A
4.WIZARD (O'Connor, et al)	RCT	3866 for AZT; 3856 for placebo	600 mg/day for 3 weeks then 600 mg/wk for 2-12 weeks	Primary end point (Death, MI, UA, revascularization)	A
5.ACES (Grayston, et al)	RCT	2004 for AZT; 2008 for placebo	600 mg/tab once weekly for 1 year	Primary composite end point (death, MI, UA, revascularization)	A
6.Gupta, et al	RCT	28 pts for AZT; 20 for placebo	500 mg/day for 3 days	Primary composite end point (nonfatal MI, UA, CV death)	B
7.ROXIS STUDY (Gurfinkel, et al)	RCT	102 for Roxithromycin; 100 for placebo	300 mg/day for 30 days	Primary end point (Death, MI, UA) Secondary end point (UA, death, MI)	A
8.CLARIFY (Sinisalo, et al)	RCT	74 for Clarithromycin; 74 for placebo	500 mg/day for 85 days	Primary composite end point (death, MI, UA) Secondary end point (stroke, UA, death, MI)	A
9.STAMINA (Stone, et al)	RCT	111 for AZT; 107 for placebo	500 mg/day for 3 days	Primary end point (death, MI)	A
10.ANTIBIO STUDY (Zahn, et al)	RCT	431 for Roxithromycin; 437 for placebo	300 mg/day for 6 weeks	Primary composite end point (death); Secondary end point (stroke, UA, death)	A

STUDY	INCLUSION CRITERIA	EXCLUSION CRITERIA
1.ACADEMIC	*Patients qualified for the study if they had CAD (documented by a previous MI, bypass surgery, or more than 50% angiographic stenosis of more than 1 major coronary artery), were 18 years old, had a life expectancy of more than 2 years, and gave written informed consent.	*Exclusion criteria included the ff: female capable of child bearing without adequate birth control; NYHA class 3 or 44 or LV EF <25%; MI within 5 days, bypass surgery within 4 weeks, or coronary intervention (any technique) within 3 months; planned CABG or coronary intervention; significant comorbid illness, including active malignancy, ongoing drug or alcohol abuse, renal failure requiring dialysis, and liver failure, with a projected life expectancy of < 2 years, known intolerance to azithromycin; and chronic macrolide (eg erythromycin) or tetracycline use.
2.PROVE IT	*Inclusion criteria are as follows - Participants at least 18 years old; hospitalized for ACS (either acute MI with or w/o EKG evidence of ST elevation) or high risk unstable angina; occurred within preceding 10 days.; patients have to be in stable condition and were to be enrolled after a percutaneous revascularizationprocedure if one had been planned.	*Patients were ineligible for the study if they had a coexisting condition that shortened expected survival to less than two years, were receiving therapy with any statin at a dose of 80 mg per day at the time of their index event or lipid-lowering therapy with fibric acid derivatives or niacin that could notbe discontinued before randomization, had received drugs that are strong inhibitors of cytochrome P-450 3A4 within the month before randomization or were likely to require such treatment during the study period (because atorvastatin is metabolized by this pathway), had undergone percutaneous coronary intervention within the previous six months (other than for the qualifying event) or coronary-artery bypass surgery within the previous two months or were scheduled to undergo bypass surgery in response to the index event, had factors that might prolong the QT interval, had obstructive hepatobiliary disease or other serious hepatic disease, had an unexplained elevation in the creatine kinase level that was more than three times the upper limit of normal and that was not related to myocardial infarction, or had a creatinine level of more than 2.0 mg per deciliter (176.8 ìmol per liter).
3. AZACS	*Patients were recruited from 7 centres in Europe, Israel, and the USA. Patients were eligible if they were aged 18 years or older and admitted with unstable angina or acute myocardial infarction.	*Patients were excluded if they had had a Q-wave myocardial infarction within the past 28 days of the current admission, were pregnant or breastfeeding, deemed unreliable as study participants, participating in another clinical study, had known hypersensitivity to azithromycin, erythromycin, or any macrolide antiniotic, or had other important diseases or comorbidities (terminal cancer, life-threatening infection) that could compromise the patient's safety or participation in the study.
4.WIZARD	*-pts are included with history of MI more than 6 weeks before screening; patients were enrolled at 271 centers from US, Canada, UK, Germany, France, Spain, Austria, India and Argentina	*-with history of CABG/PCI in preceeding 6 months-had chronic antibiotic therapy and had received antibiotics in the previous 3 months
5.ACES	*- 18 year old with stable coronary heart disease	*-during preceeding 3 months had MI, undergone coronary revascularization, or hospitalized for UA.; has severe cardiac disease (NYHA III to IV.); with allergy to macrolide antibiotics; with clinically significant viral/hepatic dysfunction, cancer, on going antibiotic therapy, immunosupression.
6. Elevated Chlamydia pneumoniae Ab..	*Between February 1995 and September 1995, 220 consecutive male patients attending a post-MI outpatient clinic at St. George's Hospital were enrolled. Patients were screened for serum IgG antibodies against Chlamydia pneuomoniae (Cp) by microimmunofluorescence assay with elementary bodies of Cp strain IOL-207 as test antigen.	*Patients were excluded if with chronic bronchitis, those currently taking macrolide antibiotics, and those with MI within the preceeding 6 months (to ensure resolution of immune responses caused by infarction). Also excluded were any subjects with serum that cross-reacted with Chlamydia trachomatis of Chlamydia psitticai antigens.
7. ROXIS	*Inclusion compose of patients with recent onset of angina at rest, lasting at least 10 minutes, and occurring within 48 hours	*No mention
8.CLARIFY	*Patients of either sex aged 18 to 80 years who entered the hospital with prolonged chest pain together with clearly documented ST-T wave changes indicating either UA or non-Q wave myocardial infarction were eligible for the study. Patients must have had an episode of angina within the 48 hours preceeding randomization.	*Exclusion were thrombolysis within the previous 48 hours; coronary angioplasty within 6 months or CABG within 3 months, or these procedures already planned; angina precipitated by obvious provoking factors (eg, tachycardia); ST T segment elevation (> 20 minutes); inability to interpret ST T segment changes on ECG; long QTc (>470 ms); severe renal or hepatic failure; and ongoing antibiotic therapy of any duration.
9.STAMINA	*-18 to 80 years old of either sex were recruited from the coronary care units of 4 hospitals in southwest London-patients with UA or MI	*-pts with cardiogenic shock-pts with marked renal ; with impairment ; with known systemic inflammatory condition ; with cancer and with previous antibiotic in 3 months
10. ANTIBIO STUDY	*Patients presenting with an ST elevation or non ST elevation AMI within 48 hours after symptom onset were randomized within 5 days after admission. Inclusion of patients did not depend on results of serological tests for previous infection with Chlamydia pneumoniae.	*Exclusion were participation in another study, pregnancy, lactation, allergy to roxithromycin or other macrolides, clinically relevant diseases of the liver or the CNS or other systemic diseases that could interfere with adherence to the study protocol, concomitant use of ergotamine or dihydroergotamine containing drugs, and foreseeable inability to complete the follow-up.

Two trials [9, 13] were included in this analysis which addressed the use of antibiotics in those who had myocardial infarction. Analysis was done on primary end point. This study did not show significant reduction in primary end point with OR of 0.92; 95% CI, .81-1.04; ARR of 1% at a p – value of 0.18.

Gupta et al [9] at St. George's Hospital in London performed a pilot trial that suggested a benefit with a brief course of azithromycin (3-6 days) in men who had had a myocardial infarction and had a high titer of anti-*C pneumoniae* IgG. The WIZARD (Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders) trial was the logical extension of this pilot study. It used short-term treatment with azithromycin (3 months) and at a mean of 2.5 years' follow-up found no significant effect on cardiovascular events. There appeared to be an early benefit after treatment with azithromycin in the risk of MI, but it was not sustained. [13]

The analysis proved to be heterogenous. The population in the Gupta study was not equally distributed. Comparing also with the population from the study by O'Connor et al, Gupta's group was small compared to the WIZARD study giving the study (Gupta et al) less power.

The author had no access on another trial – CROAAS (Croatian Azithromycin in Atherosclerosis Study), which analyzes the effect on cardiovascular events of approximately 3 weeks of azithromycin therapy given on 3 days to post-MI patients with 2 positive anti-*C pneumoniae* IgG titers obtained 2 months apart.

2. Antibiotics in CHRONIC/STABLE CAD

Two studies were included in the analysis. [20, 21] Total population consisted of 4,314 patients, of which 2,154 belonged to the treatment group. Death, Myocardial infarction, and unstable angina were all analyzed as end point. Present analysis showed no significant reduction in the respective end points. Death (OR 1; 95% CI, .86-1.16); Myocardial Infarction (OR 1.03; 95% CI, 0.78-1.37) and Unstable Angina (OR 0.95; 95% CI, 0.62-1.48). The over all OR is 1; 95% CI 0.88-1.03; 0% ARR at the p value of 0.94.

The study was homogenous.

In the ACADEMIC (Azithromycin in Coronary Artery disease: Elimination of Myocardial Infarction with Chlamydia) study, [20] azithromycin treatment for 3 months did not affect cardiovascular events, but at 6 months, it reduced inflammatory markers. The ACADEMIC study defined chronic CAD as previous MI, bypass surgery, or greater than 50% angiographic stenosis of one or more major coronary arteries. *C pneumoniae* titers were unchanged.

ACES (Azithromycin and Coronary Events Study) is unique in that it treated patients with azithromycin for 1 year. [21] There was no significant risk reduction in the azithromycin group as compared with the placebo group with regard to the primary end point. There was also no significant risk reduction with regard to any of the components of the primary end point, death from any cause, or stroke. The results did not differ when the participants were stratified according to sex, age, smoking status, presence or absence of diabetes mellitus, or *C pneumoniae* serologic status at baseline.

The author again had no access to another trial, the MARBLE (Might Azithromycin Reduce Bypass List Events?). The study treated patients who are awaiting bypass surgery with long term antibiotic therapy in an attempt to decrease cardiovascular events.

In summary, no large randomized controlled trials has shown a significant reduction in cardiovascular events with short - term antibiotic treatment in patients with a history of chronic CAD and positive *C pneumoniae* titers.

3. Antibiotics in Acute Coronary Syndrome – Primary end point.

Six trials were retrieved in the analysis of patients who had acute coronary syndrome. Total population consisted of 7,037, of which 3,510 belonged to the treatment group.

In terms of death, 6 were included in the analysis. The analysis showed no significant reduction in death with OR 1.08; 95% CI, 0.83-1.40; ARR of 0%.

Using MI as an end point, the study showed a trend favoring the treatment group in terms of reduction in MI with OR of 0.80; 95% CI, .65-0.98; ARR of 1%. Only the study by Cannon, et al had a larger population enrolled. In that study, the reduction in MI was not also significant. The rest of the study enrolled smaller group of population giving the respective studies less power.

In reduction of events in UA, 2 studies were enrolled. Again, the analysis showed no reduction in the end point with OR of 0.58; 95% CI, 0.26-1.26; ARR of 4%.

In combining the composite end point, the OR was only at 0.88; 95% CI, 0.75-1.03 at a p value of 0.11. Again, the analysis did not show reduction in composite primary end point. The study also proved to be homogenous.

4.Antibiotics in Acute Coronary Syndrome – Secondary end point

Secondary end points were measured in several studies. [15, 17, 18] The rest of the trials were not included since they [14, 16, 19] used surrogate markers as end points.

4.1. Stroke.

The Analysis showed no reduction in stroke events between the treatment and control group with the OR of 0.82; 95% CI , 0.34-2.01; ARR of 1%.

4.2. Myocardial Infarction.

In terms of reduction in incidence of MI, the 2 studies showed benefit favoring the treatment group with OR of 0.29; 95% CI, 0.11-0.81; ARR of 8%. However the population in the two groups were very small.

4.3. Unstable Angina.

In this end point, the present analysis again showed no

significant reduction in the event with OR of 1.12; 95% CI, 0.80-1.57. The analysis showed a trend favoring more the control group. The studies by Gurfenkel and Sanisilo showed reduction but it was off-set by the study by Zahn, et al.

4.4. Death.

Only two studies were enrolled proving no significant reduction in terms of death with OR of 1.19, 95% CI, 0.34-1.74; ARR of 0%. The study in secondary end point was homogenous.

The small ROXIS (Randomized Trial of Roxithromycin in Non-Q-Wave Coronary Syndromes) pilot trial suggested a possible benefit of roxithromycin in patients with non-Q-wave coronary syndromes.

The small single-center study at Siriraj Hospital in Bangkok used the same protocol as ROXIS and found no significant difference in events at 90 days.[18] Again, the author was not able to retrieve this study.

The AZACS (Azithromycin in Acute Coronary Syndromes) trial enrolled 1,439 patients (74% men) shortly after admission for acute coronary syndrome. [16] After a brief course of azithromycin vs placebo, no significant difference was noted in composite primary end point (death, cardiac arrest, nonfatal MI, and revascularization) or in any of its components. Also, there was no difference in rates of end points in patients enrolled with acute MI or with antibodies to *C pneumoniae.*

CLARIFY (Clarithromycin in Acute Coronary Syndrome patients in Finland) treated patients with non-Q-wave MI or unstable angina with clarithromycin or placebo for 85 days and found a trend toward reduced primary end point events (death, MI, or unstable angina) at 3 months. When all cardiovascular events were included (secondary end point), there was a significant reduction in events, beginning at the 3-month period and continuing until about 10 months, then remaining approximately the same thereafter.

Compared to ROXIS, CLARIFY had more patients with first time angina and fewer patients with previous MI or revascularization; however, the patient's condition was more unstable, with the number of events during the first 3 months in the placebo groups being higher. CLARIFY suggests that the beneficial effect starts during the treatment phase (3 months) and continues for at least another7 months.

In STAMINA (South Thames Trial of Antibiotics in Myocardial Infarction and Unstable Angina), the antibiotics selected were aimed at controlling infection of both *C pneumonia and H pylori.* The surprising finding in this small study was that the antibiotics produced beneficial effects whether or not the patient was a carrier of one or both infections. This suggests that the antibiotics may be working either against a different infection or in an alternative manner.

PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) is a well-powered study examining long term use of gatifloxacin in patients presenting with an acute coronary syndrome and elevated cholesterol levels. They have found out that despite long-term treatment with a bactericidal antibiotic effective against *C. pneuomoniae,* there was no reduction in the rate of cardiovascular events observed..

Two small trials showed benefit on total cardiovascular events, (ROXIS, CLARIFY); one small pilot trials showed a decrease in events with several triple therapeutic antibiotic regimens (STAMINA).

All in all, the study showed no reduction in secondary end points.

Period of Antibiotic Treatment Too Brief

The main reason that the previously mentioned studies did not extend azithromycin therapy beyond a few months is that safety and efficacy data on long-term treatment are lacking. Long-term administration may be required to exert chronic anti-C *pneumoniae*, anti-inflammatory, or other effects beneficial to plaque remodelling and stabilization. This may be analogous to the anti-inflammatory effects of statins, which lead to greater divergence of treatment and placebo event curves over the long term.

AZACS used treatment for only 5 days, and patients in WIZARD received azithromycin once weekly for 3 months; neither trial showed a significant cardiovascular effect. In WIZARD, a secondary analysis at 6 months showed a significant reduction of 33% in the secondary end point of death or MI.

Thus, AZACS and WIZARD support an early benefit after treatment in the risk of MI and a possible waning of effect once the active treatment is discontinued. In the small ROXIS pilot trial (treatment period 1 month), there was a decrease in the triple and point at 1 month which became nonsignificant as time advanced after the last antibiotic dose. In addition, reinfection by *C pneumoniae* (eg from peripheral monocytes containing viable *C pneumoniae*) during the antibiotic-free follow-up period may have led to further infection, inflammation, and instability of the plaque by *C pneumoniae* and thus excess cardiac events.

CLARIFY supports the notion that benefits occur during the treatment phase, which was longer than that in ROXIS (3 months vs 1 month), but also for several months after the treatment phase is completed.

After 3 months of treatment in ACADEMIC (a small trial), there was no significant effect on cardiovascular primary end point; however, there was a significant improvement in inflammatory markers at 6 months but not at 3 months. This suggests that a longer duration of treatment may result in greater anti-inflammatory effects; there may also be a lag effect of antibiotic treatment on subsequent inflammation.

Two trials are treating patients with antibiotics for a longer period: 1 year of azithromycin (a macrolide) in ACES and 2 years of gatifloxacin (a quinolone) in PROVE IT. To reiterate, despite the long-term treatment, there was no reduction in cardiovascular events in these two studies.

Reviewers' conclusions

This meta-analysis demonstrates that, based on evidence available, antichlamydial antibiotic therapy does not significantly improve major clinical outcomes in patients with CAD and at present cannot be recommended.

Implications for practice/ research.

The author hopes that the issue regarding the utility of antibiotics in patients with CAD will finally put into rest. Although there is also a limitation on this meta-analysis. Only macrolides and a fluoroquinolone were used in these studies, so the effect of treatment of additional pathogens that may be involved in atherosclerosis [22, 23, 24] but are not in the spectrum of activity of these drugs was not evaluated.

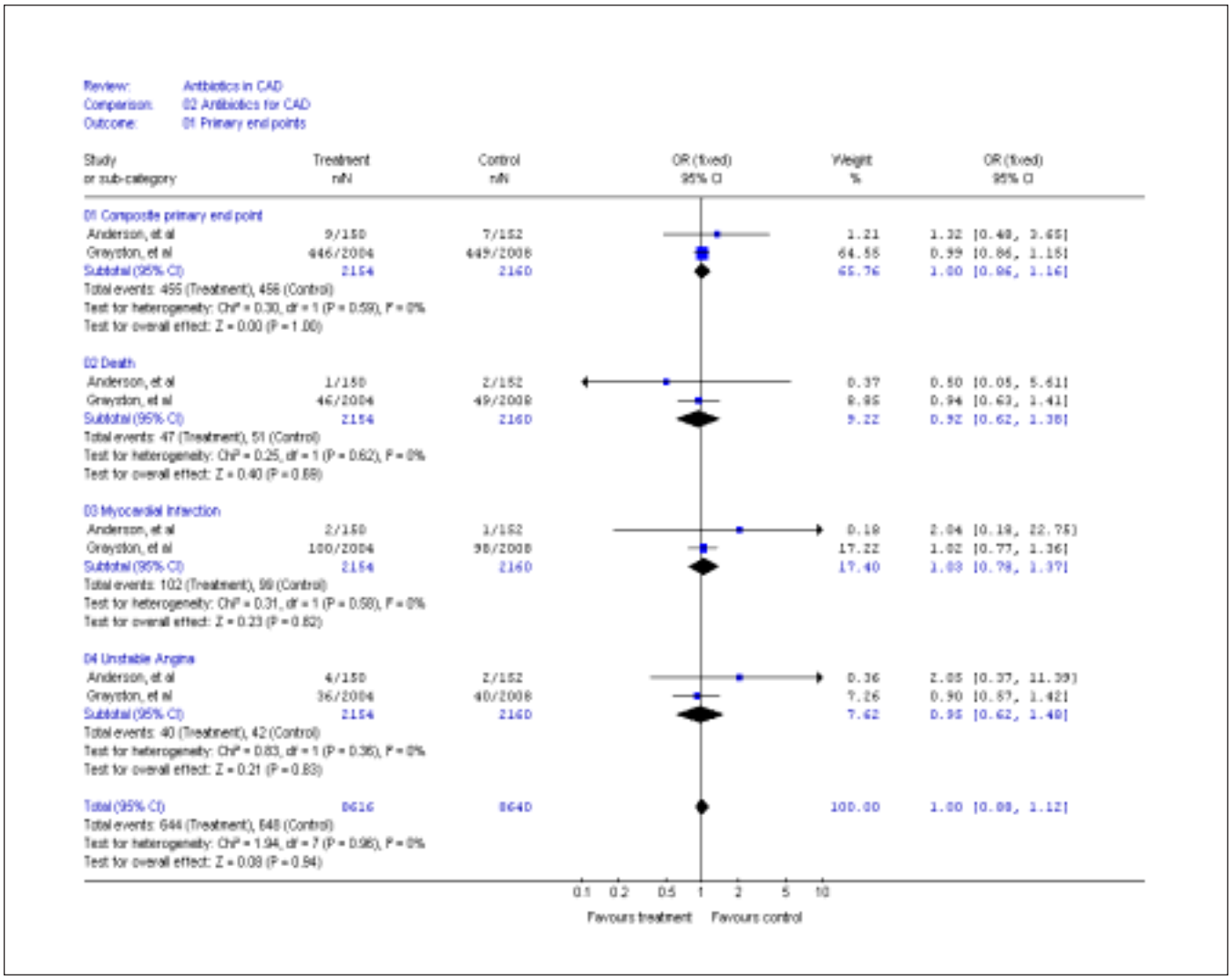

Figure 2 : Antibiotics in CAD (Chronic/Stable)

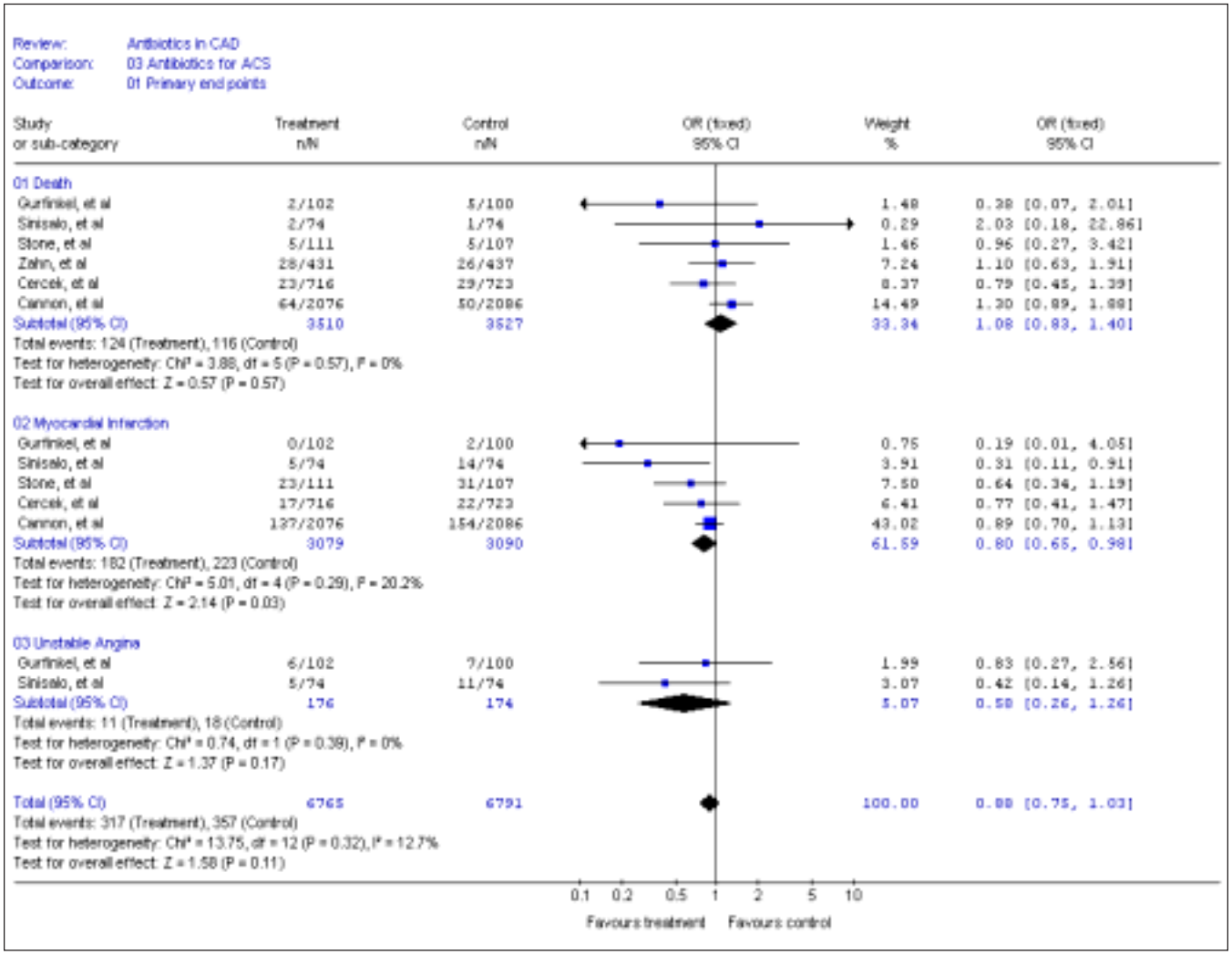

Figure 3 : Antibiotics for Acute Coronary Syndrome – Primary End Point

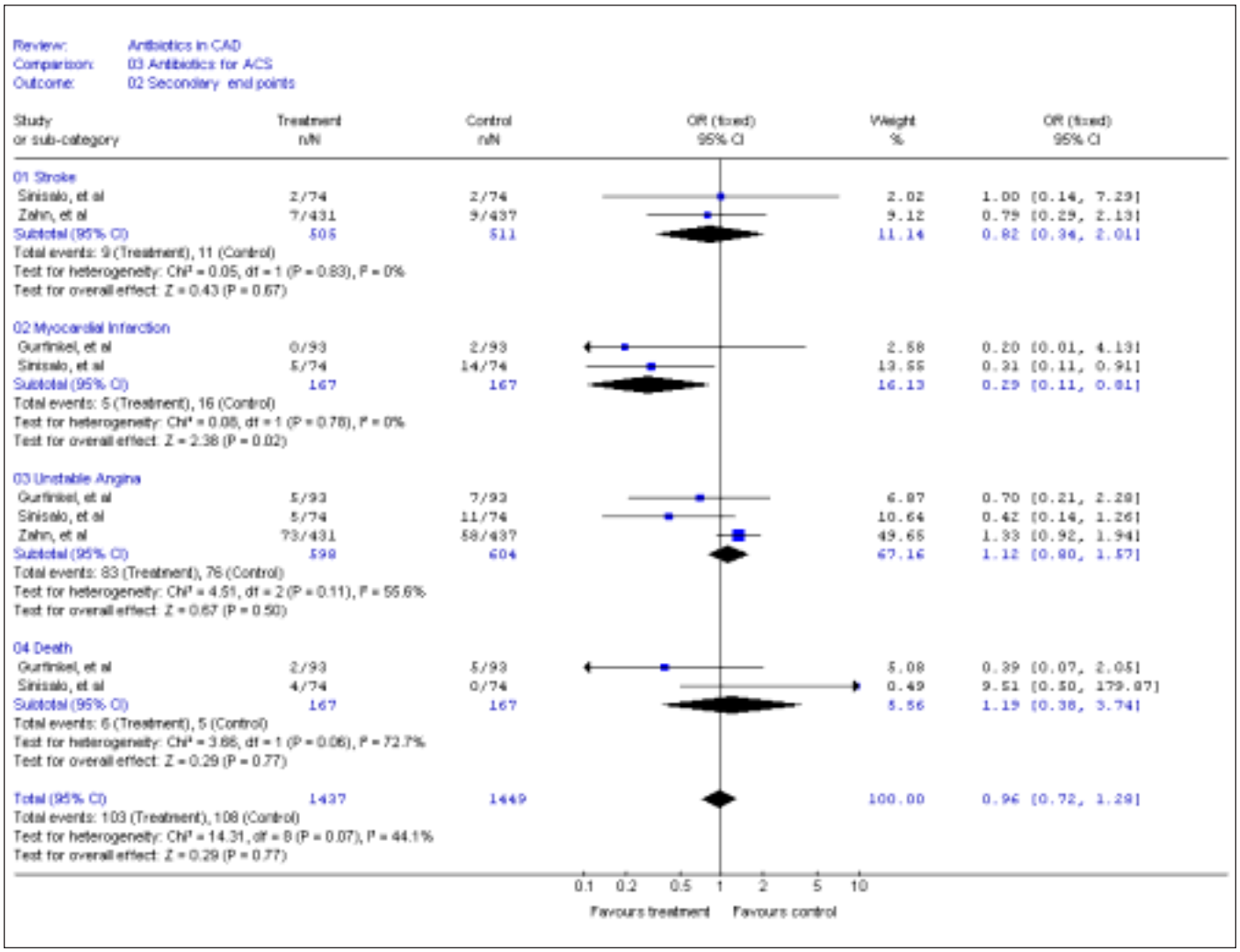

Figure 4 : Antibiotics in ACS – Secondary End Point

References

1. Braunwald, E. Shattuck lecture – cardiovascular medicine at the turn of the Mellinium; triumphs, concerns, and opportunities. NEJM 1997;37:1360-1369.
2. Danesh, JR et al. Chronic infections and coronary heart disease: is there a link? Lancet 1997;350:430-436.
   Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. Circ 2001;104:365-372.
3. Higgins, J. Mayo Clinic Proc 2003;78:321-332.
   Saikku P, et al. Serologic evidence of an association of a novel *Chlamydia* , TWAR, with chronic coronary heart disease and acute myocardial infarction. Lancet 1988;2:983-986.
4. Sander D, et al. Progression of early carotid atherosclerosis is only temporarily reduced after antibiotic treatment of *Chlamydia pneumoniae* seropositivity . Circ 2004;109:1010-1015.
5. Jackson L et al. Safety and effect on anti-Chlamydia pneumonia antibody titres f 1 month course of daily azithromycin in adults with coronary artery disease. J Antimicrob Chemo 1999;44, 411-414.
6. Berg H, et al. Effect of Clarithromycin on Inflammatory Markers in Patients with Atherosclerosis. Clinic Diag Lab Immuno 2003,July:525-528.
7. Gupta S, et al. Elevated *Chlamydia pneumoniae* antibodies, cardiovascular events, and azithromycin in male survivors of myocardial infarction. Circ 1997; 96:404-407.
8. Parchure N, et al. Effect of azithromycin treatment on endothelial function in patients with coronary artery disease and evidence of *Chlamydia pneumoniae* infection. Circ 2002;105:1298-1303.
9. Gieffers J, et al. Chlamydia pneumonia infection in circulating human monocytes is refractory to antibiotic treatment. Circ 2001;103:351-356.
   Vaughen CJ, et al. Chronic infections and coronary heart disease. Lancet. 1997;350:1029-1030.
10 O'Connor C, et al. Azithromycin for the Secondary Prevention of Coronary Heart Disease Events . The WIZARD Study. JAMA 2003;290:1459-1466.
11. Stone A, et al. Effect of Treatment for *Chlamydia pneumoniae and Helicobacter pylori* on Markers of Inflammmation and Cardiac Events in Patients with Acute Coronary Synddromes. South Thames Trial of Antibiotics in Myocardial Infarction and Unstable Angina (STAMINA). Circ 2002;106:1219-1223.
12. Zahn R, et al. Antibiotic Therapy After Acute Myocardial Infarction. A prospective Randomzed Study. (ANTIBIO STUDY) Circ 2003;107:1253-1259.
13. Cercek B, et al. Effect of short-term treatment with Azithromycin on recurrent ishcaemic events in patients with acute coronary syndrome in the Azithromycin in Acute Coronary Syndrome (AZACS) trial: a randomized controlled trial. Lancet 2003; 361:809-813.
14. Sinisalo J, et al. Effect of 3 Months of Antimcrobial Treatment With Clarithromycin in Acute Non-Q wave Coronary Syndrome. (CLARIFY). Circ 2002;105:1555-1560.
15. Gurfinkel E, et al. Treatment with the antibiotic roxithromycin in patients with acute non-Q wave coronary syndromes. The final report of the ROXIS study. Eur Heart J 1999;20: 121-127.
16. Cannon C, et al. Antibiotic treatment of Chlamydia pneumoniae after Acute Coronary Syndrome. (PROVE IT) NEJM 2005; 352: 1646-1654.
17. Anderson JL, et al. Randomzed Secondary Prevention Trial of Azithromycin in Patients with Coronary Artery Disease and Serological Evidence for *Chlamydia pneumoniae* Infection. The Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamydia (ACADEMIC) Study. Circ 1999;99:1540-1547.
18. Grayston JT, et al. Azithromycin for the Secondary Prevention of Coronary Events (ACES). NEJM 2005; 352: 1637-1645.
19. Grahame-Clarke C, Chan NN, Andrew D, et al. Human *cytomegalovirus* seropositivity is associated with impaired vascular function. Circ 2003;108:678-683.
20. Li L, Messas E, Batista EL Jr, et al. *Porphyromonas gingivalis* infection accelerates the progression of atherosclerosis in a heterozygous apolipoprotein E deficient murine model. Circ 2002;105:861-867.
21. Alber DG, Powell KL, Vallance P, et al. Herpesvirus infection accelerates atherosclerosis in the apolipoprotein E-deficient mouse. Circ 2000;102:779-785.

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

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

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

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

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

Figures

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

Legends

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

Tables

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

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