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Editorial

Original Articles

Official Publication of the Philippine Heart Center

PUSO iNFOCUS

Cardiovascular Update Series

PIERCE REGISTRY

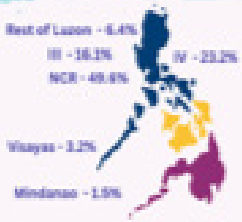
Philippine IntERventional Cardiovascular Endpoints Registry

Demographic Characteristics

7 out of 10 are males

Mean age is 59 years old

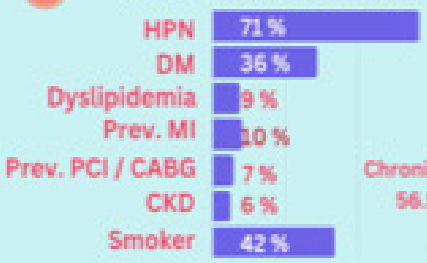
transferred from other hospitals



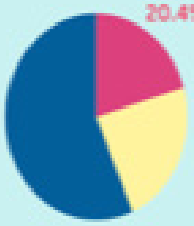
~50% of patients came from NCR

Clinical Characteristics (n= 1953)

Co-morbidities / Risk Factor



Indication for procedure



53 min. Door to balloon

56 min. Door to wire

Procedural/ Angiographic Characteristics (n= 1953)

- Access ~75% radial
- Average dye volume 35 ml
- Average radiation dose 741 mgy

- 47% have multivessel CAD
- 94% are Type B lesion
- 95% are Right Dominant
- 4% have Left Main Involvement
- 52% have lesions involving LAD
- 25% have reduced EF (<40%)

- 100% use of Drug-eluting stent (DES) for PCI
- 83 % use Everolimus
- Mean stent length: 29.7 mm
- Mean stent diameter: 3.0 mm

Outcome Data (n= 1953)

- Periprocedural MI- 0.72%

Adverse Event

Mortality Rate: 5.12% (ACS)

Renal Failure requiring Dialysis: 2.2%

Stroke- 0.3%

- Major Bleeding 0.05%

References:
PIERCE Registry as of May 31, 2023

CVRRSS

Philippine Heart Center

EDITORS AND CONSULTANTS

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Editorial

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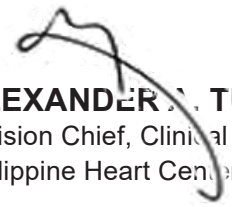

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Philippine Heart Center

Normal Weight Central Obesity Among Filipinos and Its Association with Cardiovascular Risks: a cross sectional study

Bryan Rene F. Toledano, MD; Emily Mae L. Yap, MD; Gerald C. Vilela, MD; James Ho, MD

Introduction **---** This is the first study conducted that explores the prevalence and association of normal weight central obesity (NWCO), cardiovascular risk among Filipinos.

Method **---** The participants were Filipinos age 20 years old above who had participated and completed the desired data in the National Nutrition Survey II. The participants were categorized into the following eight groups: normal weight (BMI 18.5–24.9 kg/m^2) and no central obesity (NW); normal weight with central obesity (WC ≥ 80cm or WHR ≥ 0.85 for females, WC ≥ 90cm or WHR ≥ 0.90 for males) (NWCO); overweight (BMI ≥25-29.9kg/m^2) (OW); overweight with central obesity (OWCO); obese (BMI ≥30kg/m^2) (OB) and obese with central obesity (OBCO). A Binary logistic regression was utilized to determine the odds ratio (OR) and 95% confidence intervals (CI) for hypertension, diabetes, and dyslipidemia.

Result **---** A total of 5,920 participants (2,883 men and 3,037 women) were analyzed. The prevalence of NWCO was 39.3%. In comparison to NW, the ORs for hypertension (OR=1.84, 95% CI, 1.58-2.1, p=.001), diabetes (OR=2.1, 95% CI 1.5-3.0, p=.001), dyslipidemia (OR=1.3, 95% CI 1.1-1.5, p=.002), in OBCO for hypertension (OR=2.2, 95% CI 1.7,2.8, p<.001), diabetes (OR 2.7, 95% CI 1.8,3.9, p<.001) and in OWCO hypertension (OR=1.65, 95% CI 1.43-1.9, p=.001), diabetes (OR=1.58, 95% CI 1.2-2.0, p=.001), dyslipidemia (OR 1.28, 95% CI 1.1-1.5, p=.004) were significantly higher in NWCO.

Discussion **---** A strategic approach of proper diet and exercise to prevent central obesity as measured by WC or WHR and to increase lean muscle mass to prevent NWCO may decrease cardiovascular risks.

Conclusion **---** NWCO is a common finding among Filipinos and is associated with more CVD risks such as hypertension, diabetes, and dyslipidemia in comparison with obese and overweight with or without central obesity. ***Phil Heart Center J 2022;25(2):1-10.***

Key Words: ■ Normal weight central obesity (NWCO) ■ cardiovascular risk

Obesity is a modifiable risk factor that is defined as excess body fat associated with increased morbidity and mortality.[1] It is a public health problem that needs attention and early identification. There have been several efforts to measure obesity and its application to screening large populations. The most widely used are body mass index and central obesity. Traditionally the correlation is positive, the higher the BMI and CO the greater the risk of cardiovascular disease and death.[2-6] In the Philippines, the prevalence is rising and it is now considered endemic. According to the study done by Sy. et al, obesity among Filipinos had a prevalence of 4.9% when measured by BMI while CO is 10.2% in men and 65.6% in women when measured by the waist-hip ratio (WHR).[2] However conflicting data had emerged showing that some overweight or obese patients have lower cardiovascular risk while others with normal BMI have increased risk.[7,8] This was partly explained by the concept of normal weight central obesity (NWCO), in which certain ethnicity like Asians tend to have increased fat mass compared to low lean mass with the same BMI and central obesity being a better predictor for cardiovascular risk factors.[9,10] In light of this, many countries have done prevalence studies regarding normal body weight as measured by BMI together with CO measured by waist circumference, waist to hip ratio or waist to height ratio

2nd place, Oral Presentation - Original Paper. 29th PHC Annual Research Paper Competition and Poster Presentation held on February 24, 2021 at Philippine Heart Center. Correspondence *to* ***Dr. Bryan Rene F. Toledano.*** Division of Adult Cardiology. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication** ISSN 0018-9034

to raise awareness regarding its higher association with hypertension, diabetes, dyslipidemia, and coronary artery disease compared to normal weight with no central obesity or overweight and obese with or without central obesity.[11-15] Aside from these, new studies have found that NWCO confers the highest long-term risk of major adverse clinical events and mortality especially in patients with hypertension and coronary artery disease.[16-19]

The study aims to measure the prevalence of normal-weight central obesity, its association with cardiovascular risk and disease among adults in the Philippines. The information would be useful to raise awareness and plan potential interventions.

METHODS

We conducted a cross-sectional study using the data from the National Nutrition and Health Survey in 2008 (NNHeS II). It was obtained from the Department of Science and Technology - Food and Nutrition Research Institute (DOST-FNRI) as agreed upon by Memorandum of Understanding. The NNHeS II employed a stratified multi-stage sampling that covered the entire Philippine population of adults aged 20 years old and above. The data requested are measures of blood pressure, anthropometrics of height, weight, waist circumference (WC), WHR, BMI, the medical information of cardiovascular diseases of hypertension, diabetes, dyslipidemia, coronary artery disease, cerebrovascular disease and peripheral arterial. The participants with complete data as stated were used, categorized and analyzed. This study has been approved by the Institutional Ethical Review Board of the Philippine Heart Center. A detailed description of the survey design and procedures has been published last 2012.[6]

Operational definitions

1. *Body mass index* – calculated as the weight in kilograms divided by the square of the height in meters, categories are: underweight (<18.5kg.m^2), normal (18.5 - 24.9 kg/m^2), overweight (25 - 29.9kg/m^2), obese (>/= 30kg/m^2).[6]
2. *Hypertension* - systolic BP (SBP) of 140 mmHg or higher, diastolic BP (DBP) of 90 mmHg or higher (19) using the mean of 3 measurements during a single visit, a previous diagnosis of hypertension, or use of antihypertensive medication.[6]
3. *Diabetes Mellitus* - fasting plasma glucose level of 7.0 mmol/L (126 mg/dL) or higher, or higher, or a history of diabetes, with or without the use of oral antihyperglycemic medication or insulin.[6]
4. *Dyslipidemia* – any abnormalities from the lipid profile as high total cholesterol >/=6.20 mmol/L (240 mg/dL), high LDL-C >/=4.14 mmol/L (160 mg/dL), high TG and >/=2.26 mmol/L (200 mg/dL), Low HDL-C </= 1.03 mmol/L (40 mg/dL) (20), with or without the use of anti dyslipidemia medications.[6]
5. *Coronary artery disease (CAD)* – previous heart attack, or documented ischemia or coronary artery occlusive disease diagnosed by a medical doctor or nurse.[6]
6. *Cerebrovascular accident (CVA)* – previous stroke or transient ischemic attack diagnosed by a medical doctor or nurse.[6]
7. *Peripheral arterial disease (PAD)* – previously diagnosed occlusive disease by a medical doctor or nurse.[6]
8. *Waist circumference* - measured at the midpoint between the lowest rib and the iliac crest by a field worker with comprehensive training.[6]
9. *Hip circumference* - measured at the greater trochanter or widest diameter of the hips by a field worker with comprehensive training.[6]
10. *Central Obesity* – waist-hip ratio (WHR) >/= 0.85 women, >/= 0.90 men or waist circum ference (WC) >/= 80 women and >/= 90.[21]
11. *Cardiovascular risks and diseases* – current smoker, hypertension, diabetes, dyslipidemia, coronary artery disease, cerebrovascular disease, and peripheral arterial disease.

Data organization, editing, processing, and analysis

The data obtained were checked for completeness and categorized into 8 subtypes using Microsoft Excel (version 16.30): 1. Under weight (UW), 2. Underweight with central obesity (UWCO), 3. Normal weight (NW),

4. NWCO, 5. Overweight (OW), 6. Overweight with central obesity (OWCO), 7. Obese (OB) and 8. Obese with central obesity (OBCO). The rechecking of data was done two times to ensure correctness and validity.

Statistical Analysis: All analyses were performed using the Statistical Package for the Social Sciences (version 20, with license) and MEDCALC version 10 (with license). The univariate analysis includes independent samples *T*-test for continuous variables and Chi-Square for categorical outcomes. Binary logistic regression using forward technique was utilized to determine the significant correlates for each risk factor/cardiovascular outcome. Odds ratios above 1, with p-values less than 05 indicated an association with the outcome. Adjustment for potential confounding variables was done using the Mantel-Haenszel test. Mean differences were determined using an independent T-test between obesity categories. Precision estimates were pegged at 95% confidence level.

RESULTS

The analysis included a total of 5,920 adult individuals with desired variables as screened from the National Nutrition and Health Survey II. Their baseline clinical characteristics are summarized. (*Table 1*). The mean age was 43.5 (± 15.2) years, with slight female predominance (51.3% versus 48.7%). As to body mass index classification, 11.6% were categorized as underweight, 62.7% as normal, 21.1% as overweight and 4.7% as obese.

The occurrence of central obesity across the BMI categories is also depicted. (*See also Table-2*) The average values for height, weight, systolic and diastolic pressures, lipid profile (HDL, LDL, and triglycerides) are recorded.

Among the cardiovascular disease risk and factors, dyslipidemia was present in 73.7%, followed by hypertension (34.8%), diabetes (6.3%), coronary artery disease (1.2%), peripheral arterial occlusive disease (1.2%) and cerebrovascular disease (1.0%). Current

Table 1. Baseline Clinical Characteristics of Adults Screened in the NNHES II, 2008

Characteristic	N	%
Mean Age (SD)	43.5 1	15.2
Sex		
Male	2,883	48.7
Female	3,037	51.3
BMI Classification		
Underweight	684	11.6
Normal	3,710	62.7
Overweight	1,247	21.1
Obese	279	4.7
Central Obesity		
With	3,973	67.1
Without	1,947	32.9
Mean Weight in kg (SD)	54.7	11.4
Mean Height in cm (SD)	157.8	40.8
Mean Waist circumference (SD)	77.9	17.9
Mean Hip circumference (SD)	86.7	8.1
Mean Waist-Hip ratio (SD)	0.89	.06
Mean SBP (SD	123	20.8
Mean DBP (SD)	79.7	12.3
Mean FBS (SD)	86.9	32.1
Mean HDL (SD)	40	6.8
Mean LDL (SD)	117.2	43.2
Triglyceride	141.1	82.4
Cardiovascular disease		
Dyslipidemia	4,365	73.7
Hypertension	2,062	34.8
Diabetes	375	6.3
Coronary artery disease	72	1.2
Peripheral arterial disease	68	1.2
Cerebrovascular accident	62	1.0
Current Smoking history	1,831	31.5

Table 2. Overall Prevalence of Central Obesity Across BMI Categories, NNHES II, 2008

BMI Category	Central Obesity		No Central Obesity		Total
	N	%	N	%	
Underweight	206	30.1	478	69.9	684
Normal	2,325	62.7	1,385	37.3	3,710
Overweight	1,163	93.3	84	6.7	1,247
Obese	276	98.9	3	1.1	279
Total	3,970	67.1*	1,950	32.9	5,920

*Overall prevalence, Chi value=819, p<.001, Percentages reflect horizontal sum

smokers at the time of the study were reported in 31.5%.

The prevalence of central obesity (regardless of BMI category) was 67.1% (3,973 out of 5,920) while the prevalence of normal weight central obesity in this study was 39.2% (or 2,325 out of 5920). Those who were obese had the highest prevalence of central obesity (98.9%) followed by those who were overweight (93.3%). The prevalence of central weight obesity among those with "normal BMI" is 62.7% (2,325 out of 3,710) which was statistically higher among those were underweight (30.1%) (p<.001) (*Table 2*)

Across All BMI Categories:

Table 3 displays the overall comparison of risk factors and cardiovascular conditions among those with and without central obesity across all BMI categories. Adjusting for age and sex, those with central obesity were at high risk for hypertension (OR 2.1, 95% CI 1.8,2.3, p<.001), thrice the risk for diabetes (OR 2.6, 95% CI 1.9-3.4, p<.001) and almost twice the risk for dyslipidemia (OR 1.45, 95% CI 1.2-1.6, p<.001)

Underweight Category:

Patients classified as "underweight" and who have central obesity, is not significantly different compared to those underweight without central obesity in terms of the occurrence of coronary artery disease, cerebrovascular accidents, peripheral arterial occlusive disease, hypertension, diabetes, dyslipidemia, and smoking. (*Table 4*)

The mean levels for systolic and diastolic BP, FBS, and lipids likewise were not statistically different among those with and without central obesity. (all p-values above .05)

Normal Weight Category:

Those with normal weight and with central obesity were at higher risk for hypertension (OR=1.84, 95% CI, 1.58-2.1, p=.001) as evident by a statistically higher mean difference in systolic and diastolic BP; a higher risk for diabetes (OR=2.1, 95% CI 1.5-3.0, p=.001); higher risk for dyslipidemia (OR=1.3, 95% CI 1.1-1.5, p=.002) as evident by a statistically higher mean LDL and triglyceride fraction when compared to those who had normal weight but without central obesity. (*Table 5*)

Overweight Category:

Those who were overweight and had central obesity had twice the risk for hypertension when compared to their counterparts without central obesity (OR1.93, 95% CI 1.2-3.1, p=.006) as evidenced by a statistically higher mean difference in systolic and diastolic pressure (p=.009, p=.007 respectively). Although the risk for diabetes was insignificant, even if the mean fasting glucose was higher in OWCO (mean difference =10.1, 95% CI 1.4-18.7, p=.022).(*Table 6*)

Normal Weight Central Obesity versus Obese with Central Obesity:

After adjusting for age and sex, adults with normal weight central obesity had a two-fold risk of hypertension (OR=2.2, 95% CI 1.7,2.8, p<.001), almost thrice the risk for diabetes (OR 2.7, 95% CI 1.8,3.9, p<.001). Although there was no difference in the risk for dyslipidemia, the mean difference for LDL and triglycerides among those with normal weight central obesity were significantly lower compared to the obese category with central obesity. Mean values for FBS, systolic and diastolic pressures were statistically lower in the normal weight central obesity group. (all p-values <.001)

Normal Weight Central Obesity versus Overweight Central Obesity:

When compared to those who were overweight with central obesity, patients who were with normal weight and centrally obese had almost twice the risk of hypertension (OR= 1.65, 95% CI 1.43-1.9, p=.001) and diabetes (OR=1.58, 95% CI 1.2-2.0, p=.001) were dyslipidemia (OR 1.28, 95% CI 1.1-1.5, p=.004). It is noted that levels for SBP, DBP, and FBS, LDL and triglycerides were statistically higher for those in the overweight category than those with normal weight. (*Table 7*)

There was no observable higher risk for coronary artery disease (CAD), cerebrovascular disease CVD) and peripheral arterial disease between the two types of central obesity.

Normal Weight Central Obesity versus Underweight Central Obesity

When compared to adults who are underweight with central obesity, those with normal weight central obesity had a much lower risk for hypertension (OR=0.54, 95% CI 0.39-0.76, p=.001) and dyslipidemia (OR=0.55, 95% CI 0.41-0.74, p=.001). They were associated with slightly higher mean levels of systolic and diastolic pressure, HDL, LDL, and triglycerides when compared to those who were underweight. (*Table 8*)

Table 3. Univariate Analysis of Cardiovascular Risk & Diseases in Persons with and Without Central Obesity Across All BMI Categories, NNHES II, 2008

Characteristic	Central Obesity	No Central Obesity	OR/ Mean difference	95% CI	p-value
Total Patients	N=3,973 (%)	N=1,947 (%)			
Coronary artery disease	56 (77.8)	16 (22.2)	1.76	0.98 - 3.01	.055
Cerebrovascular accident	46 (74.2)	16 (25.8)	1.4	0.79 - 2.5	.23
Peripheral arterial disease	45 (66.2)	23 (33.8)	0.95	0.57 - 1.58	.95
Hypertension	1587 (77)	475 (23)	2.1	1.8-2.3	.001*
Diabetes	313 (83.5)	62 (16.5)	2.6	1.9-3.4	.001*
Dyslipidemia	3,027(69.3)	1,338(30.7)	1.45	1.2-1.6	.001*
Smoking	1,118 (61)	713 (39)	0.67	0.44 – 3.4	.43
SBP (Mean ± SD)	119.7	119.8	.01	3.62-	.99
DBP (Mean ± SD)	(21.6)	(22.5)	1.0	3.66	.29
FBS (Mean ± SD)	76 (10)	77 (12)	.74	.89-2.9	.73
HDL (Mean ± SD)	81.9 (24)	82.7 (27)	.35	.35 -5.0	.57
LDL (Mean ± SD)	40.8	41.1	.33	.62 – .87	.89
Triglyceride (Mean ± SD)	107 (28) 111 (53)	108 (31) 111 (41)	.17	.26 – 5.3 0.02- 4.3	.96

⁺OR- Odds ratio adjusted for age and sex, *Significant if p-value is <.05, %-reflect horizontal sum

Table 4. Univariate Analysis of Cardiovascular Risk & Diseases in Persons With and Without Central Obesity Across All BMI Categories, NNHES II, 2008

Characteristic	Central Obesity	No Central Obesity	OR/ ⁺ Mean difference	95% CI	p-value
Total Patients	N=206 (%)	N=478 (%)			
Coronary artery disease	4 (50)	4 (50)	2.34	0.58-9.4	.23
Cerebrovascular accident	0	5 (100)	--	--	--
Peripheral arterial disease	3 (25)	9 (75)	0.77	.21-2.8	.69
Hypertension	48 (27.3)	128 (72.7)	0.83	.56-1.2 .	.34
Diabetes	8 (36.4)	14 (63.6)	1.34	.55-3.2	.52
Dyslipidemia	129 (30)	301 (70)	.98	.70-1.38	.70
Smoking	72 (28.8)	178 (71.2)	0.90	0.34-8.7	.12
SBP (Mean ± SD)	119.7(21)	119.7 (22)	.017	-3.6 – 3.6	.99
DBP (Mean ± SD)	76 (10)	77 (12)	1.02	.89-2.9	.29
FBS (Mean ± SD)	82 (24)	83 (26)	0.74	.35-5.0	.73
HDL (Mean ± SD)	40 (7.4)	41 (7.5)	0.35	.87-1.5	.57
LDL (Mean ± SD)	107 (28)	108 (31)	0.33	-4.6 – 5.3	.89
Triglyceride (Mean ± SD)	111.2 (53)	111 (41)	0.17	-7.6 – 8.3	.96

⁺OR- Odds ratio adjusted for age and sex, *Significant if p-value is <.05, %-reflect horizontal sum, -- Empty cells indicate HR calculation is not possible because of categories

Table 5. Univariate Analysis of Cardiovascular Risk & Diseases Among Normal Weight Adults With and Without Central Obesity, NNHES II, 2008

Characteristic	Central Obesity	No Central Obesity	OR/ + Mean difference	95% CI	p-value
Total Patients	N=2,325 (%)	N=1,385 (%)			
Coronary artery disease	30 (71.4)	12 (28.6)	1.49	.76 – 2.9	.24
Cerebrovascular accident	30 (76.9)	9 (23.1)	1.9	0.94-4.2	.07
Peripheral arterial disease	24 (64.9)	13 (35.1)	1.01	0.55-2.1	.78
Hypertension	829 (72.1)	320 (27.9)	1.84	1.58 – 2.1	.001*
Diabetes	148 (77.5)	43 (2.5)	2.1	1.5-3.0	.001*
Dyslipidemia	1749 (64.2)	977 (35.8)	1.3	1.1-1.5	.002*
Smoking	730 (63.2)	391 (36.8)	1.02	.76 - 4.33	.12
SBP (Mean ± SD)	123 (20)	120 (19)	3.3	1.8-4.4	.001*
DBP (Mean ± SD)	79 (12.3)	77 (11.1)	2.6	1.8 -3.4	.001*
FBS (Mean ± SD)	87.4 (33)	82.2 (23)	5.1	3.1 – 7.1	.001*
HDL (Mean ± SD)	40 (6.9)	39 (6.7)	.12	.03-.57	.59
LDL (Mean ± SD)	117 (40.3)	110 (40.5)	7.0	4.3-9.7	.001*
Triglyceride (Mean ± SD)	146 (92)	120 (55)	25.5	20.8-30.2	.001

+OR- Odds ratio adjusted for age and sex, *Significant if p-value is <.05, %-reflect horizontal sum

Table 6. Univariate Analysis of Cardiovascular Risk & Diseases Among Overweight Adults with and Without Central Obesity, NNHES II, 2008

Characteristic	Central Obesity	No Central Obesity	OR + /Mean difference	95% CI	p-value
Total Patients	N=1,163 (%)	N=84 (%)			
Coronary artery disease	18 (100)	0	--	--	--
Cerebrovascular accident	13 (86.7)	2 (13.3)	0.46	0.1-2.1	.31
Peripheral arterial disease	16 (94.1)	1 (5.9)	1.2	0.1-8.8	.88
Hypertension	556 (95.4)	27 (4.6)	1.93	1.2-3.1	.006*
Diabetes	113 (95.8)	5 (4.2)	1.7	0.67-4.2	.26
Dyslipidemia	926 (93.9)	60 (6.1)	1.56	0.95-2.5	.07
Smoking	264 (91.6)	24 (8.4)	0.73	0.47-3.3	.98
SBP (Mean ± SD)	128 (21)	122 (18)	6.3	1.5-11	.009*
DBP (Mean ± SD)	83 (12.5)	80 (12.7)	3.8	1.05-6.6	.007*
FBS (Mean ± SD)	94 (39)	84 (22)	10.1	1.4-18.7	.022*
HDL (Mean ± SD)	39.5 (6.3)	38.8 (6.1)	0.66	0.7 -2.1	.35
LDL (Mean ± SD)	128 (37)	134 (15)	5.7	6.0-17.5	.33
Triglyceride (Mean ± SD)	171 (90)	156 (107)	14.7	5.6-35.1	.15

+OR- Odds ratio adjusted for age and sex, *Significant if p-value is <.05, -- Empty cells indicate HR calculation is not possible because of categories

Table 7. Regression Analysis of Cardiovascular Risk Factors in Normal Weight Central Obesity versus Obese with Central Obesity, NNHES II, 2008

Conditions	Normal Weight Central Obesity	Obese with Central Obesity	OR+ /Mean difference	95% CI	p- value
Total Patients	N=2,324(%)	N=276 (%)			
Coronary artery disease	30 (88.2)	4 (11.8)	1.1	.39 - 3.2	.83
Cerebrovascular accident	30 (90.9)	3 (9.1)	.84	.25 - 2.7	.77
Peripheral arterial disease	24 (92.3)	2 (7.7)	.70	.16 - 2.9	.62
Hypertension	829 (84.4)	153 (15.6)	2.2	1.7 - 2.8	.001*
Diabetes	148 (77.5)	43 (22.5)	2.7	1.8 - 3.9	.001*
Dyslipidemia	1,748 (88.8)	220 (11.2)	1.29	0.29 - 1.76	.10
Smoking	729 (49)	730 (51)	.78	.11 - 11.1	.98
SBP (Mean ± SD)	123 (20)	130 (20)	7.5	5.0 - 10.1	.001*
DBP (Mean ± SD)	79 (12.3)	85.1 (12.1)	5.7	4.2 - 7.3	.001*
FBS (Mean ± SD)	87 (33)	96 (38)	9.5	5.3 - 13.7	.001*
HDL (Mean ± SD	40 (6.9)	39.8 (5.7)	.25	0.59 - 1.1	.55
LDL (Mean ± SD)	117 (40)	129 (36)	11.8	6.8 - 16.7	.001*
Triglyceride (Mean ± SD)	146 (92)	174 (99)	27.8	16.2 - 39.4	.001*

+OR- Odds ratio adjusted for age and sex, *Significant if p-value is <.05

Table 8. Regression Analysis of Cardiovascular Risk Factors in Normal Weight Central Obesity versus Overweight Central Obesity, NNHES II, 2008

Conditions	Normal Weight Central Obesity	Overweight- Central Obesity	OR+ /Mean difference	95% CI	p- value
Total Patients	N=2,324 (%)	N=1,163 (%)			
Coronary artery disease	30 (62.5)	18 (37.5)	1.20	0.66 - 2.1	.54
Cerebrovascular accident	30 (69.8)	13 (30.2)	0.86	0.45 - 1.6	.66
Peripheral arterial disease	24 (60)	16 (40)	1.34	0.70 - 2.5	.37
Hypertension	829 (59.9)	556 (40.1)	1.65	1.43 - 1.9	.001*
Diabetes	148 (56.7)	113 (43.3)	1.58	1.2 - 2.0	.001*
Dyslipidemia	1,749 (65.4)	926 (34.6)	1.28	1.1 - 15	.004*
Smoking	730 (73.4)	264 (26.6)	0.64	0.54 - 1.75	.11
SBP (Mean ± SD)	123 (20)	128 (21)	4.9	3.5 - 6.4	.001*
DBP (Mean ± SD)	79 (12.3)	83 (12.4)	3.8	2.9 - 4.7	.001*
FBS (Mean ± SD)	87 (33)	94 (39)	7.0	4.5 - 9.5	.001*
HDL (Mean ± SD)	40 (6.9)	39.5 (6.3)	0.5	0.1 - 1.5	.017*
LDL (Mean ± SD)	117 (40)	128 (37)	10.6	7.9 - 13.5	.001*
Triglyceride (Mean ± SD)	146 (92)	171 (91)	24.6	18.2 - 31.1	.001*

+OR- Odds ratio adjusted for age and sex, *Significant if p-value is <.05,

Table 9. Regression Analysis of Cardiovascular Risk Factors in Normal Weight Central Obesity versus Underweight Central Obesity, NNHES II, 2008

Conditions	NormalWeight CentralObesity	Underweight-CentralObesity	OR+/Mean difference	95% CI	p- value
Total Patients	N=2,324 (%)	N=206 (%)			
Coronary artery disease	30 (88.2)	4 (11.8)	1.5	0.53 - 4.3	.44
Cerebrovascular accident	30 (100)	0	--	--	--
Peripheral arterial disease	24 (88.9)	3 (11.1)	0.42	4.7	.57
Hypertension	829 (94.5)	48 (5.5)	0.54	0.39 - 0.76	.001*
Diabetes	148 (94.9)	8 (5.1)	0.59	0.28 - 1.2	.16
Dyslipidemia	1,748 (93.1)	129 (6.9)	0.55	0.41 - 0.74	.001*
Smoking	729 (91)	72 (9)	1.17	0.i87 - 1.5	.29
SBP (Mean ± SD)	123 (20)	119 (21)	3.4	0.51 - 6.4	021*
DBP (Mean ± SD)	79 (12.3)	76 (10.4)	3.7	1.9 - 5.4	.001*
FBS (Mean ± SD)	87 (33)	81 (24)	5.4	0.81 - 10.1	.021*
HDL (Mean ± SD)	40 (6.9)	41 (7.4)	0.75	0.24 - 1.7	.14
LDL (Mean ± SD)	117 (40)	107 (28.3)	9.6	3.9 - 15.2	.001*
Triglyceride (Mean ± SD)	146 (92)	111 (53)	35.2	22 - 48	.001*

+OR- Odds ratio adjusted for age and sex, *Significant if p-value is <.05,
-- Empty cells indicate HR calculation is not possible because of categories

DISCUSSION

A total of 5920 participants with desired variables were analyzed. It is lower from the original study of 7700 which explains the slight variations encountered. In our study the prevalence of obese by BMI is 4.7% compared to 4.9%, CO 67.1% to 75.8%, Hypertension 34.8% to 24.6%, Diabetes 6.3% to 5.2%, Dyslipidemia 73.1% to 72%, Smoker 31.5% to 31%, CAD 1.2% to 1.1%, CVA 1.0% to 0.9% and PAD 1.2% to 1.0% from the previous study.[6] The higher prevalence of central obesity with increasing BMI is partly due to the composition of body weight. These include the percent of fat, lean mass and bone mass.[9] It also explains the inverse prevalence of CO in the normal weight and underweight group. In the general the study showed a higher risk for hypertension, diabetes and dyslipidemia all participants with CO specifically NWCO compared to NW and higher risk for hypertension in OWCO compared to OW. The result was consistent with the previous study showing the value of CO as a clinical marker of risk.[11,25-26]

The prevalence of NWCO is 39.3% which is higher compared to other cross-sectional studies done in different countries including Chile 2.4%,[12] China 6.13%,[13] USA 14.3%,[17] Thailand 15.4%,[14] Japan 19.9%[15] and South Africa 36.9%.[16] The difference in prevalence may be due to genetic, dietary and physical activity variations. It is also important to note the possible contrasting sampling size, method and how the operational definitions were used and measured.

The NWCO has a higher risk of hypertension and diabetes when compared to OBCO and hypertension, diabetes and dyslipidemia compared to OWCO. These results are consistent with previous studies and may explain the increased risk of mortality associated.[17,18,22,23,24] While the UW as an independent risk factor for cardiovascular disease is not well studied. It is seen commonly in the younger and older age group. Few studies have shown a higher risk of coronary artery disease, stroke and diabetes compared to normal weight.[27,28] The increased cardiovascular risk in this group may be attributed to clinical factors such as aging, poor nutritional status, low bone, and lean mass.

The discrepancies seen as no association of diabetes in OWCO versus higher FBS in OW, higher risk of hypertension and diabetes in NWCO versus higher SBP, DBP, LDL, TAG, FBS in OBWC and lower risk of hypertension

and dyslipidemia in NWCO versus higher values of SBP, DBP, FBS, LDL and TAG in UWCO may be attributed to subjects which are maintained on specific medications that confounded the outcome of risk and the values.

The present study suggested that categorizing obesity using a combination of BMI and CO would be helpful in identifying cardiovascular risk factors. Those with NWCO is a common finding and is associated with higher risk compared to all subtypes except the UWCO. The screening and identification of this group will increase awareness regarding the risks associated such as hypertension, diabetes, and dyslipidemia. A long-term follow-up and prospective studies are needed to establish if these risks will translate to cardiovascular diseases such as CAD, CVA, PAD, and mortality. A strategic approach of proper diet[29,30] and exercise[31,32] to prevent central obesity as measured by WC or WHR and to increase lean muscle mass to prevent underweight and NWCO may decrease cardiovascular risks.

CONCLUSION

In conclusion, the present study showed that NWCO is a common finding among Filipinos and is associated with more CVD risks such as hypertension, diabetes, and dyslipidemia in comparison with obese and overweight with or without central obesity.

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Association of Invasive Versus Conservative Strategy with Major Adverse Cardiac Events in High-Risk and Intermediate-Risk Non-ST Elevation Acute Coronary Syndrome

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Introduction **---** Invasive evaluation and/or revascularization are indicated in patients with NSTE-ACS. In our setting, the number of NSTE-ACS patients exceeds the number undergoing coronary angiogram as part of the invasive strategy. This study aimed to compare the outcome of NSTE-ACS patients managed either with early invasive, delayed invasive strategy, or with conservative strategy.

Methods **---** Charts of patients admitted from March to November 2018 were reviewed and patients were followed up to determine the intervention done and the incidence of in-hospital MACE and 1-year mortality. Clinical parameters during admission like personal history, family history, comorbidities, renal function, systolic function, GRACE score and TIMI score were also assessed.

Result **---** There is a higher frequency of in-hospital recurrent angina and in-hospital MACE in the delayed intervention group (p-value=0.008) compared to other interventions. Better renal (eGFR>60) and systolic function (EF>50%), lower GRACE score (<140) and absence of family history of CAD, reduce in-hospital MACE. There was no association of the said treatment strategies with 1-year mortality. Increased creatinine and reduced systolic function are associated with increased 1-year mortality.

Discussion **---** Possible explanation for such findings are the intrinsically inflammatory state during the revascularization process, which may induce a rapid increase in CRP, VCAM-1 and chemokines. These findings may have an effect on the choice of treatment strategies for intermediate-risk and high-risk NSTE-ACS patients, given that in the actual setting, not all of these patients undergo the invasive strategies as recommended by the guidelines. ***Phil Heart Center J 2022;25(2):11-19.***

Key Words: Major adverse cardiac events ■ Non-ST Elevation Acute Coronary Syndrome

The leading symptom for acute coronary syndrome (ACS) suspects is chest pain. ECG differentiates these patients into ST-elevation ACS (STE-ACS), wherein there is acute chest pain and persistent (>20 min) ST segment elevation, and non-ST elevation ACS (NSTE-ACS) for patients with no persistent ST segment elevation. For the first group, the mainstay of treatment is immediate reperfusion by primary coronary intervention (PCI) or fibrinolytic therapy, because this ECG finding generally reflects an acute total coronary occlusion. For NSTE-ACS, patients presenting with ongoing myocardial ischemia warrant immediate coronary angiography, and revascularization if appropriate.[1]

According to the European Society of Cardiology (ESC) guidelines released in 2016, the indication for an invasive strategy and timing of revascularization for NSTE-ACS depends on risk stratification. Very high risk criteria (hemodynamic instability, recurrent or ongoing chest pain refractory to medical treatment, life-threatening arrhythmias or cardiac arrest, mechanical complications of MI, acute heart failure, recurrent dynamic ST-T wave changes) are indications for immediate invasive strategy done <2 hours from hospital admission. High-risk criteria

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(rise or fall in cardiac troponins compatible with MI, dynamic ST-T wave changes, Global Registry of Acute Coronary Events (GRACE) score >140) warrant coronary angiogram to be done within 24 hours of hospital admission. Intermediate-risk criteria include patients with diabetes mellitus, renal insufficiency with eGFR <60 ml/min/1.73m^2), LVEF <40% or congestive heart failure, early post-infarction angina, prior PCI, prior CABG, and GRACE risk score >109 and <140 which warrants coronary angiogram to be done within 72 hours of hospitalization.[1] While invasive evaluation and/or revascularization are indicated in patients with ischemic risk, in a proportion of them this strategy is not offered because of the perception that patients might not benefit in terms of event reduction such as very elderly or frail patients, patients with comorbidities such as dementia, severe chronic renal insufficiency or cancer and patients at high risk of bleeding complications.[1]

There have been conflicting results from various studies regarding the benefit of an early invasive strategy as compared to a conservative strategy. In a study done by Fox et al., released in 2002, the RITA-3 trial compared the outcome of interventional strategy (angiography followed by revascularization within 72 hours of hospital admission) versus conservative strategy in NSTE-ACS. The interventional strategy is preferable because of having of refractory or severe angina, and with no increased risk of death or myocardial infarction.

Primary endpoint at 4 months (combined incidence of death, nonfatal myocardial infarction or refractory angina) occurred in significantly fewer patients in the interventional strategy group with risk ratio of 1.16 and p-value of 0.61. The significant difference was maintained at 12 months (risk ratio 0.72, p-value 0.003).[2] This was supported by another study by Bavry et al., in 2006, a meta-analysis of randomized clinical trials that studied the benefit of early invasive strategy in acute coronary syndromes. It concluded that the invasive strategy provided a durable survival advantage without increasing early adverse events.[3] In another meta-analysis by O'Donoghue et al. in 2012, invasive strategy reduced recurrent nonfatal MI to a greater extent in diabetic patients.[4]

In another study done by Tubaro et al. in 2015, Early Invasive Strategy (EIS) defined as pharmacological therapy and coronary angiogram within 48 hours from hospital admission, followed by mechanical or surgical revascularization if feasible, was compared to Early Conservative Strategy (ECS), which utilized pharmacological therapy. In this group, coronary angiogram with or without PCI was performed according to clinical decision. The study showed that an ECS is not inferior to an EIS with coronary angiogram in the first 48 hours from hospital admission, in a real life registry in general hospitals with or without cardiac catheterization facilities. In a subgroup analysis according to the GRACE risk scores, the multivariate analysis did not show any difference in survival free of the events included in the primary outcome between EIS and ECS.[8] In a more recent study by Hoedemaker et al. published in 2017, early invasive strategy showed no benefit over a selective invasive strategy in reducing the 10-year composite outcome of death or spontaneous MI.[9] On studying the 5-year clinical outcomes in the ICTUS trial, Damman et al., were not able to demonstrate long-term benefit of early invasive strategy in reducing death or MI.[10]

Invasive coronary angiography, followed if indicated by revascularization is performed in the majority of patients hospitalized with NSTE-ACS in regions with well-developed healthcare systems.[1] However, in our institution, the number of cases of high-risk and intermediate NSTE-ACS, exceeds the number of patients undergoing coronary angiogram as part of the routine or early invasive strategy. Several reasons include lack of available hospital beds where patient should be admitted post-procedure, lack of patient consent, and elderly patient with high frailty index. Medical management is continued while at the emergency room, and patients get discharged after 2-3 days if with no recurrence of signs of ischemia. Patients are followed-up at

the OPD thereafter for scheduling of elective coronary angiogram. On another set of patients, the timing of coronary angiogram sometimes do not follow the recent guidelines for several reasons such as lack of consent during the time the procedure was first offered, or the patient remained hemodynamically stable and it was the attending physician's decision to delay the procedure at a more convenient time.

This study aimed to compare the outcome of patients presenting at the emergency room with non-ST elevation acute coronary syndrome managed either with early invasive strategy, delayed invasive strategy, or with conservative strategy. This could have an impact on how patients are received from other institutions and managed at the emergency room, where mostcases of high-risk and intermediate risk NSTE-ACS are not sent for coronary angiogram possible revascularization for lack of available beds for admission post-procedure. This could also help identify other patient features that would warrant an invasive strategy aside from the very high risk features established in the guidelines.

The objective of this study is to determine if there is an association of invasive strategy, delayed invasive strategy, or conservative strategy with major adverse cardiac events (MACE) among patients admitted for intermediate-risk and high-risk non-ST elevation acute coronary syndrome while its specific objectives are (1) to determine and compare the prevalence rate of in-hospital primary composite outcome of all-cause mortality, recurrent angina and heart failure in patients treated with each revascularization strategy (routine invasive strategy, delayed invasive) and conservative strategy; (2) determine the secondary outcome of 1- year mortality rate in patients treated with invasive strategy, delayed invasive strategy and conservative strategy; (3) determine the factors associated with in-hospital MACE in patients treated with routine invasive, delayed invasive and conservative strategy; and (4) determine the factors associated with 1-year mortality in patients treated with routine invasive, delayed invasive and conservative strategy.

METHODS

This was a retrospective cohort study done using charts or records of NSTE-ACS patients admitted at the emergency room who underwent routine invasive, delayed invasive or conservative strategy from March 2018 to November 2018.

Included in the study are patients more than 19 years old diagnosed with acute non-ST elevation acute coronary syndrome according to the recent ESC guidelines, within 24 hours of the index event, at our institution from March 2018 to December 2018. While excluded are patients with hemodynamic instability, defined as SBP <90 mmHg, life-threatening arrhythmia, defined as sustained ventricular tachycardia, ventricular fibrillation, or unstable supraventricular tachycardia, overt heart failure, defined as SBP <80 for >30 minutes or signs of hypoperfusion, with refractory chest pain, mechanical complications of acute myocardial infarction like ventricular septal rupture, papillary muscle rupture, free wall rupture, recent or active bleeding, previous coronary artery bypass graft or percutaneous coronary intervention, with co-existing valvular heart disease, patients with incomplete data and with was previously admitted and managed in another institution prior to admission.

Sample size calculation: Using STATA v13, a minimum of were required for this study based on 13.68% incidence rate of composite MACE as noted from the study by Tubaro M, et al.[8] This computation also accounted for 5% level of significance and 15% width of the confidence interval.

Study maneuver: Data of patients admitted for NSTE-ACS from March 2018 to November 2018 were obtained from the Emergency Room census. Private attending physicians were sent a letter of request so that patients under their care and who are included in the study may be followed up. Patients who presented at the emergency room within 24 hours of the occurrence ofith angina or equivalents and who were worked up for acute coronary

syndrome using the following diagnostics (ECG, troponin I) at our institution were included in the study. Once with confirmed diagnosis of NSTE-ACS, patients were followed as to whether routine invasive (defined as coronary angiogram possible revascularization as per ESC guidelines), delayed invasive (defined as coronary angiogram possible revascularization during admission with the timing not congruent with ESC guidelines) or conservative (defined as pharmacological therapy) strategy was performed. Clinical variables including age, sex family history, previous ACS, previous stroke, functional class, smoking, hypertension, diabetes, initial blood pressure and heart rate wereill be recorded.

Routine blood tests like baseline creatinine and troponin I as well as initial ECG at ER and 2D echocardiogram with doppler done during admission were collected. For patients who underwent coronary angiogram and/or angioplasty, the angiogram results and angioplasty outcomes were be recorded using official results. Primary in-hospital outcome of all-cause mortality, recurrent angina and heart failure were determined. The review of charts was done using a standardized data collection form. Patients included in the study were contacted to determine the 1-year secondary outcome of all-cause mortality, This was done via telephone call and a standard set of questions (as indicated below) was asked to the patient after giving consent.

Operational definitions:

1. *Non-ST elevation acute coronary syndrome* – angina chest pain occurring within 24 hours from admission to ER, described as follows: prolonged >20 minutes angina pain at rest, recent destabilization of previously stable angina which is crescendo in nature, or post-MI angina. Additional diagnostics include (a) ECG, which may show the following findings: new horizontal or downsloping ST segment depression ≥ 0.05 mV in at least 2 contiguous leads, or T wave inversion ≥ 0.1 mV or pseudo-normalization of the T wave in at least 2 contiguous leads, and (b) Troponin I, with a positive result if with at least 1 value above the99th percentile of the upper reference range limit.
2. *High-risk NSTE-ACS* – rise or fall in cardiac troponins compatible with MI, dynamic ST-T wave changes, or GRACE score >140
3. *Intermediate-risk NSTE-ACS* – diabetes mellitus, renal insufficiency with eGFR <60 ml/min/1.73m^2), LVEF<40% or congestive heart failure, early post-infarction angina, prior PCI, prior CABG, and GRACE risk score > 109 and < 140.
4. *GRACE score* – includes parameters such as Killip class, systolic blood pressure, heart rate, age, creatinine level, presence or absence of cardiac arrest at admission, ST segment deviation, presence or absence of elevated cardiac enzyme levels.

The obtained scores correspond to mortality risk, as indicated in the table below:

Grace Score Range	Mortality Risk
0-87	**0-2%**
88-128	**3-10%**
129-149	10-20%
150-173	**20-30%**
174-182	40%
183-190	50%
191-199	60%
200-207	70%
208-218	80%
219-284	90%
≥ 285	99%

5. *Routine invasive strategy* – coronary angiogram with possible revascularization within 24 hours for high-risks patients and within 72 hours for intermediate-risk patients from admission, in addition to pharmacological therapy.
6. *Delayed invasive strategy* – coronary angiogram with possible revascularization within admission, with timing not congruent with current ESC guidelines.
7. *Conservative strategy* – pharmacologic therapy, defined as administration of dual antiplatelets, anticoagulants, statins, and beta-blocker, A CEI/ARBs and/or nitrate (if without contraindication).

8. *Major adverse cardiac events* – primary composite of all-cause mortality, recurrent angina (defined as occurrence of anginal chest pain or equivalent ≥ 2x a day within hospital admission) and heart failure (defined as occurrence of orthopnea, PND or shortness of breath on ambulation at the ward within hospital admission).

Identification of study variables with definition of each variable

a. Independent: The independent variables in this study are as follows: patient's baseline characteristics, GRACE score, left ventricular ejection fraction, Killip class.

b. Dependent: The dependent variables in this study are the in-hospital outcomes of mortality, recurrent angina and heart failure, and 1-year outcome of mortality.

Statistical analysis: Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion was used for categorical variables, median and inter quartile range for non-normally distributed continuous variables, and mean and SD for normally distributed continuous variables. One-way ANOVA, Kruskal-Wallis test and Fisher's Exact test were used to determine the difference of mean, rank and frequency, respectively, among patients who underwent either routine invasive strategy, delayed invasive strategy or conservative strategy. Shapiro-Wilk was used to test the normality of the continuous variables. Likelihood ratio was computed to determine association of factors with outcome. Missing variables were neither be replaced nor estimated. Patients who were not interviewed for 1-year follow up data were censored from the analysis of 1-year outcome data. Null hypotheses was rejected at 0.05α-level of significance. STATA 13.1 was used for data analysis.

RESULTS

Among the 91 patients included in the study, 7 underwent routine intervention, 23 underwent delayed intervention while the remaining 61 patients were managed conservatively. Most of the patients were male, with hypertension, impaired renal function, preserved ejection fraction and TIMI score of 3-5.

Table 2 shows the frequency of the different in-hospital outcome according to the management done. Among the 91 patients included, 7 patients died within admission and 28 had recurrent angina. The available data suggest that patients who underwent delayed intervention who experienced recurrent angina during hospitalization had a significantly higher frequency compared with other strategies. As a result, in-hospital MACE was also higher in the delayed intervention group. As for 1 year-mortality, there was no significant difference among the 3 strategies (*Table 3*).

Table 4 shows the patient factors and intervention associated with inhospital MACE. Patients with delayed invasive strategy done were 2.85 times more likely to have in-hospital MACE compared to patients managed conservatively. Using multivariate analysis, they are 3.74 times more likely to have in-hospital MACE after adjusting for eGFR and EF. Patients with eGFR of <60 were 3.30 times more likely to have in-hospital MACE compared to patients with eGFR of >60. Patients with EF of <50 were 3.02 times more likely to have in-hospital MACE compared to patients with EF of >50. Increased GRACE score of >140 and family history of CAD also increased the likelihood of in-hospital MACE (OR 2.72 at 95% CI).

Creatinine and EF were the factors significantly associated with 1-year mortality (*Table 5*). For every 0.01 unit increase in creatinine, the odds of 1-year mortality also increase by 16.01%. Meanwhile, reduced EF of <50% conferred a 4.86 times increased likelihood of 1-year mortality compared to patients with preserved EF.

Table 1. Baseline characteristics and clinical data of patients admitted for NSTE-ACS

	Total (n=91)	Routine (n=7)	Delayed (n=23)	Conservative (n=61)	P-value
	Frequency (%); Mean + SD; Median (IQR)				
Age (years)	63 + 11	59 ± 15	62 ± 11	64 ± 11	0.57
Sex					0.383
Male	60 (65)	6 (86)	16 (70)	38 (60)	
Female	31 (35)	1 (14)	7 (30)	25 (40)	
Previous ACS	23 (25)	2 (29)	6 (27)	15 (24)	0.928
Previous stroke	9 (10)	0 (0)	2 (9)	7 (12)	1.000
Family history of CAD					0.224
Absent	69 (76)	5 (71)	14 (63)	50 (81)	
Present	22 (24)	2 (29)	8 (36)	12 (19)	
Smoking history					
Smoker	48 (53)	4 (57)	13 (59)	31 (50)	0.788
Non smoker	43 (47)	3 (43)	9 (41)	31 (50)	
Comorbidities					
Diabetes mellitus	36 (40)	4 (57)	11 (50)	21 (34)	0.248
Hypertension	66 (73)	6 (86)	14 (64)	46 (74)	0.471
SBP on admission	134 + 30	143 ± 34	122 ± 24	138 ± 31	0.063
DBP on admission	81 + 18	97 + 34	74 + 19	82 + 14	0.010
Ischemic ECG changes					0.376
Present	59 (64)	3 (43)	16 (73)	40 (63)	
Absent	32 (36)	4 (57)	6 (27)	23 (37)	
Creatinine (mmol/L)	0.10 + 0.04	0.10 ± 0.01	0.10 ± 0.03	0.10 ± 0.05	0.895
eGFR					0.154
<60	56 (62)	6 (86)	1 (4)	5 (8)	
≥60	35 (38)	1 (14)	22 (96)	58 (92)	
Killip class					0.960
1	76 (84)	6 (86)	19 (86)	51 (82)	
2	12 (13)	1 (15)	2 (14)	9 (9)	
3	3 (3)	0 (0)	1 (5)	2 (3)	
LV EF (%)					
<50	32 (34)	0 (0)	6 (26)	26 (41)	0.048
≥50	61 (66)	7 (100)	17 (74)	37 (59)	
GRACE score					
< 109	39 (44)	4 (57)	2 (9)	33 (53)	0.000
109-140	30 (32)	1 (14)	11 (50)	18 (29)	0.133
>140	22 (24)	2 (29)	9 (41)	11 (18)	0.064
TIMI score (points)					
0-2	32 (35)	3 (43)	5 (23)	24 (39)	0.350
3-5	57 (62)	4 (57)	17 (77)	36 (58)	0.252
6-7	2 (2)	0 (0)	0 (0)	2 (3)	1.000

Table 2. Primary in-hospital outcome of the patients according to intervention done

	Total (n=91)	Routine (n=7)	Delayed (n=23)	Conservative (n=61)	P-value
	Frequency (%)				
In-hospital mortality	7 (6)	1 (14.3)	2 (9.1)	4 (6.45)	0.525
Recurrent angina	28 (31)	1 (14.3)	15 (68.2)	12 (19.35)	<0.001
Heart failure symptoms	22 (24)	1 (14.3)	8 (36.4)	13 (21.0)	0.294
In-hospital MACE	38 (42)	1 (14.3)	15 (68.2)	22 (35.5)	0.008

Table 3. Secondary outcome of 1-year mortality of patients according to intervention done

	Total (n=91)	Routine (n=7)	Delayed (n=23)	Conservative (n=61)	P-value
	Frequency (%)				
All-cause mortality	12 (14.12)	0 (0)	3 (15)	9 (15.25)	0.885

Table 4. Factors associated with In-hospital MACE

Parameters	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Intervention done				
Conservative	(reference)	-	(reference)	-
Routine invasive	0.25 (0.03 to 2.23)	0.216	0.49 (0.05 to 4.72)	0.536
Delayed invasive	2.85 (1.05 to 7.71)	0.039	3.74 (1.20 to 11.7)	0.023
eGFR <60	3.30 (1.37 to 7.95)	0.008	2.93 (1.13 to 7.64)	0.028
EF <50	3.02 (1.24 to 7.36)	0.015	3.12 (1.14 to 8.57)	0.027
GRACE score of >140	2.72 (1.01 to 7.36)	0.048	-	-
Family history of CAD	2.72 (1.01 to 7.36)	0.048	-	-

Table 5. Factors associated with 1-year mortality

Parameters	OR (95% CI)	p-value
Crea 1.16	1.16 (1.02 to 1.32)	0.028
EF < 50%	4.85 (1.31 to 17.9)	0.017

DISCUSSION

There was a higher frequency of in-hospital recurrent angina and in-hospital MACE in the delayed intervention group (p-value = 0.008) and a higher likelihood of in-hospital MACE compared to the conservative strategy group. As for the clinical variables, better renal function, preserved systolic function, lower GRACE score and absence of family history of CAD all reduce the incidence of inhospital MACE. There was no association of the said treatment strategies with 1-year mortality. Increased creatinine and reduced systolic function are associated with increased likelihood of 1-year mortality.

The findings of this study are congruent with the study done by Bugiardini et al in 2013 which compared the effectiveness of in-hospital medical therapy versus coronary revascularization added to medical therapy in patients who were stabilized for 48 hours after ACS. In this propensity score-matched cohort study, ACS patients were divided into quintiles based on several variables (age, gender, smoking history, diabetes, MI, creatinine, blood pressure, family history of CAD, CCS classification, troponin and index event). The first quintile included the very elderly with more comorbid conditions, while the fifth quintile included the youngest, prevalently men with low CRP levels. The study showed that compared to standard medical treatment, revascularization was associated with a lower rate of MACE at 6 months in the patients of the first quintile, characterized by very elderly patients, more comorbid conditions like history of prior MI and renal dysfunction, high CRP and non-ST elevation ACS as index event. In this group, use of revascularization was associated with the

lowest rates of MACE as compared with medical therapy (15% vs 28.7%). In contrast, there was a higher rate of MACEs in the 5th quintile where patients were younger and had lower CRP levels. The rates of MACE were 13.8% and 6.1% in the revascularization and medical therapy groups, respectively.

These findings suggest that in-hospital coronary revascularization had no advantage with possible harm in the majority of patients (those belonging to the second, third, fourth and fifth quintiles, comprising about 80% of the study population) who were stabilized after ACS.[7] Another important point was that referral to routine in-hospital elective revascularization is associated with decreased risk of cardiovascular endpoints in approximately 20% of patients, specifically in patients of the lowest-propensity stratum (first quintile). Possible explanation for such findings are the intrinsically inflammatory state during the revascularization process, which may induce a rapid increase in CRP, VCAM-1 and chemokines.[7]

The findings of this study suggest that for the majority of patients with NSTE-ACS, a conservative treatment strategy confers more benefit compared to invasive strategy in terms of incidence of in-hospital MACE, while there's no difference among the 3 treatment strategies on 1-year mortality. Meanwhile, a follow up study of the RITA-3 trial showed no prognostic advantage of invasive management for NSTE-ACS patients over 10 years.[6] However, it should be taken into account that there are other clinical factors that affect the incidence of in-hospital MACE and 1-year mortality such as baseline renal function, LV function, GRACE score and presence or absence of family history of CAD.

LIMITATIONS

Whether the effect of these factors to primary and secondary outcomes can be modified by either conservative or invasive treatment strategy has not yet been investigated. Aside from this, another limitation of this study is the higher selection bias because of the use of consecutive sampling based on chart retrieval by records instead of stratified random sampling. The sample size is also small, with only 7% of the patients who underwent routine invasive strategy and 25% who had delayed invasive strategy.

CONCLUSION

Incidence of in-hospital recurrent angina and in-hospital MACE were significantly higher in the delayed intervention group compared to the conservative strategy group. However, there was no association of the choice of intervention with 1-year mortality. Other clinical factors associated with in-hospital MACE are eGFR < 60, LVEF < 50, GRACE score > 140 and family history of CAD. These findings may have an effect on the choice of treatment strategies for intermediate-risk and high-risk NSTE-ACS patients, given that in the actual setting, not all of these patients undergo the invasive strategies as recommended by the guidelines.

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Mitral Valve Aneurysm and Ruptured Coronary Sinus of Valsalva: complications of Infective Endocarditis

Rachel Ann Denila, MD; Joseph Jasper Acosta, MD; Edwin Tucay, MD

Background --- Mitral valve aneurysm (MVA) is a saccular outpouching of the mitral leaflet expanding into the left atrium during systole and collapsing during diastole. It is a rare condition with an incidence of 0.2 2.9%. Its most serious complication, perforation, results to acute heart failure symptoms and hemodynamic compromise. A ruptured coronary sinus of valsalva (RCSOV) is a rare cardiac anomaly with left to right shunting causing symptoms of chest pain and heart failure. Both conditions occur as a complication of infective endocarditis (IE).[1-2]

Case Presentation --- A 29 year old male with ventricular septal defect sought consult due to fever and chest pain. A continuous murmur was detected on physical examination. Transthoracic echocardiography revealed fluttering echogenic densities attached to the mitral and aortic valves and 3D transesophageal echocardiography (TEE) confirmed the presence of RCSOV and MVA. He was successfully managed with full course antibiotic and surgery.

Discussion --- There are no established guidelines for the diagnosis and management of MVA and RCSOV. Based on reports, TEE is the imaging of choice for both conditions. In both cases, surgery is the treatment of choice in the presence of severe regurgitation, heart failure and hemodynamic compromise. The acute heart failure symptoms warranted an immediate surgical intervention.[10-11]

Conclusion --- The accurate evaluation of involved cardiac structures and timely diagnosis and surgical intervention, which is the optimal intervention for both complications, helped achieve a good prognosis for this complex case. ***Phil Heart Center J 2022;25(2):20-26.***

Key Words: Superior Cavopulmonary Anstomosis (SCPA) ■ Tricuspid Valve Atresia ■ ■ Single Ventricle

Mitral valve aneurysm (MVA) is rare condition described as as a saccular outpouching of the mitral leaflet expanding into the left atrium during systole and collapses during diastole. Although the exact mechanism is unknown, it is a common consequence of infective endocarditis. The most serious complication of MVA is perforation producing symptoms of acute mitral regurgitation, pulmonary congestion and hemodynamic compromise which warrants immediate intervention.[1-2]

A ruptured coronary sinus of Valsalva (RCSOV) is a rare cardiac anomaly with an incidence of 0.09-0.15% comprising 3.5% of all congenital cardiac anomalies. It is associated with a left to right shunting causing symptoms of chest pain, shortness of breath and easy fatigagability. In 30-40% of patients, there is a coexisting cardiac anomaly such as a ventricular septal defect or aortic valve regurgitaiton.[3-5]

Ventricular septal defect (VSD) is a common congenital heart disorder frequently associated with other cardiac anomalies. In VSD of the subpulmonic type, there is a regional defect in the conal septal musculature that supports the right coronary sinus and the aortic annulus. Recent studies have shown that VSD often coexist with a ruptured coronary sinus of valsalva aneurysm regardless of the presence of an infective endocarditis.[4,6-7]

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We present a case of a 29 year old Filipino diagnosed with ventricular septal defect compli cated by infective endocarditis, ruptured coronary sinus of valsalva and mitral valve aneurysm. The patient underwent successful operation andwas discharged with improved functional status.

Case: A 23 year old male Filipino, single, came in to our institution due to chest heaviness and fever. The patient was diagnosed with a congenital heart disease, ventricular septal defect six years prior to the present admission, when a murmur was heard during a routine physical examination. The patient was given captopril, digoxin, furosemide and was advised surgical correction but was eventually lost to follow-up. The patient claimed to be asymptomatic until eight weeks prior to admission when he had onset of chest heaviness and fever associated with dyspnea and easy fatigability. Chest radiograph done showed cardiomegaly with left pleural effusion. The patient was treated with levofloxacin, losartan and spironolactone. A 2-dimensional (2D) echocardiogram done revealed congenital heart disease, ruptured coronary sinus of valsalva. Six days prior to the admission, his fever persisted accompanied by chills. The patient also had progressive dyspnea now associated with orthopnea. He was then referred to our institution and was subsequently admitted for further work-up and intervention.

The patient was born to a gravid 5 para 5 mother via normal spontaneous vaginal delivery with no fetomaternal complications. He had no other comorbidities and had no previous hospitalization nor surgery. His personal, social and family histories were all unremarkable. The patient is a college student with no vices and no history of injection drug use.

On physical examination, a wide pulse pressure was noted with a blood pressure of 160/100 mmHg. He was tachycardic with heart rate at 115 beats per minute. He was not in respiratory distress with respiratory rate of 20 breaths per minute. His body mass index was 18.75 kg/m^2. He was anicteric with pink palpebral conjunctivae with no signs of hemorrhages. There were no cutaneous lesions on the hands and feet during skin inspection. Carotid pulsations were noted to be visible.

Cardiac examination, revealed a hyperdynamic precordium with the point of maximal impulse palpated at the 5th intercostal space left anterior axillary line. A grade 5/6 continuous murmur was heard at the 4th intercostal space left parasternal border. His pulses were full and bounding and systolic pulsations were noted upon light compression of the nailbed. A loud systolic and diastolic pulsations were also auscultated on the femoral area and a bruit was appreciated on light compression.

Mild anemia and leukocytosis were noted on complete blood count. C-reactive protein was only slightly elevated at 12.1 mg/L. Erythrocyte sedimentation rate was elevated at 58 and rheumatoid factor was positive. Serum electrolytes, prothrombin time and urinalysis yielded normal results. Blood culture specimens detected growth of *Streptococcus anginosus* and *Streptococcus Sanguinis.* His 12 lead electrocardiogram revealed sinus tachycardia with left ventricular hypertrophy.

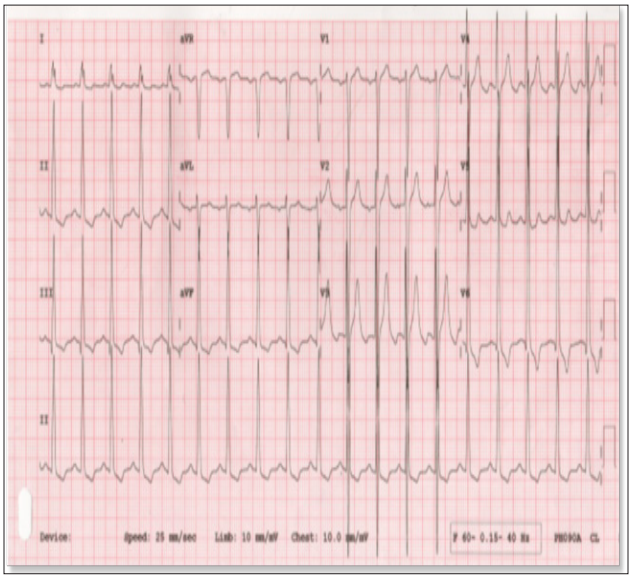

Fig. 1: 12 L electrocardiogram of sinus tachycardia with rate of 115, normal axis at + 60 degrees and left ventricular hypertrophy by voltage criteria

Chest radiograph revealed clear lungs with equalization of the pulmonary blood flow and left sided cardiomegaly.

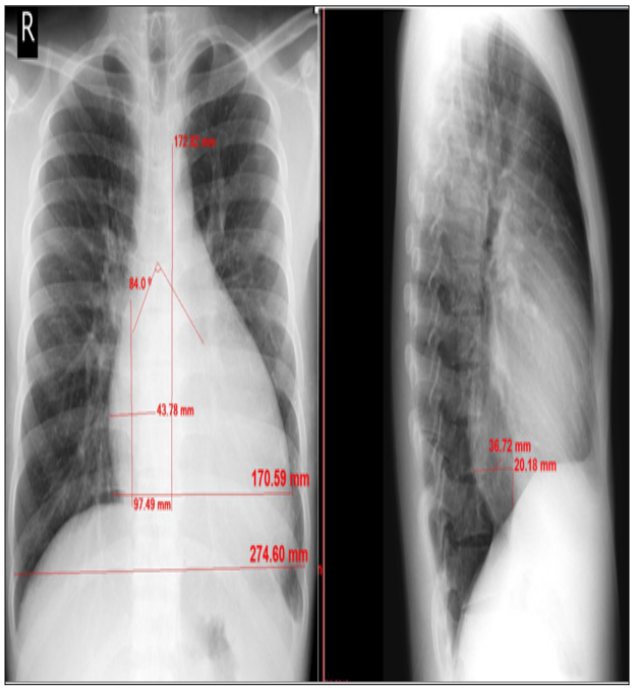

Fig. 2: Clear lungs with equalization of pulmonary blood flow and left sided cardiomegaly

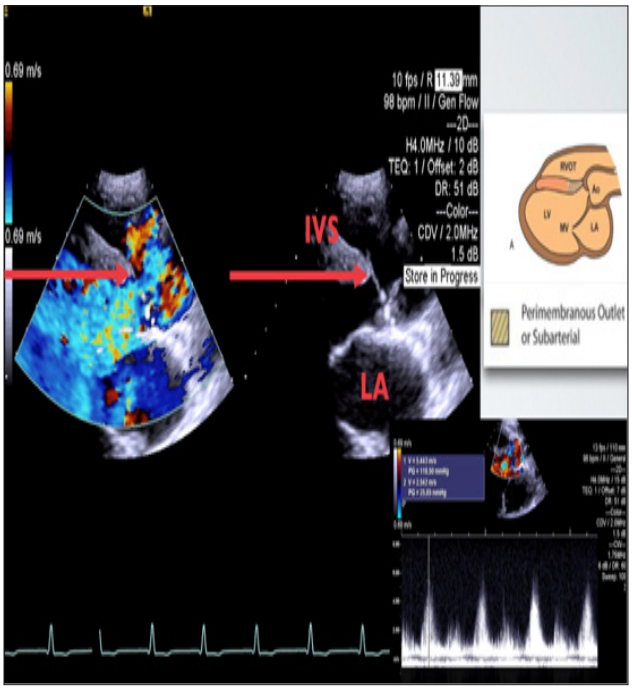

Fig. 4: Aortic valve vegetation seen on the parasternal long axis (PLAX) view on 2d echocardiography

2D echocardiogram was done which revealed vegetations on the aortic and mitral valve, measuring 1.04 x 2.3 cm and 1.8 x 1.6 cm, respectively. A ventricular septal defect with predominantly left to right shunt and severe aortic regurgitation and a rupture coronary sinus of valsalva were also seen.

Focused view of the mitral valve showed a thickened valve with a note of a saccular bulge with systolic expansion and diastolic collapse which is probably a mitral valve aneurysm. There was an echo drop out at the base of the aneurysm with note of a fluttering echogenic density.

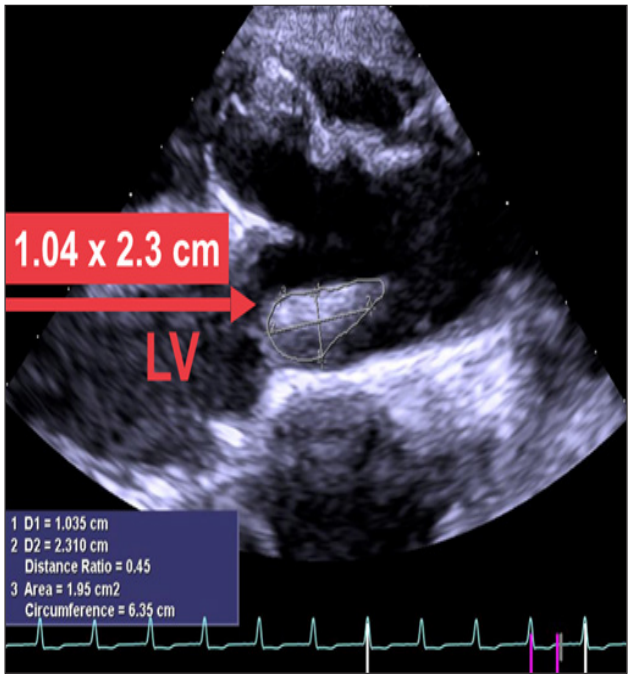

Fig. 3: Aortic valve vegetation seen on the parasternal long axis (PLAX) view on 2d echocardiography

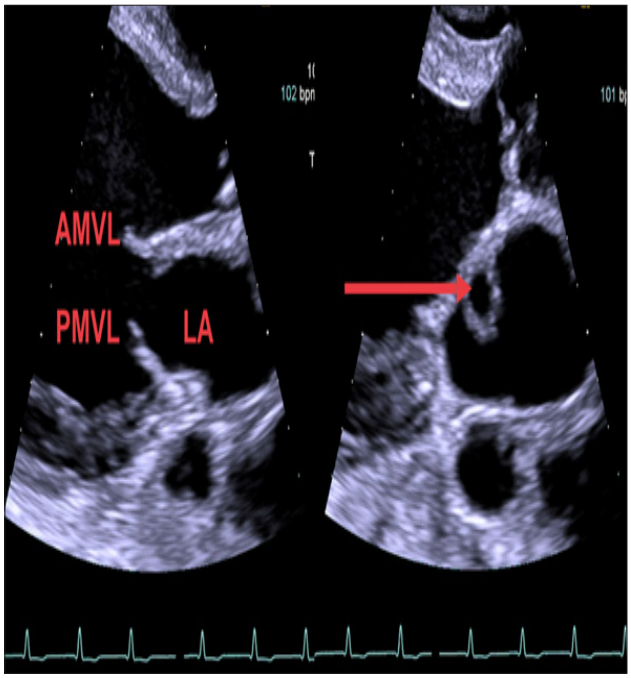

Fig. 5: Focused PLAX view showing a saccular bulge with systolic expansion and diastolic collapse

To better delineate cardiac structures and to assess the extent of the infective endocarditis, a 3D transesophageal echocardiography was done. A ventricular septal defect, subpulmonic type with left-to-right shunt was seen. A windsock-like structure is demonstrated via 3D imaging from the right coronary sinus of valsalva to the right ventricular outflow tract with an echo drop out measuring 1.8 cm consistent with a ruptured coronary sinus of valsalva.

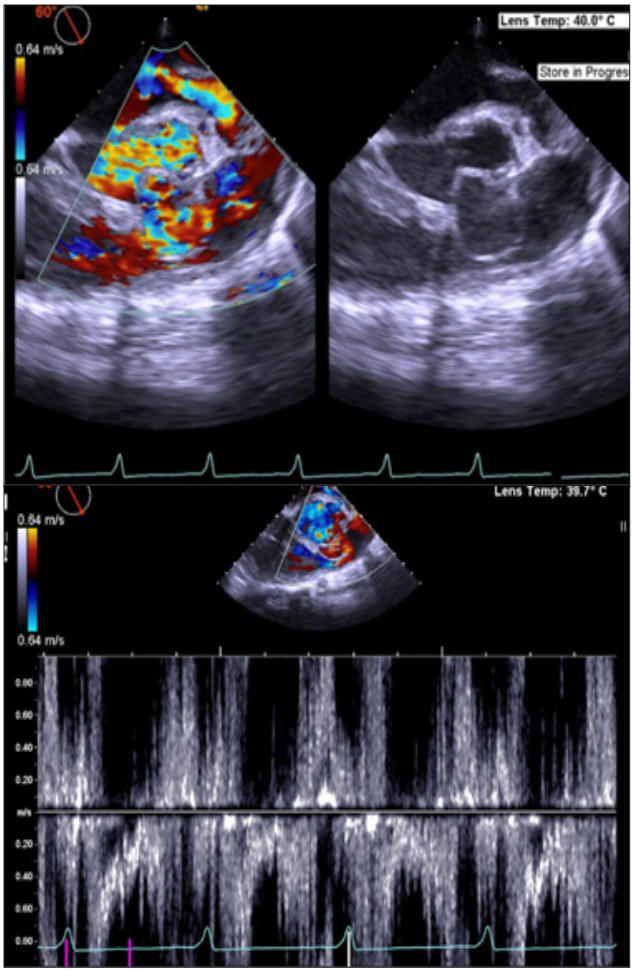

Fig. 6: Mid upper esophageal aortic valve short axis view showing a windsock-like structure from the right coronary sinus of valsalva to the right ventricular outflow tract (RVOT). Mosaic color flow is noted across the windsock-like structure to the RVOT

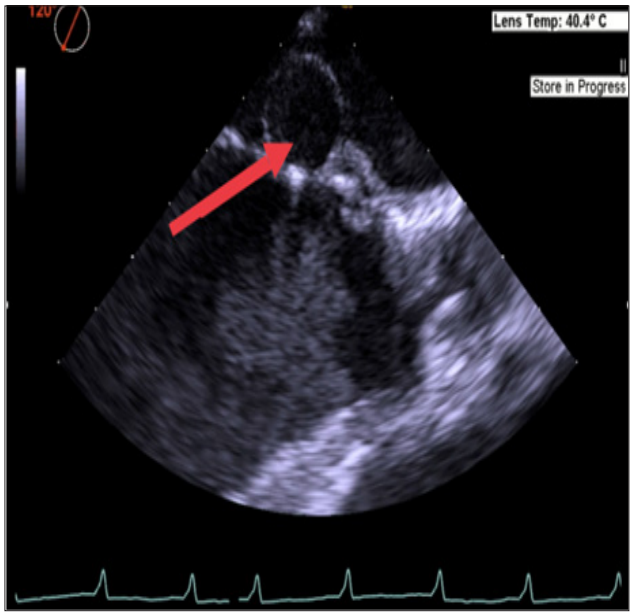

Fig. 7: 3D TEE showing a sac like formation attached to the A2 segment of the anterior leaflet protruding into the left atrium during systole with diastolic collapse

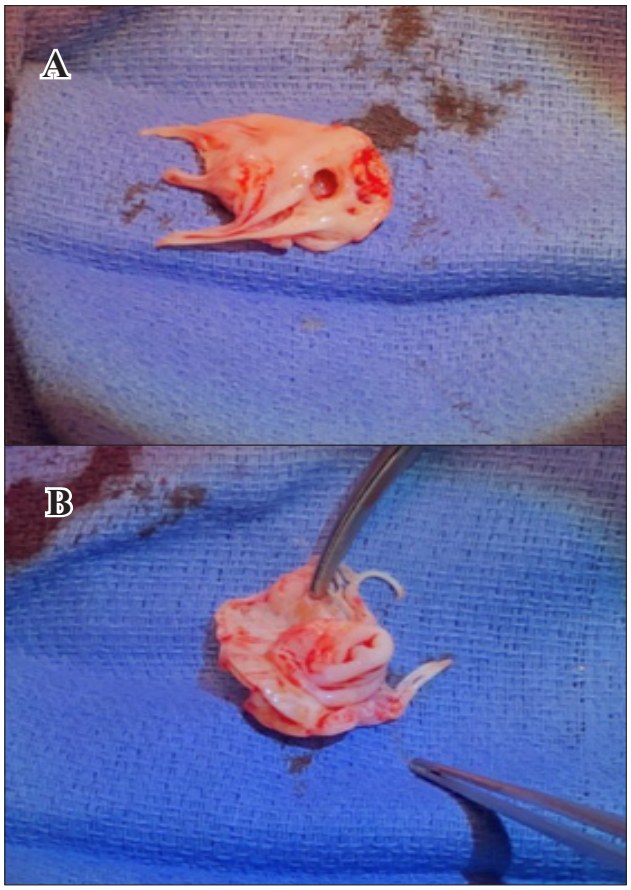

Fig. 8a: Gross specimen of the excised mitral valve showing the opening of the mitral valve aneurysm on the ventricular surface

Fig.8B. a Sac-like outpouching without out rupture is seen on the atrial side

DISCUSSION

Our patient is a diagnosed case of VSD who presented with fever, heart failure symptoms and a continuous murmur. A continuous murmur is an auscultatory finding of various pathologic cardiac conditions and its location can help identify the underlying pathology. A VSD complicated by aortic regurgitation may demonstrate a continuous murmur with a decrescendo blowing diastolic murmur component at the left lower sternal border. A ruptured coronary sinus of valsalva continuous murmur can be best heard at the lower sternal border with diastolic accentuation. The fever and heart failure symptoms warranted immediate work-up for infective endocarditis.[8] Echocardiography, along with blood culture is central to IE diagnosis and plays an essential role across all disease phase of IE from diagnosis to follow. In this case, blood culture was positive and echocardiography revealed vegetations fulfilling the modified Duke Criteria for definite IE.[9-11] The 2D echocardiogram also provided information to exclude other disorders which causes continuous murmur. In our case, mitral valve aneurysm, ruptured right coronary sinus of valsalva, ventricular septal defect with severe aortic regurgitation were initially detected by TTE.

Mitral valve aneurysm (MVA) is a saccular outpouching of the mitral leaflet expanding into the left atrium during systole and collapsing during diastole. It is a rare condition with an incidence reported to be at 0.2-of 2.9% only. Although the exact mechanism is unknown, it occurs more commonly as a consequence of infective endocarditis. The development of MVA is likely caused by trauma and mitral leaflet infection due to the striking of an infected aortic regurgitant jet on the surface of the anterior mitral valve leading to trauma, seeding, and subsequent aneurysm formation. Other proposed mechanisms for MVA formation are direct extension of the infection through the mitral-aortic intervalvular fibrosa and transmission of infection through the direct contact of the prolapsed aortic vegetation with the anterior mitral valve. MVA increases the risk for septic embolization but its most serious complication is perforation producing symptoms of acute mitral regurgitation, pulmonary congestion and hemodynamic compromise which warrants immediate intervention.[1-2,12-15]

Our patient is a case of ventricular septal defect with severe aortic regurgitation with vegetations noted in the aortic and mitral valve. Outlet type VSD is located below the semilunar valve and is the least common type, present in only 6% of VSDs. In the asian population, however, this subtype is the most common and accounts for approximately 30% of cases. In many cases, the defect is adjacent to the aortic valve annulus. In cases of subpulmonic VSD, aortic valve regurgitation becomes common caused by the lack of support of the right and/or non coronary cusps of the aortic valve. A deficiency in the support by the parietal band in the sinus of valsalva and aortic annulus also contributes to the aortic prolapse. Moreover, the left to right shunting of the blood during systole draws the unsupported aortic valve into the right ventricular lumen.[6-7,16-19] A ruptured coronary sinus of valsalva is also an uncommon cardiac anomaly which can be congenital in origin but more commonly associated with infective endocarditis. In the asian population, VSD and AR also commonly coexist with RCSOV, mostly arising from the right coronary sinus and draining into the right ventricle. Manifestations of rupture include dypsnea, chest pain, and fatigue.[3-5,19-21]

In this case, both uncommon entities occurred as a complication of infective endocarditis and were detected initially by 2D TTE. In most cases of IE, a transthoracic echocardiography is sufficient for the diagnosis of IE but a transesophageal echocardiography may provide complementary information and is recommended for the assessment of IE complications. Moreover, 3-dimensional TEE has the advantage of better delineation of IE lesions, its complications, and its relationship with surrounding structures. For both MVA and RCSOV, TEE is a more accurate imaging modality. The 3D TEE allowed for better visualization of structures without the need for costly and high risk imaging.[10-11,22]

The management of MVA has no established guideline because of its rarity. There have been reports of MVA managed conservatively

but in cases of large MVA with increased susceptibility to rupture, surgical intervention is the treatment of choice. To date, we have two cases of mitral valve aneurysm in our institution. he first case was in the setting of infective endocarditis in ventricular septal defect with aortic regurgitation treated surgically with VSD patch closure with mitral and aortic valve replacement. The second was a case of MVA on a patient with mitral valve prolapse and infective endocarditis who underwent mitral valve repair.[16,23]

Based on ESC guidelines, aortic and mitral valve infective endocarditis with severe regurgitation, heart failure symptoms, and vegetation size of more than 10 mm are all indications for urgent surgery. Moreover, in this case, the coexistence of mitral valve aneurysm and ruptured coronary sinus of valsalva warranted a more immediate surgical intervention since both complications lead to symptoms of acute heart failure and severe hemodynamic compromise.[10-11]

CONCLUSION

Infective endocarditis is associated with serious complications. The development of mitral valve aneurysm is likely caused by trauma and mitral leaflet infection due to the striking of an infected aortic regurgitant jet on the surface of the anterior mitral valve. Other proposed mechanisms are direct extension of the infection through the mitral-aortic intervalvular fibrosa and transmission of infection through the direct contact of the prolapsed aortic vegetation with the anterior mitral valve. A ruptured coronary sinus of valsalva is also associated with infective endocarditis and is likely caused by the weakening of the aortic wall secondary to the inflammatory process. Patient education, therefore, for infective endocarditis prevention is of utmost importance.

In patients presenting with fever in the setting of a congenital heart disease, early recognition of infective endocarditis and its complications is essential and life saving. Antiobiotic treatment as well as appropriate diagnostics should not be delayed. In this case, the 3D transesophageal echocardiography allowed for the identification of the mitral valve aneurysm and ruptured coronary sinus of valsalva. The timely diagnosis, accurate evaluation of involved cardiac structures and appropriate surgical intervention, which is the optimal intervention for both complications, helped achieve a good prognosis for this complex case.

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Risk Factors Associated with Early and Late Outcome for Palliated Single Ventricle Physiology Following Superior Cavopulmonary Anastomosis

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Background **---** Due to advancement in diagnostics and surgical techniques, there has been a steady increase in patients operated with single ventricle physiology. The aim of this study was to evaluate the pre-operative and intraoperative factors associated with early and late outcome in patients who underwent Superior Cavopulmonary Anastomosis (SCPA).

Methods **---** Thirty patients underwent Superior Cavopulmonary Anastomosis from January 2016 to December 2018 in a tertiary cardiac referral center. Review of charts and Medtrak entries were done to investigate risk factors associated with development of early morbidity and mortality. Follow-up was done via a telephone interview to determine the development of late mortality and post-operative complications.

Result **---** Total mortality was noted at 26.7%. There were four patients who had early mortality and four patients who had late mortality. The most common diagnosis was Tricuspid Valve Atresia (23%). The mean age was 43 months and there were more males who underwent the operation. Early post-operative complications were seen in 40% of patients while late post-operative complications were seen in 6.7% of patients. Only one patient underwent completion Fontan operation, which was done two years after the SCPA.

Conclusion **---** Outcome after Superior Cavopulmonary Anastomosis in the local setting is comparable to foreign studies. Age, cardiac diagnosis, preoperative atrioventricular regurgitation and cardiopulmonary bypass time were seen to be associated with outcome. ***Phil Heart Center J 2022;25(2):27-34.***

Key Words: Superior Cavopulmonary Anstomosis (SCPA) ■ Tricuspid Valve Atresia ■ ■ Single Ventricle

There has been a steady increase in pediatric cardiac surgery for congenital heart diseases. Consequently, due to advancement in diagnostics and surgical techniques, there are more patients operated with complex heart diseases particularly with single ventricle physiology. The goal for palliation of patients with single ventricle physiology is to establish better long-term survival and quality of life.[1] Palliation is composed of 3 stages. Whether there is restricted or unrestricted blood flow to the pulmonary circulation, the first stage consists of placement of a modified Blalock-Taussig shunt or a pulmonary artery band, respectively. The second stage is composed of a Superior Cavopulmonary Anastomosis (SCPA) e.g. bidirectional Glenn shunt (BDG) or a hemi-Fontan (HF) operation. The BDG is done when it is anticipated that an extracardiac Fontan operation will be done while the HF operation is performed when a lateral tunnel Fontan operation is the plan for future surgery. The final stage of palliation is the Fontan surgery which results in near normal arterial oxygen saturation.[2] It involves connecting the systemic venous circulation particularly the inferior vena cava to the pulmonary circulation through a lateral tunnel or an extracardiac conduit.

In a study by Pajak et al. regarding early outcomes of second-stage palliation, mortality rate was at 13.3% with preoperative atrioventricular valve regurgitation, single ventricle heart dysfunction, pneumonia or sepsis and arrhythmias as the most common associated risk factors.[3] In another study done to investigate morbidity and mortality after bidirectional Glenn Shunt, mortality was seen at 0.7% with mean

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length ICU and hospital stay at 50 hours and 5 days, respectively. A right ventricular morphology, prolonged bypass time, elevated central venous pressure and transpulmonary gradient are risk factors associated with adverse outcomes. Lower weight at the time of operation was also seen to be associated with prolonged hospital stay.[4] According to Lee et al, left ventricular dominance and diagnosis of tricuspid atresia were protective factors while age younger than 3 months, heterotaxy syndrome, diagnosis of unbalanced atrioventricular septal defect, hemodynamically significant atrioventricular valve regurgitation were associated with poor outcome.[5] This was also seen in a study done in the Medical University of South Carolina wherein atrioventricular valve regurgitation was noted to be an independent factor for mortality.[6] Conversely, in the study of Talwar et al, they noted that age at presentation was not associated with mortality although younger patients had longer hospital stay.[7]

Patients with single ventricle physiology is at increased risk of early and late complications after surgery. Most important principle in the management of these children is to avoid injury to the heart, preserving ventricular, valvular and electrophysiologic function.[2] Surgical planning is important in these patients including knowledge of risk factors associated with morbidity and mortality. The purpose of the study is to determine the risk factors associated with early and late outcome in pediatric patients with single ventricle physiology following Superior Cavopulmonary Anastomosis. Specifically, the goal is to determine the pre-operative and intraoperative risk factors associated with early and late mortality, prolonged hospital stay and development of post-operative complications. Knowledge of risk factors affecting outcome will help the pediatric cardiologists, intensivists, cardiothoracic surgeon and anesthesiologists in patient selection for surgery, as well as in the pre-operative, intraoperative and post-operative management of such patients.

METHODS

The study was conducted in accordance to to the guiding principles which have their origin in the Declaration of Helsinki as well as in compliance with existing international and local guidelines and regulations. Prior to study initiation, the investigator requested a waiver of written informed consent since there will be difficulty obtaining signed individual written authorization to participate. Upon telephone follow-up, an IERB approved script for verbal consent was used. If there is objection to their part, the data of the patient was excluded from the study. The risk to the participant's privacy was minimal and no sensitive information was obtained. The investigators ensured that the participant's anonymity was maintained. All data were encoded using a password protected Excel spreadsheet. A code number was assigned to each participant. Only the primary investigator had access to this file. After encoding, all data collection forms were kept in a secured cabinet. The investigators adhered fully to the provisions of the Data Privacy Act of 2012. No identifying information was included in the publication or presentation of the results of the study.

This is a retrospective cohort study done at the Pediatric Surgical Intensive Care Unit from January 1, 2020 to June 31, 2020. The participants included in the study were all patients less than 19 years old who have undergone SCPA palliation for single ventricle physiology from January 1, 2016 to December 31, 2018. Exclusion criteria included patients with incomplete data and those with history of infection prior to the surgery.

Study Maneuver: All pediatric patients who underwent SCPA operation for single ventricle physiology from January 1, 2016 to December 31, 2018 was considered for the study. Review of charts and Medtrak entries was done. Baseline characteristics of the participants including age, weight, single ventricle morphology, preoperative echocardiographic findings e.g. presence of atrioventricular and/or semilunar regurgitation and ventricular ejection fraction, and presence of preoperative catheterization were noted prior to surgery. Intraoperative variables including cardiopulmonary bypass and cross-clamp time in minutes were recorded.

A telephone interview was done using an IERB approved script for verbal consent for telephone follow-up. The participant's parents and/or legal guardian were asked regarding the status of the patient including late mortality and presence of late post-operative complications.

Negative outcomes included mortality, prolonged hospital stay and development of postoperative complications. Early mortality included those who have died within 30 days from the time of operation while admitted in the hospital. Prolonged hospital stay was defined as hospital stay of more than 10 days. Early post-operative complications included prolonged intubation, prolonged chest tube drainage, presence of chylothorax, acute kidney injury, infection, arrhythmia, presence of neurologic injury or seizure, presence of pulmonary hypertension or Glenn failure, and need for extra-corporeal membrane oxygenation (ECMO). In addition, late mortality was defined as death after 30 days from surgery until the time of telephone follow-up. Late postoperative complications included recurrent admissions due to cardiac disease and symptoms of cardiac failure e.g. facial and/or upper extremity edema, easy fatigability and arrhythmia. All data collected was encoded and analyzed.

Sample Size Calculation: Using G*Power 3.1.9.2, a minimum of 29 patients were required for this study based on 9.33 odds ratio of patients with post-operative arrhythmia to have early mortality,[8] 5% level of significance and 90% power.

Statistical Analysis: Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion was used for categorical variables and median and inter quartile range for non-normally distributed continuous variables. Mann-Whitney U test and Fisher's exact test was used to determine patients with and without early post-operative outcome as well as late post-operative outcome. Odds ratio and corresponding 95% confidence intervals from binary logistic regression was computed to determine significant predictors for early post-operative outcome. All statistical tests were two tailed test. Shapiro-Wilk was used to test the normality of the continuous variables. Missing variables was neither replaced nor estimated. Null hypotheses were rejected at 0.05α-level of significance. STATA 13.1 was used for data analysis.

RESULTS

Between 2016 to 2018, a total of 30 patients who underwent SCPA for single ventricle physiology were included in the study. Median age on operation was 43 months. The youngest was 7 months old and the oldest was 18 years old (224 months). Majority of those operated were male (60%) and median weight was 12.5kg. Twenty-two participants (73%) had a left ventricle morphology. The top cardiac diagnoses were tricuspid valve atresia (23%), single ventricle (20%) and double outlet right ventricle (17%). Other cardiac morphologies were Ebstein's anomaly, pulmonary valve atresia, unbalanced atrioventricular septal defect, double outlet left ventricle, d-transposition of the great arteries and severe tricuspid stenosis (*Figure 1*). Table 1 shows the pre-operative clinical and demographic characteristics associated with early outcome. Eighteen patients (60%) had a positive outcome while twelve patients had a negative outcome. There were four patients who died in-hospital within thirty days after the operation. The first early mortality was an 8-month old male with a diagnosis of Ebstein's Anomaly with Partial Anomalous Pulmonary Venous Return who died on the second post-operative day due to low cardiac output syndrome. The patient also developed acute kidney injury postoperatively.

The second patient is a 10-month old male with also a diagnosis of Ebstein's Anomaly who developed pulmonary hypertension and developed Glenn shunt failure.The patient underwent take down of the Glenn shunt on the 4th post-operative day, however, he died in the operating room. The third patient is a 7-month old female with a diagnosis of Single Ventricle of Right Ventricle morphology, Malposed Great Arteries with Pulmonary Valve Atresia. Unfortunately, the patient died at the operating room table. The last early mortality is an 8-year old male with a diagnosis of Atrio-

ventricular Septal Defect, unbalanced canal, Malposed Great Arteries with severe Pulmonary stenosis. Post-operatively, he developed acute respiratory distress syndrome and acute kidney injury. He was also noted with junctional rhythm and was temporarily paced. On the 3rd post-operative day, severe regurgitation was noted hence Glenn shunt was taken down and an aortopulmonary shunt was placed instead; however, the patient expired on the 7th post-operative day.

Computing for the odds ratio of negative outcome, it showed that age and preoperative findings of semilunar and atrioventricular valve regurgitation are associated with increased risk of negative outcome. On the other hand, female sex, weight, right ventricular morphology and preoperative catheterization findings were associated with decreased risk of negative outcome. These, however, were not statistically significant. Nine patients (30%) underwent stage 1 operation prior to SCPA operation. Two patients underwent ductal stenting, two patients underwent pulmonary artery banding while five patients underwent a modified Blalock-Taussig shunt. Median time interval between the 1st stage and 2nd stage was 72 months. Intraoperative factors associated with early outcome is seen in Table 2. 43% had cardiopulmonary bypass time of 60-120 minutes and cross-clamp time was less than 60 minutes in 65% of the participants. There was no significant difference in cardiopulmonary bypass time and cross-clamp between patients with negative and positive outcomes.

On follow-up, there were 6 patients who developed negative outcomes. Four patients had late mortality and two patients developed late post-operative complications. Pre-operative clinical and demographic characteristics were not significantly associated with development of late negative outcome (*Table 3*). Moreover, intraoperative factors e.g. cardiopulmonary bypass and cross-clamp time were noted to be not significantly associated with late outcome. The 1st late mortality is an 8-year old male with a diagnosis of Double Outlet Right Ventricle with Atrial Septal Defect and Mitral Valve Atresia who developed chylothorax and underwent chest tube insertion two months after the SCPA. The 2nd patient is an 18-year old female with diagnosis of Tricuspid Valve Atresia type 1B who developed multi-organ dysfunction syndrome post-operatively. The 3rd patient is a 1-year old male with a diagnosis of Single Ventricle of Left Ventricle morphology, Malposed Great Arteries with Pulmonic Stenosis. The patient died two years after the operation. The last mortality is a 3-year old female with diagnosis of severe Tricuspid Stenosis with severe Pulmonic Stenosis, Atrial Septal Defect and Patent Ductus Arteriousus. She is the only patient who was able to undergo Fontan operation, two years after the SCPA. Regrettably, the patient expired on the 8th post-operative day of the Fontan operation. The patients who had negative outcome was noted to be older of age and with presence of semilunar valve regurgitation pre-operatively. Intraoperatively, the patients who developed late negative outcomes had longer cross-clamp time but shorter cardiopulmonary bypass time (*Table 4*).

Table 5 shows the summary of the outcomes. Two patients had prolonged intubation, one patient had prolonged chest tube drainage, two patients developed chylothorax, two patients developed acute kidney injury, two patients developed postoperative infection, two patients developed arrhythmia, one patient developed seizures and three patients had pulmonary hypertension or Glenn failure. Two of the patients who was noted post-operative pulmonary hypertension expired but the other one survived and was extubated on the 6th post-operative day. Sixteen patients (53%) had a hospital stay of more than ten days. The only late post-operative complication noted is easy fatigability, which was reported by two patients.

Table 1.1. Pre-operative Demographic and Clinical Characteristics Associated with Early Outcome

	Total (N = 30)	Negative Outcome (N = 12)	Positve Outcome (N = 18)	P Value
		Frequency (%) (%); Mean (IQR)		
Age at surgery (months)	43 (20 to 80)	45.5 (28.5 to 91)	38.5 (18 to 69)	0.567
Sex				
Male	18 (60%)	4 (33.33%)	8 (44.44%)	0.709
Female	12 (40%)	8 (66.67%)	10 (55.56%)	
Weight (kg)	12.5 (9.4 to 20)	14.35 (9.6 to 18)	10.4 (9.4 to 21.5)	0.658
Single ventricle physiology				
Right	8 (26.67%)	5 (41.67%)	3 (16.67%)	0.210
Left	22 (73.33%)	7 (58.33%)	15 (83.33%)	
Preoperative echocardiographic findings				
Semilunar valve regurgitation	2 (7.14%)	1 (9.09%)	1 (5.88%)	1.000
Atrioventricular valve regurgitation	14 (50%)	8 (72.73%)	6 (35.29%)	0.120
Ventricular function	24 (85.71%)	10 (90.91%	14 (82.35%)	1.000
Preoperative catheterization findings				
Yes	21 (70%)	7 (58.33%)	14 (77.78%)	0.418
No	9 (30%)	5 (41.67%)	4 (22.22%)	
Stage 1 Operation				
Yes	9 (30)	4 (33.33)	5 (27.78)	1.000
No	21 (70)	8 (66.67)	13 (72.22)	

Table 1.2. Association of Pre-operative Clinical and Demographic Characteristics with Early Negative Outcome

	Odds Ratio	95% CI	P Value
Age at surgery (months)	1.003	0.99 to 1.02	0.673
Sex			
Male	(reference)	-	-
Female	0.635	0.14 to 2.85	0.544
Weight (kg)	0.99	0.91 to 1.08	0.850
Single ventricle physiology			
Right	0.28	0.05 to 1.52	0.140
Left	(reference)	-	-
Preoperative echocardiographic findings			
Semilunar valve regurgitation	1.6	0.08 to 28.57	0.749
Atrioventricular valve regurgitation	4.8889	0.93 to 25.67	0.061
Ventricular function	2.1429	0.19 to 23.72	0.534
Preoperative catheterization findings	0.4	0.08 to 1.98	0.261

Table 2. Intraoperative Factors Associated with Early Outcome

	Total (n=30)	Negative outcome (n=12)	Postive outcome (n=18)	P-Value
		Frequency (%); Median (IQR)		
Time interval (months)	72 (40 to 96)	107.5 (67 to 150)	42 (40 to 72)	0.221
Cardiopulmonary bypass time	121 (78 to 162)	125.5 (102 to 162)	117 (77 to 149)	0.515
< 60 minutes	0	0	0	0.402
60-120 minutes	10 (43.48%)	7 (70%)	6 (46.15%)	
>120 minutes	13 (56.52%)	3 (30%)	7 (53.85%)	
Cross-clamp time	27 (15 to 90)	35 (15 to 90)	17 (15 to 104)	0.923
< 60 minutes	11 (64.71%)	6 (66.67%)	5 (62.5%)	1.000
60-120 minutes	3 (17.65%)	2 (22.22%)	1 (12.5%)	
>120 minutes	3 (17.65%)	1 (11.11%)	2 (25%)	

Table 3. Pre-operative Clinical and Demographic Characteristics Associated with Late Outcome

	Negative outcome (n=6)	Postive outcome (n=24)	P-Value
	Frequency (%); Median (IQR)		
Age at surgery (months)	74.5 (16 to 125)	42 (21 to 64.5)	0.350
Sex			0.660
Male	3 (50%)	15 (62.5%	
Female	3 (50%)	9 (37.5%)	
Weight (kg)	20.5 (9.5 to 32.5)	12.5 (8.2 to 19)	0.258
Single ventricle physiology			1.000
Right	1 (16.67%)	7 (29.17%)	
Left	5 (83.33%)	17 (70.83%)	
Preoperative echocardiographic findings			
Semilunar valve regurgitation	2 (8.70%)	0	1.000
Atrioventricular valve regurgitation	2 (40%)	12 (52.17%)	1.000
Ventricular function	4 (80%)	20 (86.96%)	1.000
Preoperative catheterization findings		1.000	1.000
Yes	3 (50%)	17 (70.83%)	
No	3 (50%)	7 (29.17%)	
Stage 1 Operation			0.329
Yes	3 (50%)	6 (25)	
No	3 (50%)	18 (75)	

Table 4. Intraoperative Factors Associated with Late Outcome

	Negative outcome (n=6)	Postive outcome (n=24)	P-Value
	Frequency (%); Median (IQR)		-
Time interval (months)	95 (40 to 80)	57 (39 to 96)	0.439
Cardiopulmonary bypass time	117	122.5 (78 to 162)	0.784
< 60 minutes	0	0	0.560
60 - 120 minutes	2 (66.67)	8 (40)	
>120 minutes	1 (33.33)	12 (60)	
Cross-clamp time	77	22.5 (14.5 to 96)	0.488
< 60 minutes	2 (66.67)	9 (64.29)	1.000
60-120 minutes	1 (33.33)	2 (14.29)	
>120 minutes	0	3 (21.43)	

DISCUSSION

The incidence of surgical palliation for single ventricle pathway has been increasing. Survival after each stage is dependent on a number of factors. In this study, early mortality rate was at 13.3%. This was comparable to the studies of Pajak and d'Udekem.[3,8] This was higher compared to the studies of Al-Dairy and Cnota, which showed an early mortality rate of 2.5-3% after a Superior Cavopulmonary Anastomosis.[9,10] Patient characteristics and surgical practices affect the mortality rate.[11]

As with previous studies, age was not seen to be a significant risk factor for negative outcome.[9-11] Age was not seen to be associated with prolonged hospital stay, significant pleural drainage, presence of morbidity or mortality.[4] Mean age, however, was seen to be higher in patients with negative outcome. Older patients are more desaturated after SCPA since there is decreased systemic venous return from the upper body compared to the lower body.[11] It is still recommended that patients undergo surgery at a younger age.[9]

Table 4. Intraoperative Factors Associated with Late Outcome

	Frequency (%) (n=30)
Early mortality	4 (13.33)
Early post-operative complications	12 (40)
Prolonged intubation	2 (6.67)
Prolonged chest tube drainage	1 (3.33)
Chylothorax	2 (6.67)
Acute kidney injury	2 (6.67)
Infection	2 (6.67)
Arrhythmia	3 (10)
Neurologic or presence of seizure	1 (3.33)
Pulmonary hypertension or Glenn Failure	3 (10)
Extracorporeal membrane oxygenation	0
Prolonged hospital stay	16 (53.33)
Later mortality	4 (13.33)
Long term complications	
Recurrent hospitalizations	0
Easy fatigability	2 (6.67)
Facial/upper extremity edema	0
Arrhythmia	0

Tricuspid valve atresia was the most common diagnosis for a single ventricular pathway. This was also observed by the study of Talwar, et al.[11] According to Lee, et al, diagnosis of tricuspid atresia was noted to be a protective factor.[5] In addition, it has been shown that right ventricular dominance is an important risk factor for mortality.[4,8]

Studies have shown that preoperative atrioventricular regurgitation was a significant risk factor for poor outcome.[5,6] In this study, eight patients (72.7%) who had atrioventricular regurgitation had a negative outcome; however, this was not noted to be a significant factor for early and late morbidity and mortality. Cardiac catheterization prior to SCPA is usually deemed necessary, particularly to answer questions regarding anatomy and to evaluate chamber pressures. This procedure; though, is not without complications especially in young patients. Pre-operative cardiac catherization was not a significant risk factor in the study. In the study comparing outcomes and utility of cardiac catherization prior to SCPA, they noted that the procedure rarely provides additional information unless therapeutic intervention is needed.[12]

Depending on the type of SCPA, the patient may or may not be subjected to cardiopulmonary bypass. According to the study done by Kogon, et al, cardiopulmonary bypass exposes the patient's brain to higher venous pressure, subsequently leading to a lower transcranial pressure gradient and poor neurologic outcome. Although this was seen not to be significant, patients with a negative early outcome had a longer cardiopulmonary bypass time compared to those with positive early outcome (125 minutes vs 117 minutes).

Majority of the patients (53%) had prolonged hospital stay of more than 10 days. This may be secondary to presence of post-operative complications. The most common of which was Glenn failure or pulmonary hypertension. In the study of time and outcome of SCPA, prolonged hospital stay was associated with prolonged mechanical ventilation, lower weight, younger age and greater number of concurrent cardiac procedures during the surgery.[10]

The study is retrospective and has a short follow-up period of 1-2 years. This is a limitation since availability of data in the charts and Medtrak can be inadequate. A prospective or randomized controlled trial is recommended.

CONCLUSION

Outcome after Superior Cavopulmonary Anastomosis in the local setting is comparable to foreign studies. Although not significant, age, cardiac diagnosis, preoperative atrioventricular regurgitation and cardiopulmonary bypass time were seen to be associated with outcome.

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Fractional Exhaled Nitric Oxide (FeNO) and Eosinophil Count and its Correlation with the Severity of Airflow Limitation and Symptom or Risk of Exacerbation Among COPD Patients

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Background --- Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities.[1] This study determined the association of fractional exhaled nitric oxide and absolute eosinophil count with severity of airflow limitation and risk of exacerbation in COPD.

Methods --- This is a cross sectional, analytic study which included 38 patients aged 40 and above diagnosed COPD patients. FeNO and absolute eosinophil count were taken and correlated with the patients' severity of airflow limitation and symptom or risk of exacerbation.

Result --- Patients enrolled in the study were predominantly elderly males with a mean BMI of 23 ± 3.27. Patients had a mean age of 65.13 ± 8.34 years and a median smoking history of 22.5 pack smoking years. The percentage of patients classified with COPD Severity 1, 2, 3, and 4 was 18.4%, 50%, 23.68% and 7.89% respectively. 26 (68.42%) of the patients have no history of exacerbations while 10 patients (26.32%) have 2 or more history of exacerbations. The median FeNO level is 23ppb and the median absolute eosinophil count was 283.5 cells per microliter. FeNO levels decreased with increasing severity of COPD from GOLD 1 to 4 and the absolute eosinophil count also tends to show decreasing trend with increasing GOLD severity except in GOLD 2.

Discussion --- COPD Classification with less symptoms and COPD Classification with more symptoms have almost the same median level of FeNO. The level of absolute eosinophil count is higher in COPD Classification with more symptoms than in COPD Classification with less symptoms. Patients with COPD Classification with low risk of exacerbation and COPD Classification with high risk of exacerbation have almost same median level of FeNO. The absolute eosinophil count in COPD Classification with low risk of exacerbation hashigher levels as compared to COPD Classification with high risk of exacerbation.

The sensitivity and specificity of FeNO for predicting risk of exacerbation was 66.67% and 30.0% respectively. On the other hand, the absolute eosinophil count had a sensitivity of 55.56% and specificity of 20.0% for predicting risk of exacerbation. The sensitivity and specificity of FeNO level to predict risk COPD patient to have more symptoms were 62.07% and 44.44% respectively. The absolute eosinophil count has a sensitivity of 62.07% and a specificity of 66.67% to predict patients to have more symptoms.

Conclusion --- There is no clear association between FeNO and absolute eosinophil count to the severity and risk of exacerbation in COPD patients. There seems to be an inverse relationship between FeNO and the severity of airflow limitation. There is no association between absolute eosinophil count and severity of airflow limitation. However, between the two, the absolute eosinophil count seems to have better association. ***Phil Heart Center J 2022;25(2):35-42.***

Key Words: Chronic Obstructive Pulmonary Disease ■ Eosinonphils ■ fractional exhaled intric oxide ■ exacerbation

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Chronic Obstructive Pulmonary Disease (COPD) is a common preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

The extent of inflammation, fibrosis and luminal exudates in the small airways correlates with the reduction in the FEV1 and FEV1/FVC ratio, and probably with the accelerated decline in FEV1 that is characteristic of COPD.[1]

The classification of airflow limitation severity in COPD is based on post-bronchodilator FEV1. in patients with FEV1/FVC of < 0.70, patients are classified as GOLD 1 if FEV1 ≥ 80% predicted, GOLD 2 if FEV1 <50% - 80% predicted, GOLD 3 if FEVl 30%-50% predicted and GOLD 4 if FEVl <30% predicted. Once patients are classified according to airflow limitation, patients will be categorized according to symptoms and history of exacerbation.

According to GOLD guidelines, patients are categorized into 4 groups A, B, C, D and grouped in rubrics as shown in Figure 1. Severity of symptoms is based on the CAT and mMRC score. In patients who are more symptomatic (CAT score of ≥ 10 and mMRC ≥ 2) are classified as either B or D. Patients who are less symptomatic (CAT score of <10 and mMRC 0-1) are classified as either A or C. Patients with exacerbation history of ≥ 2 or ~ 1 which leads to hospital admission are classified as Cor D. In patients with 0 or ≥ 1 exacerbation history not leading to hospital admission are classified as A or B.

FeNO measurements have been considered as a surrogate for eosinophilic airway inflammation, especially in asthma, In most mild asthmatics, high FeNO at 50mLs-l (>45 ppb) has been regarded as a marker for steroid responsiveness including improvement in spirometry and ailway hyperresponsiveness.[2]

A study done by Antus and Barta demonstrated that measurements of FeNO provided a predictive tool for assessing the frequency of hospitalization-associated exacerbations in COPD patients. COPD patients with low FeNO concentration at the time of an acute exacerbation are more susceptible to developing severe acute exacerbations in the future. Patients with elevated FeNO level at exacerbation were less frequently hospitalized for exacerbations.[3]

In patients with chronic obstructive pulmonary disease, FeNO has been reported to be high in exacerbations compared with stable patients, and a report suggested that FeNO falls after inhaled steroids in stable chronic obstructive pulmonary disease.[4]

Blood eosinophil counts are 1.) a biomarker of exacerbation risk in patient with a history of exacerbations and 2.) can predict the effects of ICS on exacerbation prediction.[1]

For patients with one exacerbation per year, a peripheral blood level ~ 300 eosinophils/μL identifies patients more likely to respond to LABA/ICS treatment. For patients with ~2 moderate exacerbations per year or at least one severe exacerbation requiring hospitalization in the prior year, LABA/ICS treatment can be considered at blood eosinophil counts ~ 100 cells/μL, as ICS are more pronounced in patients with greater exacerbation frequency and/or severity.[1]

Based on these studies, we now seek to determine the association of fractional exhaled nitric oxide and absolute eosinophil count with clinical classification and severity of airflow limitation and symptom or risk of exacerbation in COPD.

The general objective is to determine the association of FeNO levels and the absolute eosinophil count with the severity of airflow limitation and symptom or risk of exacerbation among COPD patients. While its specific objectives are to determine the FeNO level and absolute eosinophil count in COPD; to determine the correlation of FeNO levels and absolute eosinophil count to the severity of COPD; to determine the correlation of FeNO levels and absolute eosinophil count on symptoms of COPD patients; determine the correlation of FeNO levels and absolute eosinophil count with risk of exacerbation in COPD and to establish a threshold for FeNO and absolute eosinophil count on symptoms and risk of exacerbations.

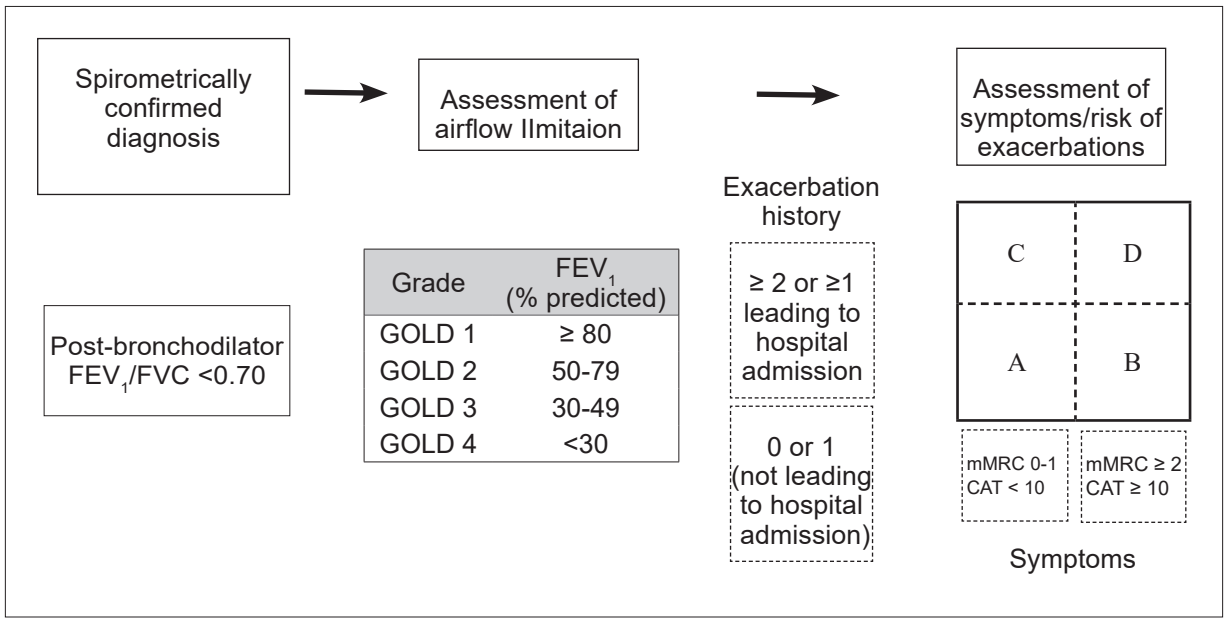

Fig. 1: ABeD Assessment Tool

METHODS

This is a cross-sectional, analytic study design. Conducted at the Philippine Heart Center, Pulmonary and Critical Care Medicine between September 2019 to January 2020.

Included in the study were patients aged 40 and above seen at the out-patient department or as in-patient with the following criteria: patients clinically diagnosed with COPD and with spirometry (post bronchodilator FEV1/FVC of <70%) done within six (6) months at PHC. While those excluded are patients with history of atopy, diagnosed with bronchial asthma, those patients with history of malignancy for the past 5 years, with bronchiectasis or idiopathic lung disease, with parasitism present in stool examination, patients with allergies to certain drugs, with pneumothorax, fractured ribs, with vocal cord dysfunction and cardiac instability (unstable angina, recent myocardial infarction) and patients with current respiratory tract infection.

Sample Size: A minimum of 38 patients were required for this study based on 0.81 area under the curve of FeNO level to predict increased exacerbation rate during follow-up period. This computation also accounts for 5% level of significance and 25% total half width of the confidence interval.

Study Maneuver: Ethical approval for this study was obtained from the Philippine Heart Center Institutional Ethics Review Board. Written informed consent was obtained from all patients before enrolment in the study.

All admitted and seen in the Out-Patient Department diagnosed with COPD through spirometry and patients referred to pulmonary laboratory with spirometry post bronchodilator FEVl/FVC of <70% which confirmed the diagnosis of COPD were included in the study. Clinical and demographic data were obtained which included age, sex, smoking history, medications being taken, duration of disease, other comorbid and baseline characteristics including height, weight, body mass index, and history of exacerbation.

For OPD patients, once the inclusion criteria were met, stool examination was submitted at the laboratory on follow-up to check for parasitism. For admitted patients, stool examination was requested while patient was at the hospital. If stool exam was negative for parasites, the patient was enrolled in the study. If stool examination was positive, patient was excluded. Patient's FeNO level and CBC were taken on the same

day. FeNO was done at pulmonary laboratory for outpatient patients or at the patient's room for admitted patients. Patients were grouped based on their severity of airflow limitation. Patients' FeNO level and absolute eosinophil count were correlated with patient's number of admissions and exacerbations.

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Statistical Analysis: Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion was used for categorical variables, median and inter quartile range for non-normally distributed continuous variables, and mean and SD for normally distributed continuous variables. Sensitivity, specificity, and likelihood ratios as well as its area under the ROC curve was used to determine the FeNO and absolute eosinophil count to predict exacerbation. Spearman correlation analysis was used to determine the association of FeNO level and absolute eosinophil count to other parameters. ShapiroWilk was used to test the normality of the continuous variables. Missing variables were neither replaced nor estimated. Null hypotheses was rejected at 0.05 a-level of significance. STATA 13.1 was used for data analysis.

RESULTS

A total of 38 patients who met the criteria were included in this study. Table 1 shows the demographic and clinical profile of the patients enrolled in the study which were predominantly elderly males (32 males and 6 females) with a mean BMI of 23 ± 3.27.

Patients had a mean age of 65.13 ± 8.34 years and a median smoking history of 22.5 pack smoking years. The percentage of patients classified with COPD Severity 1,2,3, and 4 was 18.4%, 50%, 23.68% and 7.89% respectively. The percentage of patients with COPD Class A, B, C and D was 21%, 50%, 2.6%, and 26.3% respectively. 63.15% of the patients enrolled in the study have an mMRC score of 2 and above whereas the median CAT score of the patients was 18.5 (13 to 22). Their mean FEV1% is 61.88 ± 22 with 19 of the patients having GOLD II severity of disease. 19 and 10 patients fall under Class B & D respectively with 26 (68.42%) of the patients having no history of exacerbations while 10 patients (26.32%) have 2 or more history of exacerbations. The most commonly used medication was ICS + LABA (44.74%) followed by LAMA + LABA (31.58%). The median FeNO level is 23ppb and the median absolute eosinophil count was 283.5 cells per microliter.

Table 2 showed that the median FeNO levels decreased with increasing severity of COPD from GOLD 1 to 4 whereas the median absolute eosinophil count also tends to show decreasing trend with increasing GOLD severity except in GOLD 2 that suddenly did not follow the general trend. Instead, it even showed the lowest level of FeNO.

Table 3 showed the median FeNO levels and absolute eosinophil count according to COPD Classification. It was noted that COPD Classification with less symptoms (COPD Class A and COPD Class C) and COPD Classification with more symptoms (COPD Class B and COPD Class D have almost the same median level of FeNO. The level of absolute eosinophil count is higher in COPD Classification with more symptoms (COPD Class B and COPD Class D) than in COPD Classification with less symptoms (COPD Class A and COPD Class C).

Patients with COPD Classification with low risk of exacerbation (COPD Class A and COPD Class B) and COPD Classification with high risk of exacerbation (COPD Class C and COPD Class

D) have almost same median level of FeNO. The absolute eosinophil count in COPD Classification with low risk of exacerbation (COPD A and B) has higher levels as compared to COPD Classification with high risk of exacerbation (COPD C and D).

Table 1. Demographic and clinical profile of the patients (n=38)

	Frequency (%); Mean + SD; Median (IQR)
Age (yrs)	65.13 ± 8.34
Gender	
Male	32 (84.21)
Female	6 (15.79)
BMI (kg/m2)	8.84 ± 1.76
Duration of disease (yrs)	11.86 ± 1.83
Smoking (pack years)	11.78 ± 2.25
MMMRC	
0	4 (10.53)
1	10 (26.32) 14
2	7 (18.42)
3	11 (28.95)
4	6 (15.79) 24
Comorbidities	
Hypertension	24 (63.16)
Diabetes	8 (21.05)
CAD	15 (39.47)
CAT score	18.5 (13 to 22)
%FEV1	61.88 ± 22
FEV1 (l)	1.55 ± 0.61
FeNO (ppb)	23 (17 to 32)
Absolute Eosinophil Count (cells per microliter)	283.5 (192 to 448)
Medications	
SABA	3 (7.89)
LAMA + LABA	12 (31.58)
ICS	0
ICS + LABA	17 (44.74)
NONE	6 (15.79)
History of Exacerbation	13 (34.21)
No. of exacerbation	
no exacerbation	26 (68.42)
1 with hospitalization	1 (2.63)
1 without hospitalization	1 (2.63)
≥ 2 exacerbation	10 (26.32)
GOLD severity	
GOLD 1	7 (18.42)
GOLD 2	19 (50)
GOLD 3	9 (23.68)
GOLD 4	3 (7.89)
COPD classification	
COPD A	8 (21.05)
COPD B	19 (50)
COPD C	1 (2.63)
COPD D	10 (26.32)

Table 2. Comparison of Median FeNo Levels and Absolute Eosinophil Count and Its Association with GOLD Severity

	FeNO Median (IQR)	Absolute Eosinophil Count Median (IQR))
GOLD 1 (n=7)	29 (15 to 31)	427 (272 to 450)
GOLD 2 (n=19)	24 (18 to 37)	216 (107 to 438)
GOLD 3 (n=9)	22 (15 to 27)	385 (148 to 448)
GOLD 4 (n=3)	17 (15 to 29)	300 (282 to 712)
P Value	0.508	0.167

Table 3. Comparison of Median FeNO levels and Median Absolute Eosinophil Count According to COPD Classification ABCD

		FeNO Median (IQR)	Absolute Eosinophil Count Median (IQR))
SEVERITY OF SYMPTOMS			
Less Symptoms	A and C (n=9)	24 (15 to 36)	236 (180 to 435)
More Symptoms	B and D (n=29)	23 (17 to 31)	300 (206 to 448)
P-value (total less vs total more)	17 (15 to 29)	0.85	0.303
RISK OF EXACEBATION			
Low Risk	A and B (n=27)	24 (17 to 36)	300 (206 to 450)
High Risk	C and D (n=11)	22 (15 to 32)	240 (126 to 415)
P Value (total low vs total high)		0.847	0.431

Table 4. Threshold of FeNO and absolute Eosinophil count to outcomes

	Cutoff	Sensitivity	Specificity	LR+	LR-	Accuracy
Exacerbation						
FeNO level	≥ 22	66.67%	30.0%	0.9523	1.111	47.37%
Absolute eosinophil count	≥ 240	55.56%	20.0%	0.6944	2.222	36.84%
More symptoms						
FeNO level	≥ 20	62.07%	44.44%	1.1172	0.8534	57.89%
Absolute eosinophil count	≥ 272	62.07%	66.67%	1.8621	0.5690	63.16%

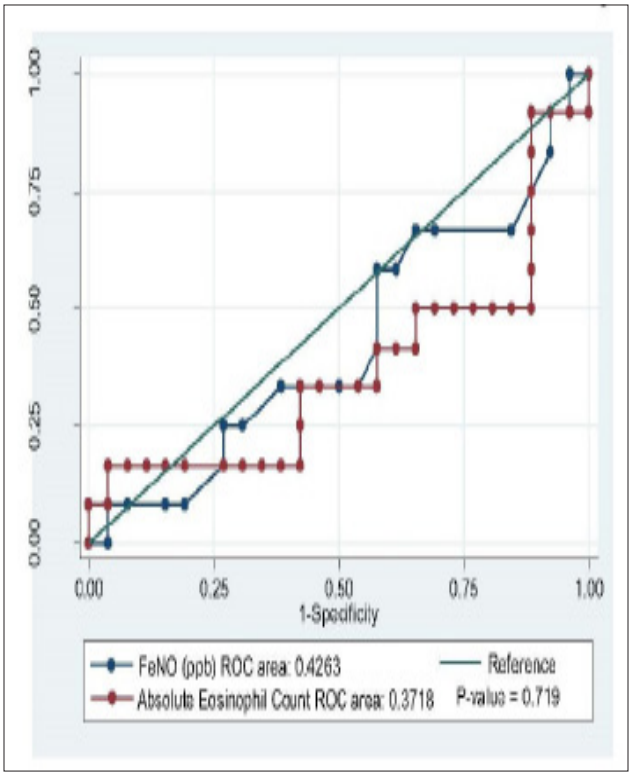

Fig. 2: Area under the ROC curve of FeNO and Absolute eosinophil count topredict exacerbation

Table 4 showed the threshold of FeNO level and absolute eosinophil count to predict risk to present with more symptoms and risk of exacerbation. For risk of exacerbation, the sensitivity of FeNO using a cutoff level of ≥ 22 was 66.67% with a specificity of 30.0%. On the other hand, the absolute eosinophil count at a cut-off of ≥ 240 has a sensitivity of 55.56% and specificity of 20.0%. For risk of symptoms, the sensitivity of FeNo level using a cut-off level of ≥ 20 was 62.07% and a specificity of 44.44%. The absolute eosinophil count using a cut-off of ≥ 272 has a sensitivity of 62.07% and a specificity of 66.67%.

Figure 1 showed the area under the ROC curve of both FeNO and Absolute Eosinophil Count in predicting exacerbation with FeNO level showing higher predictability than absolute eosinophil count.

DISCUSSION

The presence of eosinophilic inflammation in chronic obstructive pulmonary disease (COPD) has been reported in both stable disease and during exacerbations. High levels of blood eosinophils are a potential biomarker of eosinophilic airway inflammation in patients with COPD, and higher blood eosinophil counts have been associated with an increased risk of exacerbations in clinical studies of patients with COPD. However, data are limited on blood eosinophils and exacerbations among individuals with COPD in the general population.[6]

Measurement of FeNO is the only clinical test for evaluating Th-2 mediated airway inflammation that can be perfomed quickly and easily, providing consistent and accurate results in clinical practice at the point-of-care. The measurement of FeNO in human breath provides a rapid, noninvasive, and inexpensive tool to assess airway inflammation.[7] Race, sex, atopy, age, and smoking have been regarded as major factors influencing FeNO measurement in adults. Asians are reported to have higher FeNO levels than other ethnic groups, presumably due to dietary habits or genetic variations in NOS genes.[8]

Based on some reports, response to corticosteroids is likely to be greater in patients with COPD who have sputum eosinophilia or elevated FeNO. Significant correlations have also been reported between baseline FeNO and FEV1 improvement after 2 months following treatment with inhaled budesonide 800 mg/day. This finding raises the possibility that FeNO measurements might also be used to predict steroid responsiveness in COPD.[8]

In our study, the FeNO level decreases with increasing GOLD severity. According to Malerba et. al, FeNO levels can be influenced by disease severity. Severe COPD (particularly in combination with cor pulmonale) show lower levels of exhaled NO than ex-smokers and mild/moderate COPD. Increased exhaled NO levels have been reported in hospitalized patients during an exacerbation of COPD. This suggests the different inflammatory mechanisms in COPD.[2] The observational study done by Donohue et. al showed that increases in FeNO do occur in patients with COPD and there was no overall observable relationship between GOLD classification and FeNO level.[7] Our study also showed that the absolute eosinophil count levels tend to decrease with increasing GOLD severity except for patients in COPD GOLD 2 which showed the lowest levels of absolute eosinophil count. The study done by Canillas-Amancio et. al., showed that there was no relationship between severity of airflow limitation and the level of eosinophil count. [9]

It was noted that COPD Classification with less symptoms and COPD Classification with more symptoms have almost the same level of FeNO. The level of absolute eosinophil count is higher in COPD Classification with more symptoms than in COPD Classification with less symptoms. This shows that absolute eosinophil count seems to have an association with the severity of symptoms in COPD patients.

Patients with COPD Classification with low risk of exacerbation and COPD Classification with high risk of exacerbation have almost same median level of FeNO. The absolute eosinophil count in COPD Classification with low risk of exacerbation has higher levels as compared to COPD Classification with high risk of exacerbation. These results show that there is no association between the levels of FeNO and absolute eosinophil count with the risk of exacerbation in patients with COPD this may be due to our low sample size and unequal number of patients in each COPD Classification hence the results may not be truly representative.

The sensitivity and specificity of FeNO for predicting risk of exacerbation was 66.67% and 30.0% respectively. On the other hand, the absolute eosinophil count had a sensitivity of 55.56% and specificity of 20.0% for predicting risk of exacerbation. The sensitivity and specificity of FeNo level to predict risk COPD patient to have more symptoms were 62.07% and 44.44% respectively. The absolute eosinophil count has a sensitivity of 62.07% and a specificity of 66.67% to predict patients to have more symptoms. In the study of Yun, et. al, the threshold blood eosinophil count of ≥300 cells/μL to be associated with exacerbations. It showed that the increased COPD exacerbation risk associated with elevated eosinophil counts was driven by subjects with a history of frequent exacerbations, defined as two or more exacerbations per year.[10] FeNO is increased in patient with COPD exacerbation, compared to the levels observed in patients with stable COPD and current smokers and severe COPD (particularly in combination with cor pulmonale) show lower levels of exhaled NO than ex-smokers and mild/moderate COPD.[2] According to Antus and Barta, COPD patients with low FeNO concentration at the time of an acute exacerbation are more susceptible to developing severe acute exacerbations in the future. In contrast, patients with elevated FeNO level at exacerbation were less frequently hospitalized for exacerbations.[3] Individuals with blood eosinophils above versus below 0.34 x 109 cells per liter had an excess risk of exacerbations. The higher total numbers of blood eosinophils are associated with increased risk of exacerbations. Blood eosinophils greater than or equal to 0.34 x109 cells per liter had an increased risk of both severe and moderate exacerbations. The risk of exacerbations was further increased in a subgroup with clinical COPD, defined on the basis of reduced lung function, smoking, and exacerbation history.[6]

CONCLUSION

There is no clear association between FeNO and absolute eosinophil count to the severity and risk of exacerbation in COPD patients. There seems to be an inverse relationship between FeNO and the severity of airflow limitation.

There is no association between absolute eosinophil count and severity of airflow limitation. However, between the two, the absolute eosinophil count seems to have better association.

RECOMMENDATIONS

Due to the low sample size of this study, the association of FeNO and absolute eosinophil count to the COPD Classification was not clearly seen. We recommend that this study be conducted with a larger sample size be used.

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Factors Associated with Outcomes of Patients Who Underwent Bioprosthetic Heart Valve Replacement

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Background **---** Prosthetic heart valves are commonly used in the treatment of valvular heart disease. They are divided into two types, mechanical heart valves (MHV) and bioprosthetic heart valves (BHV). Bioprosthetic valve was made and promoted to be used as an alternative to the mechanical valve because of its better performance and usability without the need for life long blood thinning medication. As a result, the use of bioprothetic valve has been increasing since then. However, they have also noticed that the post-implantation complications have become more evident, such as: calcification, cusp tears, pannus growth, infective endocarditis, valve thrombosis and other factors specific to valve type.

The objective of this study is to delve into these complications, thereby raising awareness among cardiac surgeons, clinicians and pathologists. Early detection, management and prompt action can help prevent complications and further improve the patient's status after heart valve replacement.

Methods **---** 45 patients were included in the study from January 2009 up to December 2018. Data collection was gathered and processed from various sources, such as phone interviews, data collection forms and review of charts after obtaining consent from the patients. Two out of 45 participants found out to have an outcome (pannus growth). One patient developed pannus growth formation within >1-5 year post operation while the other had pannus growth formation within >5-10 years post operation.

Two patients had an outcome out of 45 patients who underwent bioprosthetic valve replacement. Patient A is a 31 y/o female while patient B is a 61 y/o female and both are functional class II. Patient A had valvular disease secondary to RHD while patient B was due to Degenerative. Patient A developed pannus growth formation 7 years post operation while patient B had pannus growth formation 5 years post operation.

Result **---** F In this study, patients' demographics, clinical and operative characteristics showed no significant correlation with the occurrence of the complication. A p-value of >0.05 was computed for the clinical and perioperative.

Conclusion **---** There were no short term outcomes (within 1 year post surgery) noted in the data collected. However, 1 out of 17 patients (5.88%) who underwent valve replacement using porcine bioprosthetic valve had pannus growth in ≤5 years while 1 out of 19 patients (5.26%) who received porcine bioprosthetic valve had pannus growth within 10 years. The complication that occurred within 1 to 5 years in this study is higher as compared to the one reported by other studies (<1%), while the complication rate that occurred between 5 to 10 years after surgery is lower than in some reports (20 - 30%). ***Phil Heart Center J 2022;25(2):43-49.***

Key Words: Bioprosthetic Heart Valve ■ Valve Replacement ■ Valvular Heart Disease ■ Mechanical valve ■

Prosthetic heart valves are commonly used in the treatment of valvular heart disease. They are divided into two types, mechanical heart valves (MHV) and bioprosthetic heart valves (BHV). Better performance and usability without the need for life long blood thinning medication are the main advantages of BHV. This will signify lower the risk of bleeding. Therefore, it becomes the preferred choice over their mechanical counterparts.[1] BHVs will likely have an even more important role in the treatment of cardiac valve disease given their almost exclusive use in transcatheter valve prostheses.[2] The advantages of BHVs include a reduced risk of thrombosis compared with increased usage of BHVs, post-implantation complications have also become more evident such as: calcification, cusp tears, pannus growth,

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infective endocarditis, valve thrombosis and other factors specific to valve type.[1]

In this paper we will look into these complications, thereby raising awareness among cardiac surgeons, clinicians and pathologists. Early detection, management and prompt action can help prevent complications and further improve the patient's status after heart valve replacement.

This is a cross-sectional analytical study over a ten-year period of cases seen at the Philippine Heart Center. The records of patients with BHV were reviewed and collected. The data collection was complemented by accessing the hospital's electronic medical records (EMR) and data collection form.

The general objective is to determine the factors associated with short and long term outcomes of patients post bioprosthetic heart valve replacement in the Philippine Heart Center from 2009-2018. While the specific objectives are: (1) to determine the short (within 1 year post-operative) and long term prevalence rates of mechanical deterioration, infective endocarditis, and bioprosthetic valve thrombosis of patients who underwent bioprosthetic heart valve replacement, (2) determine the short (within 1 year post-op) and long term prevalence rates of complications associated with BHV replacement such as stroke, acute limb ischemia, reoperations and mortality, (3) determine clinical and demographic factors associated with short and long term outcomes of patients who underwent bioprosthetic heart valve replacement, (4) determine perioperative factors associated with short and long term outcomes of patients who underwent bioprosthetic heart valve replacement.

METHODS

This is a cross-sectional analytical study conducted at the Philippine Heart Center. Included in the study are patients aged 19 to 90 years old who underwent bioprosthetic heart valve (aortic, mitral, tricuspid and pulmonary) replacement surgery (bioprosthetic, bioprosthetic mechanical) in the Philippine Heart Center from January 2009 to December 2018. While those exluded are patients who concurrently underwent other heart related surgeries such as CABG, etc. Patients whom immediate postop and long term data cannot be obtained/ incomplete data.

Study Maneuver: Patients who underwent bioprosthetic heart valve (aortic, mitral, tricuspid and pulmonary) replacement surgery (bioprosthetic, bioprosthetic-mechanical) from January 2009 up to December 2018 were identified. Basic clinical and surgical data were acquired from the hospital medical records and from pre-constructed data collection forms. Their clinical charts, their 2D echo results such as presence of calcification, cusp tears, pannus growth, infective endocarditis, valve thrombosis (done outside and inside PHC) and IOTEE results before and after valve replacement have been collected and retrieved. All adult post BHV replacement surgery cases were included in the study, whether done on elective or emergency basis, and whether it was a first time surgery or re-operation. Associated studied factors with outcomes of patients (calcification, cusp tears, pannus growth, infective endocarditis, valve thrombosis) post BHV replacement surgery were examined thoroughly.

A chart review was conducted for data collection, reporting clinical outcomes after bioprosthetic heart valve surgery. The list of patients who underwent bioprosthetic valve replacement was acquired from the census in the surgery office. Patients' charts were pulled out from the medical records. Each chart was reviewed for inclusion and exclusion criteria; patients with incomplete data were automatically excluded. Data collection was gathered and processed from various sources, such as data collection forms and review of charts after obtaining consent from the patients. Patients who haven't been contacted were excluded from the study.

Sample Size Calculation: A minimum 45 patients are required for this study based on

13.2% of reoperation rate at 10 years,[4] 10% desired half width of confidence interval and 5% level of significance.

Statistical Analysis: Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion was used for categorical variables, median and inter quartile range for non-normally distributed continuous variables, and mean and SD for normally distributed continuous variables. Fisher's exact test was used to determine the difference of frequency between patients with and without outcome. All statistical tests are two tailed tests. Shapiro-Wilk was used to test the normality of the continuous variables. Missing variables are not replaced nor estimated. Null hypotheses will be rejected at 0.05 α-level of significance. STATA 13.1 was used for data analysis.

RESULTS

Table I shows patient demographics and clinical characteristics of bioprosthetic heart valve replacement. There were 32 females (71.11%) and 13 males (28.89%). Majority of the population are functional class II 41 (91.11%) and belongs to the 5th decade of life or beyond, 26 (57.78%). All the subjects did not have history of previous surgery and all were scheduled as an elective case. Majority had an etiology of Rheumatic Heart Disease 25 (55.56%) followed by Degenerative causes 10 (22.22%), Congenital 6 (13.33%) and IE 4 (8.89%).

Single valve surgery was performed in 29 patients (64.44%) while 16 patients, (56.56%), had multiple valve surgeries. Majority had no comorbidities 21 (46.67%) followed by hypertension which is present in 18 patients (40%), diabetes in 10 patients (22.22%), CAD 2 (4.44%), and CVD 2 (4.76%).

Table II shows the operative characteristic associated with outcomes of patients who underwent bioprosthetic valve replacement. Bioprosthetic valve size 25mm is used in 18 patients, (35.29%), 21mm in 14 patients, 27.45%), 27mm 11 (21.57%), 19mm 6 (11.76%), 29mm 2 (3.92%). Majority received porcine bioprosthetic heart valve 41 (80.39%), bovine in 10 patients (19.61%). Cross clamp time of >2hours was recorded in 20 patients (44.44%), 1hour-1.5 hours in 11 patients (24.44%), and 1.5 hours - 2 hours, 4 (8.89%). 31 patients (60.78%) had bioprosthetic valve replacement in mitral valve position, Aortic position 20 (39.22%). Majority underwent single bioprosthetic valve replacement 39 (86.67%), double valve replacement in 6 patients (13.33%).

Table III and IV shows the frequency of short term (within 1 year) and long term (>1 year- 10 years) outcomes of patients who underwent bioprosthetic valve replacement. 2 patients were recorded to have complications. 1 patient developed pannus growth formation within >1-5 year post operation while the other had pannus growth formation within >5-10 years post operation.

Two patients had an outcome out of 45 patients who underwent bioprosthetic valve replacement. Patient A is a 31 y/o female while patient B is a 61 y/o female and both are functional class II. Patient A had valvular disease secondary to RHD while patient B was due to Degenerative. Both have comorbidities, patient A had CVD, patient B had DM and hypertension. Both did not have a history of previous valve surgery and were scheduled as an elective case. Patient A received a 25mm porcine bioprosthetic valve on.the mitral position. Patient B had 27mm porcine on the same valve position. Patient A developed pannus growth formation 7 years post operation while patient B had pannus growth formation 5 years post operation.

Table 1. Patient Demographics and Clinical Characteristics of Bioprosthetic Heart Valve Replacement

	Total (n=45)	With outcome (n = 2)	Without (n = 43)	P Value
	Frequency (%)			
Gender				1.000
Male	13 (28.89)	0	13 (30.23)	
Female	32 (71.11)	2 (100)	30 (69.77)	
Age at time of initial replacement				0.672
19 - 30	9 (20)	0	9 (20.93)	
30 - 50	10 (22.22)	1 (50)	9 (20.93)	
>50	26 (57.78)	1 (50)	25 (58.14)	
New York Heart Association Class				1.000
I	1 (2.38)	0	1 (2.5)	
II	41 (91.11)	2 (100)	39	
III	2 (4.76)	0	2 (5)	
IV	1 (2.38)	0	1 (2.5)	
Previous Valve Surgery				-
Yes	0	0	0	
No	45 (100)	2 (100)	43 (100)	
Type of Surgery				
Emergency	0	0	0	-
Elective	45 (100)	2 (100)	43 (100)	
Etiology				0.697
Congenital	6 (13.33)	0	6 (13.95)	
RHD	25 (55.56)	1 (50)	24 (55.81)	
Degenerative	10 (22.22)	1 (50)	9 (20.93)	
IE	4 (8.89)	0	4 (9.30)	
Others	0	0	0	
Single Valve Surgery	29 (64.44)	2 (100)	27 (62.79)	
Multiple Valve Surgery	16 (35.56)	0	16 (37.21)	0.531
Comorbidities				
CAD	2 (4.44)	0	2 (4.65)	1.000
Diabetes Mellitus	10 (22.22)	1 (50)	9 (20.93)	0.399
Hypertension	18 (40)	1 (50)	17 (39.53)	1.000
CVD	2 (4.76)	1 (50)	1 (2.33)	0.088
None	21 (46.67)	0	21 (48.84)	0.491

Table 2. Operative Characteristics Associated with Outcomes of Patients Who Underwent Bioprosthetic Valve Replacement

	Total (n=45)	With out-come (n = 2)	Without (n = 43)	P Value
	Frequency (%)			
Bioprosthetic valve size (n=51)				0.791
19 mm	6 (11.76)	0	6 (12.24)	
21 mm	14 (27.45)	0	14 (28.57)	
25mm	18 (35.29)	1 (50)	17 (46.28)	
27mm	11 (21.57)	1 (50)	10 (20.41)	
29mm	2 (3.92)	0	2 (4.08)	
Type (n=51)				1.000
Bovine	10 (19.61)	0	10 (20.41)	
Porcine	41 (80.39)	2 (100)	39 (79.59)	
Cross clamp time				0.206
30mins- 1hr	2 (4.44)	0	2 (4.65)	
1hr - 1.5hr	17 (37.78)	1 (50)	16 (37.21)	
1.5hr - 2hrs	6 (13.33)	1 (50)	5 (11.63)	
> 2 hrs	20 (44.44)	0	20 (46.51)	
Bypass Time				
30mins- 1hr	0	0	0	0.227
1hr - 1.5hr	11 (24.44)	0	11 (25.58)	
1.5hr - 2hrs	4 (8.89)	1 (50)	3 (6.98)	
> 2 hrs	30 (66.67)	1 (.50)	29 (67.44)	
Location of BPV (n=51)				
Aortic	20 (39.22)	0	20 (40.82)	0.514
Mitral	31 (60.78)	2 (100)	29 (59.18)	
Tricuspid	0	0	0	
Pulmonic	0	0	0	
Number of Valves replaced				
Single	39 (86.67)	2 (100)	37 (86.05)	1.000
Double	6 (13.33)	0	6 (13.95)	
Triple	0	0	0	

Table 3. Frequency of Short Term Outcomes (with-in 1 year post-op) of Patients Who Underwent Bioprosthetic Valve Replacement

	Within 6 months	6 months - 1 year
1. Mechanical deterioration (Clacification, Cusp tears, Pannus growth)	1	1
2. Infective Endocarditis	0	0
3. Bioprosthetic valve thrombosis	0	0
4. PV leak	0	0
5. Stroke	0	0
6. Acute Limb Ischemia	0	0

Table 4. Frequency of Long term Outcomes (>1 year post-op up to 10years) of Patients Who Underwent Bioprosthetic Valve Replacement

	>1 year - 5 years	>5 years - 10 years
1. Mechanical deterioration (Clacification, Cusp tears, Pannus growth)	1	1
2. Infective Endocarditis	0	0
3. Bioprosthetic valve thrombosis	0	0
4. PV leak	0	0
5. Stroke	0	0
6. Acute Limb Ischemia	0	0

Table 5. Patients with Outcome

Patient	A	B
Age	31	61
Gender	r	F
NYHA Class	II	II
Etiology	RHD	Degenerative
Comorbidities	CVD	DM, HTN
Previous valve surgery	None	None
Elective case	Yes	Yes
Bioprosthetic valve size	25mm	27mm
Bioprosthetic valve type	Porcine	Porcine
Valve position	Mitral	Mitral
Pannus growth formation (no. of years)	7 years post operation	5 years post operation

DISCUSSION

Management for people with valvular heart diseases depends on how severe their condition is. It can either be repaired or replaced. Currently, patients with faulty heart valves are having better quality of life as a result of the advances in prosthetic heart valve design.[5] Today, the most commonly used bioprosthetic valves are those from animal tissues, these include: porcine aortic valves and bovine pericardial tissue. Compared to standard porcine valves, bovine pericardial valves are more durable and known to have an outstanding hemodynamic performance even up to 10 years after valve replacement.[6] According to some studies, the process of tissue degeneration in most BHVs is gradual and progressive. The probability of failure is typically time dependent.[7] At present, patients implanted with porcine aortic valve, experience structural dysfunction of the valve in less than 1% of cases.[8] Statistics shows that within 10 years, 20– 30% becomes defective while in 12-15 years after operation, more than 50% of failure is due to primary tissue degeneration.[9]

In patients with outcome as mentioned in Table V, patient A is a 31 y/o female while patient B is a 61 y/o female. Patient A had pannus growth formation 7 years post operation. Patient B had pannus growth formation 5 years post operation. These results are in harmony with the study of Cohn L, Collins J, DiSesa V et al. In their study, they mentioned that in individuals less than 35 years of age, the overall possibility of structural failure is greater and age-linked. Same complications were observed in individuals less than 35 years old after 5 years from operation while in individuals more than 65 years old, failure of valve was observed only in 10% of cases.[10]

In the study of Diaz et al., it was observed that in younger individuals, greater competence of the immune system has greatly influenced the outcome.[11] They explained that the mechanism is due to IgM/IgG antibodies that enter the valve matrix. This action will

lead to macrophage deposition on the valve surface, followed by the breakdown of collagen and lastly calcification.[12] It evidently shows that the immune system plays a big role in the formation of calcification. Among individuals who are high risk for anticoagulant related hemorrhage and elderly, bioprosthetic valves are said to be more suitable. Due to higher closing pressures in the mitral valve, porcine valves tend to develop complications in the mitral location as compared to the aortic position.[9]

Both patients had pannus growth formation after several years from their operation according to the result of this study. This formation is expected as stated by Siddiqui R F, Abraham JR and Butany J, et al. In their study, they mentioned that in prosthetic valve replacement, pannus growth is viewed as a part of the normal healing process of the body. Pannus growth can extend onto the adjacent portions of the cusps, which in turn can cause BHV failure in the future. The effect of surgery can result in the formation of myofibroblasts, fibroblasts and capillary endothelial cells (pannus) overgrowth which are possibly initiated by small amounts of thrombus and inflammatory cells. As the abnormal growth of tissue matures, it leads to changes of the underlying tissue as a result of increased deposition of collagen to the pannus formation, wherein the collagen eventually retracts. For that reason, BHV survival and dysfunction is greatly influenced by the degree and quantity of pannus growth formation.[1] The growth of abnormal tissue around a prosthetic heart valve (pannus formation) has both beneficial and harmful effects. For a healing process to be completed, a small amount of tissue growth (forming a non-thrombogenic surface) over the suture line is desirable.[13] On the other hand, structural dysfunction (cuspal thickening, stiffening and progressive stenosis) that results from excessive pannus growth formation can be problematic.[1]

As mentioned in other studies, the etiology of pannus growth formation is mainly due to immunologic reaction of the body in response to the injury as caused by the implantation and the foreign body itself. Therefore, with regard to gender and the mitral position in relation to the formation of the pannus, they are not related to its growth.

Surgeons, clinicians and pathologists should be aware of these complications and the possible diagnosis, treatment and preventive measures in dealing with them. Having a fundamental knowledge about these complications will improve the quality of care of patients who underwent bioprosthetic valve replacement.

A study that includes bigger sample size is recommended. Furthermore, longer follow-up care, better documentation of diagnostic and laboratory results, and updated contact information should be done for easy retrieval and access for future studies.

The limitation of the study is that only those patients with retrievable chart, echocardiographic records, and those patients with updated contact information were only included in the study. More than half of the patients who underwent bioprosthetic valve replacement, especially those who were done 5-10 years ago, do not have updated phone numbers and echocardiographic results.

CONCLUSION

In this study, patients' demographics, clinical and operative characteristics showed no significant correlation with the occurrence of the complication. A p-value of >0.05 was computed for the clinical and perioperative factors.

There were no short term outcomes (within 1 year post surgery) noted in the data collected. However, 1 out of 17 patients (5.88%) who underwent valve replacement using porcine bioprosthetic valve had pannus growth in ≤5 years while 1 out of 19 patients (5.26%) who received porcine bioprosthetic valve had pannus growth within 10 years. The complication that occurred within 1 to 5 years in this study is higher as compared to the one reported by other studies (<1%), while the complication rate that occured between 5 to 10 years after surgery is lower than in some reports (20– 30%).

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Management of Coronary Artery Fistula

Karl Derrick O. Sia, MD; Jetz Marion P. Cruz, MD

Coronary artery anomalies (CAF) is a rare congenital anomaly with a prevalence of 0.2–2%.[4] It is defined as an abnormal communication between a coronary artery and a cardiac chamber bypassing the capillary bed or any part of the systemic or pulmonary.[1] Guidelines on the diagnosis and management of CAF are still inconsistent and evolving due to its' differing pathophysiologic mechanisms and clinical presentation.

A case of a 39 year old female who consulted at our institution due to intermittent palpitations diagnosed with coronary artery fistula underwent repair of coronary artery fistula. Intraoperatively they found a 3 mm opening noted 6 mm inferior to left main coronary artery ostium, coursing along the superior border of the left atrium underneath the SVC and ends into the right atrium. The fistula was plicated in a layered fashion. The patient tolerated the procedure and was discharged improved.

CAF are rare anomalies that are often asymptomatic. However, the "coronary steal" phenomenon can result in a variety of cardiac symptoms. Work up and imaging that can be done include echocardiography, CT scans and the gold standard, angiography. Treatment options include minimally invasive transcatheter closure or surgical ligation. These are low risk procedures with good prognosis on low term follow up.[2] ***Phil Heart Center J 2022;25(2):50-54.***

Key Words: Scimitar Syndrome ■ partial anomalous pulmonary venous return ■

Coronary artery anomalies (CAF) is a rare congenital anomaly with a prevalence of 0.2–2%.[4] It is defined as an abnormal communication between a coronary artery and a cardiac chamber bypassing the capillary bed or any part of the systemic or pulmonary.[1]

CAFs may show small changes in size over a span of 10-15 years. Small fistulas can also gradually become larger.[3]

Guidelines on the diagnosis and management of CAF are still inconsistent and evolving due to its' differing pathophysiologic mechanisms and clinical presentation. Since patients are often asymptomatic, CAFs are noted only as incidental findings in radiology or angiography. CAF could present as reversible ischemia and angina caused by 'coronary steal phenomenon'. Wengrofsky et al. describes this as an abnormal pressure gradient from a high pressure coronary artery to a low pressure venous capacitance chamber. Patients presenting with myocardial infarction have been reported in literature, but this rarely occurs in the absence of CAF thrombosis.[8] Other studies reported cases that were associated with congestive heart failure, rupture of the aneurysm, pulmonary hypertension, and sudden cardiac death.[3]

Case: This is a case of a 39 year old female who consulted at our institution due to intermittent palpitations of approximately 25 years duration. There were no complaints of chest pain or difficulty of breathing. She has no history of hypertension or diabetes mellitus.

A 2D echo was done, with the following results: left ventricular hypertrophy, end-diastolic diameter (6.1 cm), with segmental wall motion abnormality and depressed systolic function (EF 40%). Dilated right ventricular dimension with adequate contractility (RVFAC of 57%, TAPSE of 2.9 cm). There is aneurysmal dilated left main coronary artery was noted commencing from the left coronary sinus measuring 1.8 cm at its widest diameter at the base. It courses anterior then behind the left atrium and then behind the right atrium and is seen draining both into the left and right atria.

Finalist, Case Report. 29th PHC Annual Research Paper Competition and Poster Presentation held on February 24, 2021 at Philippine Heart Center. Correspondence *to* ***Dr. Karl Derrick O. Sia.*** Department of Cardiovascular Surgery and Anesthesia. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication** ISSN 0018-9034

Diameter of the fistula within the left and right atria areas are within 0.9-2.0 cm. The patient underwent coronary angiography which revealed large fistula from the left coronary cusp coursing posteriorly and draining to the right atrium.

A cardiac CT scan was performed to determine the coronary fistula anatomy. CT scan images documented that there was an aortico-bi-atrial fistula with the length of tunnel measuring 10 cm x AP of tunnel measuring 4.3 cm. This aortico-bi-atrial tunnel started from the left side of sinus of Valsalva and drains to the right atrium, and left atrium, coursing behind the right atrium. Its origin appeared to be immediately below the origin of left main coronary artery. (*Figures 1 and 2*).

The procedure done was repair of coronary artery fistula. The patient was placed in supine position under general endotracheal anesthesia. A midline sternotomy was made. Cannulation involved the aorta, SVC, IVC, with caval tapes placed. CPB was instituted and the patient was cooled to 34^0C. The cross-clamp was applied and retrograde cold blood cardioplegia was initially given. The aorta was then opened and antegrade cold blood cardioplegia was given via the two coronary ostia. The aorta was then transected. Two small fistula openings were noted. The smaller one was cannulated with a Fr 5 feeding tube, which encountered resistance when threaded. The larger one was cannulated with a Fr 10 feeding tube, which freely passed into the outpouching lateral to the right atrium (*Figure 3 and 4*).

The caval tapes were then tightened and the right atrium was opened. A small opening was noted connecting the right atrium to the fistula. It was enlarged and the outpouching was plicated in a layered fashion until the opening itself was closed. The right atrium was then closed in two layers of 5-0 polypropylene. The caval tapes were then released. The left atrium was opened to inspect for any fistulous connection, and then was closed in two layers of 4-0 polypropylene. The two openings in the left coronary sinus of valsalva were closed. The dilatation of the sinus was then patched with PTFE. Rewarming was done as the aorta was being closed. Deairing maneuvers were done and the cross-clamp was released. Cardiopulmonary bypass was then gradually weaned. Decannulation proceeded during protamine infusion. Hemostasis was followed. A Fr 28 thoracic catheter was placed in the right pleura, while a Fr 32 thoracic catheter was placed within the pericardium. A Fr 19 silicone drain was likewise placed within the pericardial cavity. A pacing wire was attached onto the right ventricle. The sternum was closed with wires. The wound was closed in layers and was dressed afterwards. The patient tolerated the procedure well and she was transferred to surgical ICU stable.

Post operatively, patient was stable and post-operative course was unremarkable. She was transferred to a regular ward and was eventually discharged.

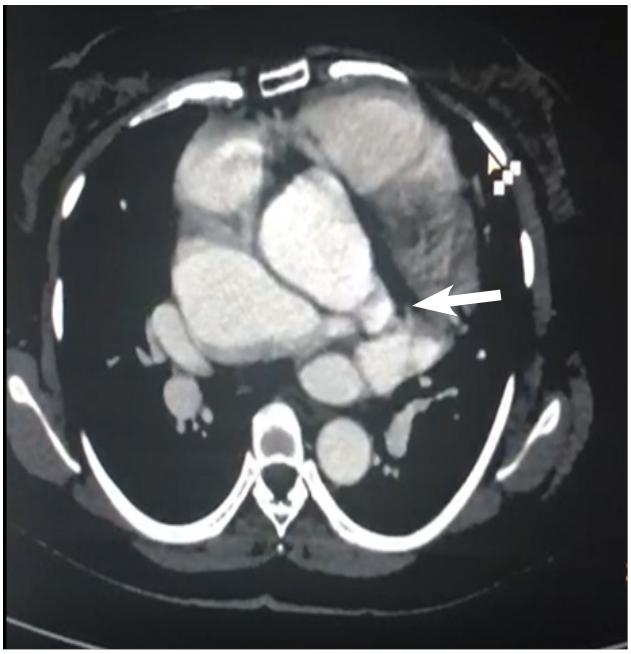

Fig. 1: Aortico-bi-atrial tunnel started from the left side of sinus of Valsalva and drains to the right atrium coursing behind the right atrium

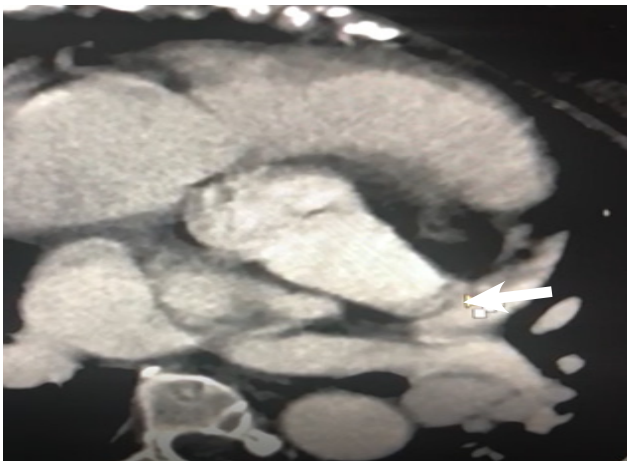

Fig. 2: Aortico-bi-atrial tunnel started from the left side of sinus of Valsalva and drains to the left atrium coursing behind the right atrium

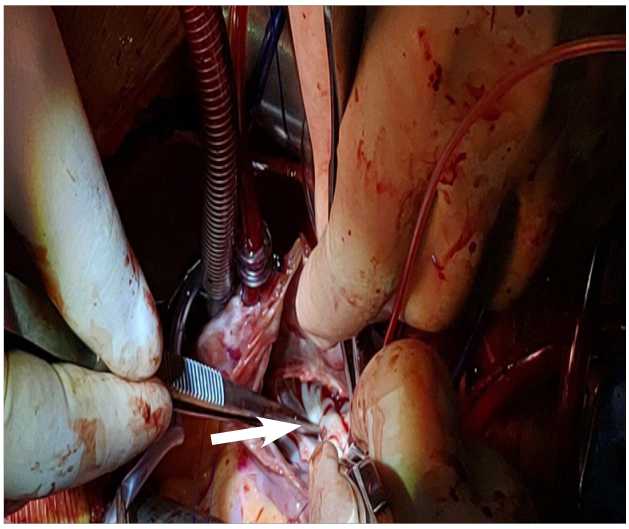

Fig. 3: Fistula noted at posterior wall of right atrium

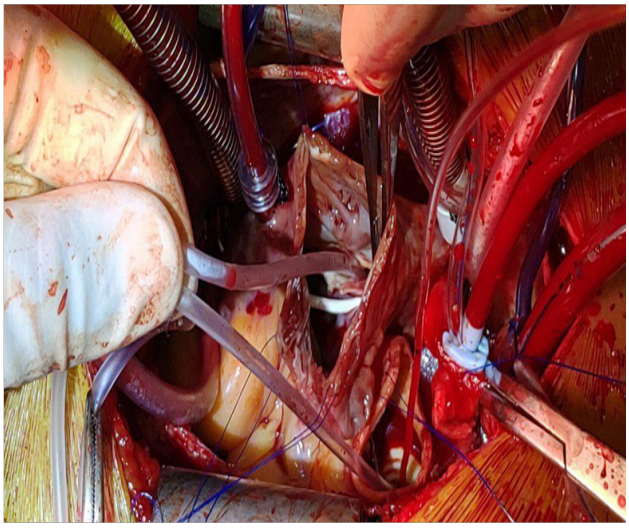

Fig. 4: Fistula cannulated with a Fr 10 feeding tube, which freely passed into the outpouching

DISCUSSION

Coronary artery fistulae are rare anomalies, presenting in 0.002% of the population.[2,6] Majority are congenital in origin, comprising 48.7% of congenital coronary anomalies.[2] Reddy et al. defined it as an abnormal communication between coronary arteries and vascular structures without an interposed capillary bed. A coronary cameral fistulae drains into a cardiac chamber. A coronary arteriovenous fistulae drains into a vein, such as the vena cava, coronary sinus, bronchial veins, or pulmonary artery.[6] A classification for CAF by Reddy et al. is further described in Table 1. The Sakakibara CAF classification was described by Wengrofsky et al. This categorizes the CAF based on its origin from the coronary artery as shown in Table 2. Our patient exhibited Sakakibara Type B classification where the origin of the fistula is beyond proximal third of the native vessel.

Table 1. Classification of Coronary Artery Fistulas

Vessel of origin
Left coronary artery
Left anterior descending
Ramus intermedius
Left circumflex coronary
Right coronary artery
Anomalous coronaries

Table 2.

Segment of origin
Sakakibara type A: originating from the proximal third of the native vessel
Sakakibara type B: beyond proximal third or as continuation of native vessel

Imaging is important in determining origin, dilatation and termination of the CAF. This can be demonstrated using magnetic resonance imaging (MRI), 2D echocardiogram, CT Angiogram, or cardiac catheterization with coronary angiography.[8] Angiography shows the most detailed anatomy of the fistula such as the size, course, origin, presence of stenosis, and the drainage site.[2]

Patients do not present with symptoms since majority of CAFs are small and blood supply to the myocardium is still sufficient. CAF can grow with age and become symptomatic if left untreated. Symptoms are noted in 19% of patients less than 20 years old and 63% in older patients. Only 1-2% of cases had spontaneous closure of the fistula as a result of spontaneous thrombosis. Patients become symptomatic and develop complications especially when the shunt has a Qp-to-Qs ratio greater than 1.5. Mangukia described four complications of CAF. The first is *excessive load to the cardiac chamber.* CAFs lead to increased left ventricular end-diastolic pressure, left ventricular hypertrophy, and cardiac congestion in older patients. *Coronary complications* are caused by increased flow to the coronary artery branches proximal to the shunt site, causing hypertrophy. Coronary steal is common. This leads to chronic myocardial ischemia and angina, congestive heart failure, cardiomyopathy, and myocardial infarction. *Valvular and endocardial complications* result from papillary muscle dysfunction. Lastly, extracardiac complications can occur such as associated aneurysms and pulmonary hypertension. Aneurysms can rupture, leading to hemopericardium.[4]

Early surgical intervention is recommended due to the aforementioned complications and low rates of spontaneous closure.[4] The American College of Cardiology/ American Heart Association (ACC/AHA) guidelines state that "Percutaneous or surgical closure is a Class I recommendation for large fistulae regardless of symptoms and for small- to moderate size fistulae with evidence of myocardial ischemia, arrhythmia, ventricular dysfunction, ventricular enlargement, or endarteritis"[2]
.

Mangukia describes three main surgical techniques: The most common is epicardial identification and mobilization of the fistula, with ligation or division of the fistula. An arteriotomy in the dilated proximal coronary artery can also be done to close the fistula site. The third method exposes the fistula from within the cardiac chambers or pulmonary artery and close it by direct suture. This was the same method used in the case presented in this report. If the fistula is larger, placing an autologous pericardial patch is also an option.

Transcatheter closure (TCC) can be another option for patients with a proximally located fistula or a single drainage site and for those at high risk for open surgery.[3] TCC avoids related complications of surgery such as bleeding, infections, inflammatory response due to cardiopulmonary bypass, and general anesthesia exposure.[2] According to Mangukia et al, transcatheter closure uses occlusion coils in the form of umbrella device detachable balloons,vascular plugs, covered stents and histoacryl resin. Contraindications to TCC described are very young age, a large and wide fistula, a fistula with several communications, a distal fistula, an adjacent vessel at risk, and the need for other concomitant surgical repairs.[4]

Patients that undergo closure of CAF have an excellent prognosis. Recurrence rates are as range from 9 to 19% for TCC and 25% in surgical ligation. The post-operative outcome is influenced by severity of the shunt and associated complications such as heart failure, bacterial endocarditis and pulmonary hypertension. Challoumas et.al recommends long-term follow-up to monitor complications such as recanalization, persistent dilatation of the coronary artery and ostium, thrombus formation, calcification, arrhythmias, myocardial infarction and residual leaks.[2]

CONCLUSION

CAF are rare anomalies that are often asymptomatic. However, the "coronary steal" phenomenon can result in a variety of cardiac symptoms. Work up and imaging that can be done include echocardiography, CT scans and

the gold standard, angiography. Treatment options include minimally invasive transcatheter closure or surgical ligation. These are low risk procedures with good prognosis on low term follow up.[2]

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The Association of Intraoperative Rocuronium Infusion with the Occurrence of Postoperative Residual Curarization Among Post Coronary Artery Bypass Graft Patients in a Surgical Intensive Care Unit

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Background **---** Short-acting and intermediate-acting neuromuscular blocking agents have gained favor in fast-track cardiac anesthesia since these are associated with early extubation. However, despite the use of these drugs, postoperative residual curarization (PORC) still occur in the post anesthesia care unit. This study aims to determine if intraoperative Rocuronium infusion contributes to the development of PORC among post-coronary artery bypass graft (CABG) patients in the surgical intensive care units (SICU) of the Philippine Heart Center.

Methods **---** A prospective observational cohort study was undertaken among 60 patients for elective CABG surgery. Within an hour from SICU arrival, Train of Four (TOF) ratio was obtained and a value of <0.7 signified the presence of PORC.

Result **---** Fifty-seven (57) out of 60 (95%) were found to have PORC. The rocuronium induction dose and duration ofinfusion did not contribute to the occurrence of PORC while the use of reversal drug was seen to significantly preventits occurrence(p-value=0.003). Patients without PORC were significantly warmer (36.4oC vs 34.8oC, p-value=0.019) upon SICU arrival compared to those with PORC.The duration of ventilatory support was significantly longer in those with PORC (510 min vs 305 mins, p-value=0.021).

Conclusion **---** This study showed a high incidence of PORC among post-CABG patients in the SICU with the current practice of Rocuronium infusion during surgery. The use of muscle relaxant reversal drug was seen to significantly prevent the development of PORC while higher body temperature upon SICU arrival was observed in patients that did not develop PORC. This study was also able to show that the development of PORC prolonged post-operative mechanical ventilatory support hindering goals of fast track cardiac surgery.

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Key Words: operative residual curarization ■ residual muscle paralysis ■ Rocuronium ■ fast track cardiac sur ■ ERACS

Fast Tract Cardiac Anesthesia, now known as Enhanced Recovery After Cardiac Surgery (ERACS) integrates the practice of early tracheal extubation and promotes a decrease in the number of days in the intensive care unit (ICU), which in effect lessens the total duration of hospital stay[1] contributing to cost reduction in cardiac surgery and have shown to be acceptably safe for patients.[2] The demand for ERACS affect all aspects of cardiac anesthesia and behooves cardiovascular anesthesiologists to re-evaluate their current perioperative strategies, preferring to use short or intermediate acting muscle relaxants since these drugs are associated with early extubation and reduced symptoms of residual paresis.3 However, despite the use of shorter-acting muscle relaxants, residual muscle paralysis or postoperative residual curarization (PORC) do occur in the post anesthesia care unit among fast-track cardiac surgery patients.[4]

Currently, there are no guidelines for the dosing, monitoring and reversal of muscle relaxants in fast track cardiac anesthesia. An expert consensus for optimal perioperative care in cardiac surgery was released last 2018 by the

Finalist, Oral Presentation - Original Paper. 29th PHC Annual Research Paper Competition and Poster Presentation held on February 24, 2021 at Philippine Heart Center. Correspondence *to* ***Dr. Marion R. Nuevo.*** Department of Cardiovascular Surgery and Anesthesia. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication** ISSN 0018-9034

ERAS Cardiac Surgery Society,[5] however, no recommendations were given regarding the dosing, monitoring and reversal of neuromuscular blockade. In this institution, almost all muscle relaxants are given as continuous infusion intra-operatively and the use of neuromuscular blockade monitoring and reversal are not part of routine standards of care during cardiac surgery. In addition, there has not been any study regarding the incidence of postoperative residual curarization and its associated contributing factors among cardiac surgery patients in the Philippine Heart Center (PHC).

With this prospective study, the data obtained can help us determine if PORC do occur in post-coronary artery bypass graft CABG patients in PHC. This study shall encourage a review of the current anesthesia practice particularly with regards to the use of muscle relaxants, its delivery and monitoring. Also, the data from this research can contribute to the improvement of the current routine practices of anesthesia in our institution. Lastly, our observations may also contribute to the practice guidelines regarding the use of neuromuscular blocking drugs in fast-track cardiac anesthesia and ERACS.

The general objective of this study aimed to determine if the current practice with regards to Rocuronium, delivered by continuous infusion technique until end of surgery, contributed to the development of postoperative residual curarization among post-coronary artery bypass graft (CABG), patients in the surgical intensive care units (SICU) of the Philippine Heart Center. While the specific objectives are: to estimate the incidence of PORC among post-CABG patients by measuring their train-of-four (TOF) ratio upon arrival at the SICU; determine the following data regarding the use of Rocuronium infusion among those with and without PORC , (total intraoperative dose, dose infusion and duration of infusion); and to determine any association regarding the use of Rocuronium infusion and the occurrence of PORC among post-CABG patients.

METHODS

Study Design: This is a prospective observational cohort study. Data collection was conducted at the Surgical Intensive Care Units (SICU) 1 and 2 of the Philippine Heart Center from the months of November 2019 to September 2020.

Included in the study were patients who are Filipino aged 19 years old and above who were able to give an informed consent a day prior their elective CABG surgery. These patients must have been given Rocuronium intra-operatively delivery by continuous drug infusion. In addition, qualified participants must have been admitted at the surgical intensive care units 1 and 2 for further postoperative monitoring.

On the other hand, patients that had the following characteristics were excluded from the study: patients that received other types of muscle relaxants, patients with ejection fraction less than 30%, preoperative use of inotropes or intra-aortic balloon pump, patients with severe chronic pulmonary disease, patients with known renal, hepatic and neuromuscular diseases and any patient who refused to be part of this study.

Sample Size Calculation: A minimum of 56 patients was required for this study based on 66% prevalence of residual neuromuscular blockade,[6] 5% level of significance and 12.5% desired half width of the confidence interval.[10]

Study Maneuver: Prior to the performance of this study, approval from the PHC-IERB was obtained. All qualified study participants were asked to accomplish an informed consent form before being included in the research.

The informed consent was obtained at least a day prior to their scheduled surgery in the patient's respective ward where they were admitted. The principal investigator conducted the process for the informed consent as long as she was not be the primary anesthesiologist of the surgery of the patient being recruited. The process of informed consent for this study was done separately from the process of informed consent for the surgery.

Within an hour of the admission of qualified study subjects at the surgical intensive care unit, the principal investigator measured the train-of-four ratio of the patients. Figure 1 shows how the patient's hands were positioned and where the electrodes were placed. An accelero-myograph was utilized to obtain the TOF ratio using the adductor pollicis muscle of the hand. The strength of the contraction of the adductor pollicis was then measured. Three readings were obtained and the average of the three measurements was the reported TOF ratio. This was done in order to determine if the TOF ratio is < 0.7, which signified the presence of postoperative residual curarization or residual paralysis.

The occurrence of postoperative residual curarization among post-op CABG patients was the dependent or outcome variable in this study. This was determined by the presence of TOF ratio <0.7 upon arrival at SICU. After which, subjects were divided to those with PORC and those without PORC.

Independent or exposure variables of this study on the other hand were the following: total dose of Rocuronium given intraoperatively, dose of Rocuronium infusion and duration of Rocuronium infusion. Confounding variables in this study were hypothermia, prolonged anesthesia time or prolonged exposure to sevoflurane and the sedative effects of opioids and benzodiazepine. All of these are known to be synergistic to the effects of muscle relaxants and may contribute to the occurrence of post-operative residual curarization.

Statistical Analysis: Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables, median and inter quartile range for non-normally distributed continuous variables, and mean and SD for normally distributed continuous variables.

Fishers Exact test for categorical variables and Wilcoxon rank sum test for continuous variables were used to determine the difference between patients with and without PORC. Odds ratio and corresponding 95% CI from binary logistic regression were computed to determine the significant factors of PORC. Null hypotheses was rejected at 0.05α-level of significance and STATA 13.1 was used for data analysis.

Ethical Considerations: This study was conducted in accordance to the ethical principles stated in the Declaration of Helsinki and ICH-GCP. Participants in this study were patients admitted in the Philippine Heart Center during the duration of the study period. Study participants were 19 years old and above that fit the given inclusion criteria and were able to give an informed consent.

The informed consent were obtained at least a day prior to their scheduled surgery in the patient's respective ward where they were admitted. The principal investigator conducted the process for the informed consent as long as she was not the primary anesthesiologist of the surgery of the patient being recruited. The process of informed consent for this study was done separately from the process of informed consent for the surgery.

The study participants were assigned a patient's code number and was kept anonymous in the data collection form that was used in this research. All information obtained in this study were kept private and confidential in password protected files and computers. Only the author of this study and the Institutional Ethics Review Board of the Philippine Heart Center have access to these files.

No incentives or compensation were given to the qualified study participants that agree to be included in this research. Likewise, the participants did not receive any direct personal benefit from this research. However, their participation greatly contributed to the current knowledge regarding the use of Rocuronium during coronary artery bypass graft surgery.

Information obtained in this research also helped create standardized clinical practice among anesthesiologist that will further promote patient safety. The participation of the qualified subjects was during their stay in the SICU. This lasted up to the point that they were transferred back to their room or ward.

All study participants received the current standards of care given to patients who underwent coronary artery bypass graft surgery in PHC. The qualified subjects were exposed to minimal discomfort during the measurement of their train-of-four ratio or TOF ratio upon admission at the SICU. Any pain or discomfort that the patient feltduring the measurement the TOF ratio was addressed with pain medications already provided in their postoperative pain regimen.

RESULTS

A total of 60 patients were included in the study and only 3 out of 60 (5.0%) are without PORC while 57 out of 60 (95%) were found to have residual paralysis in the immediate postoperative period at the SICU. Those with PORC were further divided based on their TOF count as shown in Figure 2. Three out of the 57 (5.0%) had TOF>4, 21 out of the 57 (35.0%) had TOF 1-4 and 33 out of the 57 (55.0%) had TOF 0.

There was no significant difference with regards to the demographic profile of the patients in both groups as well as in the duration of bypass, cross clamp, surgery and anesthesia times as shown in Table 1. As shown in Table 2, the Rocuronium induction dose and duration of Rocuronium infusion among patients without PORC was comparable with those with PORC. The Rocuronium infusion dose was not consistently reflected in the anesthesia records hence the total Rocuronium dose was not obtained in both groups. Intraoperative TOF monitoring was not done in all patients included in this study. Lastly there was a significant difference in the proportion that used the drug Sugammadex, a muscle relaxant reversal, between those without PORC (66.7%) and those with PORC (1.7%) (p-value= 0.005).

All patients in this study received fentanyl and midazolam intraoperatively. The median Fentanyl dose and the median Midazolam dose of the patients without PORC was comparable with those with PORC. For the intraoperative temperatures of the subjects in this study, there was likewise no significant difference between the two groups as shown in Table 3.

The postoperative recovery data is shown in Table 4. The median TOF ratio in patients without PORC was 81% while the median TOF count in those with residual paralysis was 1.0. In both groups, majority of the patients were still sedated upon arrival at SICU. Patients without PORC were significantly warmer (36.4oC, IQR=0.6) compared to those with PORC (34.8oC, IQR=1.2) (p-value=0.019). The duration of the interval between SICU arrival and weaning as well as the duration of ventilatory weaning in patients without PORC did not differ significantly from those who had PORC. However, the duration of ventilatory support was significantly shorter in those without residual paralysis (305 min, IQR=108.5) compared to those with PORC (510 min, IQR= 645.0) (p-value=0.021). None of the patients without PORC were reintubated while 2 (3.5%) among those with PORC were reintubated. Lastly, the duration of ICU stay of the patients without PORC was shorter but not significantly different from those with PORC.

Only use of reversal drug was seen to be significantly associated with occurrence of PORC (p-value=0.003). Use of reversal drug significantly reduced the likelihood of PORC by 0.009 times (95%
CI= 0.0004 to 0.2).

Table 1. Demographic and Procedural Profile of the Patients

	Without PORC (n=3)	With PORC (n=57)	P Value
	Frequency (%); Mean + SD; Median (IQR)		
Age	56.0 ± 12.3	58.5 ± 8.1	0.852
	61.0 (11.5)	60.0 (12.0	
Sex			1.000
Male	3 (100.0%)	47 (82.5%)	
Female	0 (0.0%)	10 (17.5%)	
Weight (kg)	70.0 ± 8.7	70.8 ± 11.7	0.959
	66.0 (8.0	68.5 (13.9)	
Height (cm)	162.0 ± 4.4	163 ± 8.3	0.734
	160.0 (4.0)	163.0 (10.)	
BMI	27.0 ± 4.6	26.4 ± 3.2	0.932
	26.0 (4.5)	26.0 (5.0)	
Comorbidities			
Hypertension	1 (33.3%)	34 (59.6%)	0.565
Diabetes Mellitus	0 (0.0%)	28 (49.1)	0.241
Duration of CPB (mins)	166.7 ± 50.2	107.8 ± 66.0	0.118
	154.0 (49.0)	122.0 (43.2)	
Duration of AXC (mins)	115.0 ± 48.8	89.0 ± 56.1	0.665
	98.0 (46.5)	97.5 (53.5)	
Duration of surgery (mins)	325.3 ± 40.2	393.5 ± 78.9	0.635
	330 (40.0)	390 (97)	
Duration of anesthesia (mins)	380.0 ± 53.3	336.7 ± 68.6	0.709
	360 (50.5)	335 (78.0)	

Table 2. Clinical Characteristics and Income Class of the Study Group

	Without PORC (n=3)	With PORC (n=57)	P Value
	Frequency (%); Mean + SD; Median (IQR)		
Induction Dose (mg/kg)	0.97 ± 0.29	0.79 ± 0.22	0.168
	0.80 (0.25)	0.80 (0.10)	
Infusion Duration (min)	292.7 ± 31.5	315.5 ± 71.9	0.487
	286.0 (31.0)	306.0 (88.0)	
Intra-op TOF Monitoring	0	0	-
Rocuronium Reversal	2(66.7%)	1 (1.75)	0.005

Table 3. Clinical Characteristics and Income Class of the Study Group

	Without PORC (n=3)	With PORC (n=57)	P Value
	Frequency (%); Mean + SD; Median (IQR)		
Fentanyl Dose	8.0 ± 4.3	8.5 ± 4.3	0.168
	7.6 (4.3)	7.8 (5.5)	
Midazolam Dose	0.08 ± 0.06	0.07 ± 0.04	0.487
	0.04 (0.06)	0.07 (0.05)	
Temperature Range	286.0 (31.0)	306.0 (88.0)	
Highest	36.4 ± 0.2	36.4 ± 0.5	
	36.3 (0.2)	36.0 (0.8)	
Lowest	31.6 ± 1.0	31.4 ± 2.0	0.671
	32.0 (0.9)	32.0 (2.2)	

Table 4. Postoperative Recovery Data

	Without PORC (n=3)	With PORC (n=57)	P Value
	Frequency (%); Mean + SD; Median (IQR)		
TOF Ratio/ Count at SICU	82% ± 8%	1.2 ± 1.1	-
	81% (8%)	1.0 (1.7)	
Level of consciousness			
Awake	0 (0.0%)	0 (0.0%)	
Drowsy	1 (33.3%)	10 (17.5%)	0.462
Sedated	2 (66.6%)	47 (82.5%)	
Temperature at SICU	36.0 ± 0.7 36.4 (0.6)	34.6 ± 1.0 34.8 (1.2)	0.019
Interval from SICU arrival to Weaning (mins)	140.7 ± 105.1 100.0 (99.0)	480.7 ± 552.4 290.0 (285.0)	0.053
Duration of Ventilatory Weaning (mins)	180.0 ± 143.1 105.0 (127.5)	305.8 ± 404.3 175.0 (185.0)	0.270
Duration of Ventilatory Support	300.7 ± 108.6 305.0 (108.5)	858.1 ± 886.8 510.0 (645.0)	0.021
Reintubation	0 (0.0%)	2 (3.5%)	1.000
SICU Stay (hours)	43.7 ± 5.9 46.0 (5.6)	63.9 ± 48.9 47.3 (23.7)	0.476

Table 5. Factor of PORC

Factors	Odds Ratio	95.1% CI	P - Value
Intubation Dose	0.1	0.005 to 3.3	**0.217**
Duration of Infusion of Rocuronium	1.0	0.99 to 1.0	0.578
Use of reversal drug	0.009	0.0004 to 0.2	0.003

DISCUSSION

This study showed an incidence of postoperative residual paralysis among post-CABG patients in the SICU to be 95.0%. The induction dose and infusion duration of Rocuronium did not affect the occurrence of PORC. While the use of reversal drug however was seen to be significantly associated with the incidence of PORC wherein it was shown to be a preventive factor. Upon SICU arrival, those with residual paralysis had significantly lower body temperatures compared to those without PORC. The duration of mechanical ventilatory support was found to be significantly shorter in those without PORC. No difference was seen between those with PORC and those without PORC in terms of sedation doses, intraoperative body temperatures, level of consciousness in SICU, the interval between SICU arrival and weaning, duration of ventilatory weaning and length of SICU stay.

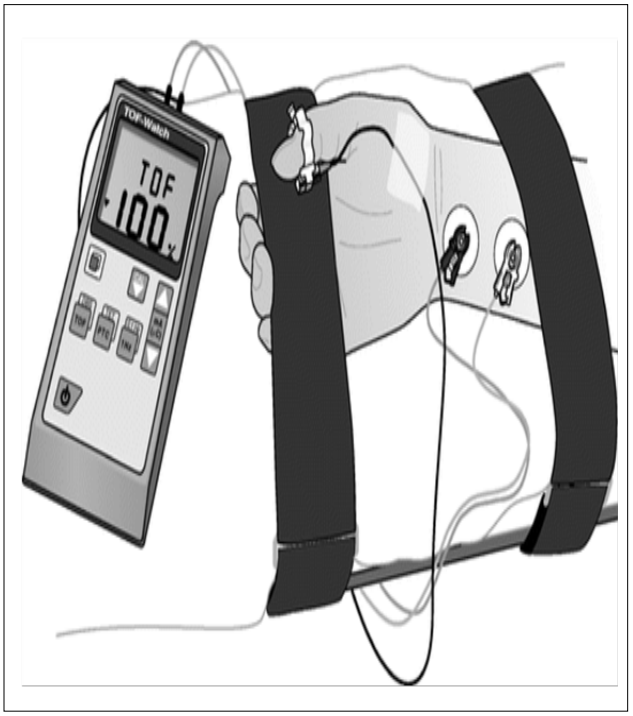

Fig. 1: TOF Ratio Measurement

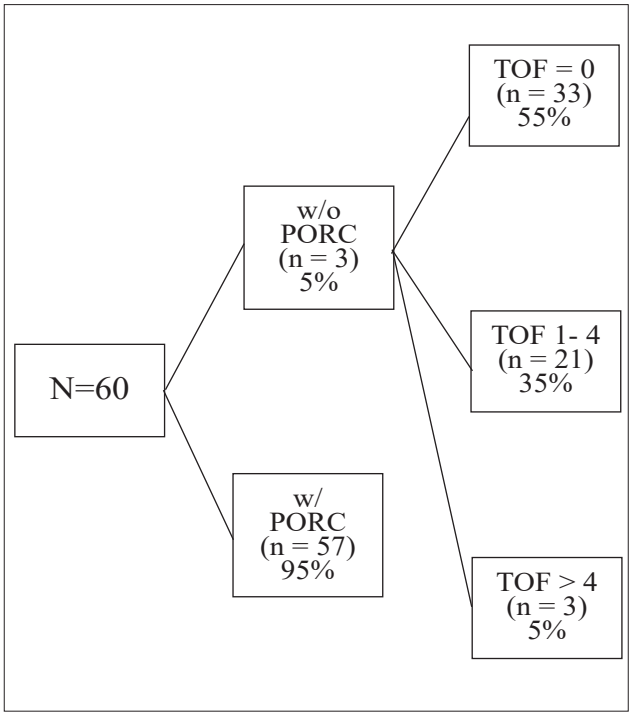

Fig. 2: Incidence of PORC

The use of muscle relaxants is an essential and non-negotiable component of anesthesia because these drugs facilitate not only good airway control, smooth endotracheal intubation and ventilation, but also ensures good surgical operative conditions which includes surgical immobilization and optimal surgical field.[6] In cardiac anesthesia, the perioperative use of muscle relaxants enable smooth quick induction, counteracts opioid-induced rigidity seen during opioid induction, decrease oxygen consumption during cardiopulmonary bypass (CPB) and prevent hypothermia-induced shivering.[7]

Residual curarization or residual neuromuscular blockade is defined as the inadequate neuromuscular recovery as measured objectively thru neuromuscular monitoring, like the 'Train of Four'. A residual block is present when the train-of-four (TOF) ratio is less than 0.7, in some literature 0.9.4 Unfortunately, without proper neuromuscular monitoring, residual blockade is a commonly unrecognized complication in the early postoperative period and has been associated with awake-paralysis, generalized weakness,[8] weakness of upper airway muscles, airway obstruction and impaired pharyngeal function. Furthermore, such has been shown to increase the risk of aspiration, impair the hypoxic ventilatory response and lead to inadequate recovery of pulmonary function, all of these contributing to critical respiratory events,[4,10] which sometimes even lead to a reintubation and resumption of mechanical ventilation.

In the meta-analysis of Naguib et al. (24 trials with 3375 patients), findings showed that approximately 40% of patients receiving intermediate-acting neuromuscular blocking drugs during their operation had a TOF ratio <0.9 in the post-anesthesia care unit.[9] Roy et al. in his observational study reported a 66% incidence of PORC among fast-track cardiac surgery.[8] In the current study, the 95% incidence of PORC was higher compared to previous literatures.

Rocuronium, an intermediate acting neuromuscular blocking agent, has shown to reduce tracheal extubation times and symptoms of residual pares is when compared to longer acting muscle relaxants such as Pancuronium.[7,11] However, no other studies were found which determined the association of Rocuronium induction dose and infusion duration with PORC in a group of post-coronary artery bypass graft patients. This study showed lack of significant association between induction dose of Rocuronium as well as duration of Rocuronium infusion and PORC. The lack of association however may be due to the limitation of the study wherein only a small number of patient did not develop PORC (three only) resulting to reduced power of the statistical analysis.

Cardiopulmonary bypass contributes to an increased risk of residual muscle paralysis in the immediate postoperative period because of the effects of CPB on the pharmacokinetics and pharmacodynamics of muscle relaxants. The CPB-related factors include the increased sensitivity of the neuromuscular junction to muscle relaxants, the decreased drug metabolism and the decreased elimination by the liver and kidneys, particularly during hypothermic CPB or in patients with deranged liver and renal functions. Other factors that contribute to the prolongation of effects of neuromuscular blockers in cardiac surgery are the altered volumes of distribution during CPB and the decreased concentrations of calcium and magnesium. In this study, the duration of CPB did not show to contribute to the occurrence of PORC.

Other conditions that enhance muscle paralysis based on studies are the following: prolonged exposure to volatile anesthetics, hypothermia and large doses of opioids intraoperatively.[12,13] These were not consistently seen in this study since the duration of anesthesia, the doses of the sedative drugs used as well as the intraoperative temperatures of the subjects did not differ from those that developed PORC compared to those that did not. However, body temperatures upon SICU arrival of subjects that developed PORC were seen to be significantly lower (34.6 versus 36.0, p-value = 0.019).

A very crucial aspect when administering continuous muscle relaxant infusion is the determination of depth of neuromuscular blockade and adjusting the drug delivery as appropri-

ate which can be objectively done by using the 'train of four' (TOF) ratio. The routine practices of emphasis on hemodynamic management, with inattention for monitoring objectively the depths of paralysis and preference for NMB continuous drug infusion techniques predispose cardiac surgery patients to occurrence of residual paralysis in the immediate postoperative period.[4,7,14] In a national survey done by Murphy et al, only 28% of cardiac anesthesiologists routinely monitor the neuromuscular blockade in the operating room and only 8% routinely reverse muscle paralysis post operatively.[10] In this study, TOF monitoring was not done and only 3 of out the 60 patients received a reversal agent at the end surgery. There was a significant difference in the proportion that used a muscle relaxant reversal between those without PORC (66.7%) and those with PORC (1.7%) (p-value=0.005). Further analysis also revealed that the use of reversal drug was seen to be significantly associated with occurrence of PORC (p-value=0.003), significantly reducing the likelihood of PORC by 0.009 times (95% CI= 0.0004 to 0.2).

Adverse respiratory events in the immediate postoperative period, namely reintubation, upper airway obstruction and the need for air way support, are related to a multiplicity of causes and several studies have been made associating these with the occurrence of postoperative residual paralysis.[15] In this study, the median duration of ventilator support was indeed significantly longer among those with PORC (510 minutes vs. 305 minutes , p-value =0.021).

Fast Track Cardiac Anesthesia or ERACS is a popular recent development in the perioperative management and anesthesia care for cardiac surgery.One of its goal is to decrease ICU length of stay by practicing early tracheal extubation. The occurrence of PORC in post CABG patients is a hindrance to this objective. The results of this observational study have shown the importance of reversing muscle paralysis, keeping our patients normothermic and monitoring the depth of paralysis as important considerations in managing patients for fast-track cardiac surgery that are on continuous rocuronium infusion intraoperatively.

However, further studies with larger sample size are needed to validate the findings of this study and improve generalizability of results.

A randomized control trial comparing different rocuronium dose and comparing different modes of rocuronium administration that will prevent occurrence of PORC is recommended. Also, a randomized control trial to determine if the use of intraoperative TOF monitoring and use of muscle relaxant reversal will prevent the occurrence of residual paralysis.

CONCLUSION

This study showed a high incidence of postoperative residual paralysis among post-CABG patients in the SICU with the current practice of Rocuronium infusion during surgery. This study failed to show an association betwee the Rocuronium induction dose and infusion duration and the occurrence of PORC. The use of muscle relaxant reversal drug however was seen to significantly preventthe development of PORC while higher body temperature upon SICU arrival was observed in patients that did not develop residual paralysis. This study was also able to show that the development of PORC prolonged postoperative mechanical ventilatory support hindering goals of ERACS.

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Factors Associated with Persistent Leg Pain Secondary to Saphenous Vein Graft Harvest in Post Coronary Artery Bypass Grafting Patients

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Background ---

Methods ---

Results ---

Conclusion ---

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Key Words: Coronary Artery Bypass Grafting (CABG) ■ Persistent Postoperative Pain ■ Saphenous Vein Graft ■ Quality of Life ■

Coronary Artery Bypass Grafting (CABG) remains the mainstay treatment for Coronary Artery Disease (CAD).[1] The great saphenous vein remains to be the most commonly used conduit chosen.[2] The great saphenous vein lies very close to the Saphenous Nerve. Pain inflicted by its harvest may affect post-operative recovery because of delayed ambulation. The persistence of this leg pain can affect activities of daily life, hence the quality of life of post-CABG patients.

Post-operative pain is one of the consequences of Coronary Artery Bypass Grafting (CABG). This is one of the main concerns of patients undergoing this procedure.[4] Pain is described as persistent if it has been present for three months. Persistent pain is a problem, and provision of effective treatments has important clinical and economic implications.[3] Insufficient pain control during the postoperative period comes with complications such as increased heart rate and oxygen consumption, respiratory problems and mental health problems.[5] Severe pain after surgery can cause problems in the nervous system. This may lead patients to suffer persistent postoperative pain that can extend for months to years after CABG. Difficulty in mobilization due to pain can impair a person's quality of life.[6,7]

Pain at the site after saphenous vein graft harvest in CABG surgery is common, as reported by Hakim et al. Majority of the studies done targeted populations with post-sternotomy pain. In fact, majority of the patients complain of leg wound rather than sternal wound. The incidence of saphenous vein harvest site infection is reported to be between 1% and 24% in the literature.[8-11]

Large doses of intravenous (IV) opioids have been used in the anesthetic management and

Finalist, Poster Presentation, Case Report. 28th PHC Annual Research Paper Competition and Poster Presentation held on February 24, 2021 at Philippine Heart Center. Correspondence *to* ***Dr. Anne Reichel M. Lasquite.*** Department of Cardiovascular Surgery and Anesthesia. Philippine Heart Center, East Avenue, Quezon City, Philippines 1100 Available at **http://www.phc.gov.ph/journal/publication** ISSN 0018-9034

pain control of CABG patients. Because of the expected adequate pain control, not much attention was given to the pain status of the patient.[12] This method was not without repercussion – this required long ventilator therapy postoperatively.

Enhanced Recovery After Cardiac Surgery (ERACS) aims to shorten the hospital stay of CABG patients. Anesthetic techniques using balanced anesthesia replaced the opioid-based technique in managing patients. This regimen made use of low-dose and short-acting amnestic, analgesics, and sedatives. It is currently the method widely adopted for cardiac surgery. ERACS requires a more thorough and complicated postoperative pain control approach in order to prevent problems arising from high-dose opioid administrations. In general surgery, effective methods for pain control include multimodal techniques using regional analgesia, non-opioid pain relievers, and IV opioid delivery techniques using patient-controlled analgesia (PCA) devices.

However, in cardiac surgeries such as CABG, regional analgesia is potentially hazardous because of systemic anticoagulation with full heparinization --- there is a high risk for epidural hematoma.[13] Nonsteroidal Anti-Inflammatory Drugs (NSAID) can be regarded as risky to use in CABG due to their detrimental effects on renal function and hemostasis.[14] Identification and evaluation of efficacy and safety of different pain relievers is therefore necessary in patients undergoing CABG.

This study intends to determine the incidence and factors associated with postoperative leg pain associated with Saphenous Vein Graft harvest after CABG in a prospective cohort.

Complications of SVG Harvest in CABG:
These are the common complications reported in post-SVG harvest in CABG, namely persistent leg pain, peripheral neuropathy on lower limb and wound site infection. Risk factors associated with saphenous vein harvest site complications can be divided into preoperative (host) factors, perioperative, and postoperative factors. Preoperative factors associated with increased incidence of Saphenous Vein complications include increased age,[32,33] female sex,[31,34-36] increased body mass index,[31,32,35-37] and comorbidities such as DM,[31,32-35,39] PVD,[32-35] low preoperative hemoglobin levels,[52] congestive heart failure, and chronic renal failure, whereas the perioperative factors include duration of surgery, open technique of harvesting,[40,41-44] harvesting from the leg with deep vein thrombosis, inappropriate use of electrocautery, and IABP use. These factors are modifiable.

Causes of Continuous Pain After Cardiac Surgery: Iatrogenic injury to peripheral nerves can cause continuous pain postoperatively. This injury may cause inflammation and neuropathic pain that can last from months to years.[33,45] Characteristics of neuropathic pain include sensory loss, hypersensitivity, and at times, paroxysmal pain. Patients are predisposed to persistent pain after cardiac surgery because of different mechanisms that may include damaged anatomical structures of the nervous system.

Presence of Postoperative Leg Pain After CABG:
Most studies regarding post-operative pain after CABG refer to the post-sternotomy site. Limited literature can be found regarding complications at graft harvest sites. Impaired leg wound healing occurs in as many as 1-25% of patients.[46-47] Other factors that can prolong recovery include wound infections, hematomas, cellulitis, and saphenous neuropathy.[48] Difficulty in mobilization due to pain can impair a person's quality of life.[49,50] Presence of acute postoperative pain after cardiac surgery has been classified as mild in other studies. However, this is not true with persistent leg pain after surgery, which has a 21-56% prevalence rate.

Sensitivity disorders around surgical scars are believed to regress spontaneously within a few weeks to months after surgery,[51-52] however, these alterations may persist. According to scarce literature, may concern up to 24% of the patient.[52] Numbness, paresthesia, and/or dysesthesia were still mentioned by an equal percentage (39%) of the interrogated patients at the saphenous vein harvest sites. Although this disorder is considered minor from a surgical point of view, its high frequency cannot be

ignored, especially as it is persistently reported by patients after months or years after surgery has been completed.

The objectives of the study is to determine factors s associated with persistent postoperative leg pain associated with Saphenous Vein Graft harvest in post-CABG patients. This also aims to determine incidence of persistent postoperative leg pain associated with Saphenous Vein Graft harvest in post-CABG patients, the association of clinical factors in the incidence of persistent post-SVG harvest leg pain, association of surgical techniques in the incidence of persistent post-SVG harvest leg pain and the association of anesthesia management in the incidence of persistent post SVG harvest leg pain.

METHODS

This study is a prospective cohort done at the Philippine Heart Center, East Ave, Diliman, Quezon City. The study started after approval by the Technical Review Board (TRB) and the Institutional and Ethics Review Board (IERB). The study done had a flexible timeline that targeted the end of patient enrollment once the required number of participants was followed-up for the planned period.

Included in the study are patients included in this study were 19 years old and above. Patients who will undergo planned CABG surgery, wherein saphenous vein graft was to be used, were requested to join the study, provided that they had no history of surgery or persistent pain in the lower extremities. Patients with history of psychiatric illness and mentation problem were excluded. Other patients who were excluded in the study are those with peripheral neuropathies and vascular diseases, and those with history of stroke.

The investigator developed a questionnaire validated by experts. These questionnaires were distributed and completed by the investigator, research assistant, and cardiovascular perfusionists with various timelines.

A written informed consent was taken from participants in the study during the preoperative anesthesia evaluation. The patients were also questioned regarding the presence of pain, or any other unusual sensation in the lower extremities. Physical examination was also done to determine if there are any other abnormalities in the anatomic site supplied by the saphenous nerve.

Pain Scoring Scale: The Numeric Pain Rating Scale (NPRS) was used. It is a unidimensional rating of pain intensity in adults, including those with chronic pain.[73,74]

The NPRS is a segmented numeric version of the visual analog scale (VAS) in which a respondent selects a whole number (0–10 integers) that best reflects the intensity of his/her pain. The 11-point numeric scale ranges from '0' representing one pain extreme (e.g. "no pain") to '10' representing the other pain extreme (e.g. "pain as bad as you can imagine" or "worst pain imaginable"). The NPRS can be administered verbally (therefore also by telephone) or graphically for self-completion.[75] The patient was asked to indicate the numeric value on the segmented scale that best described their pain intensity.[76]

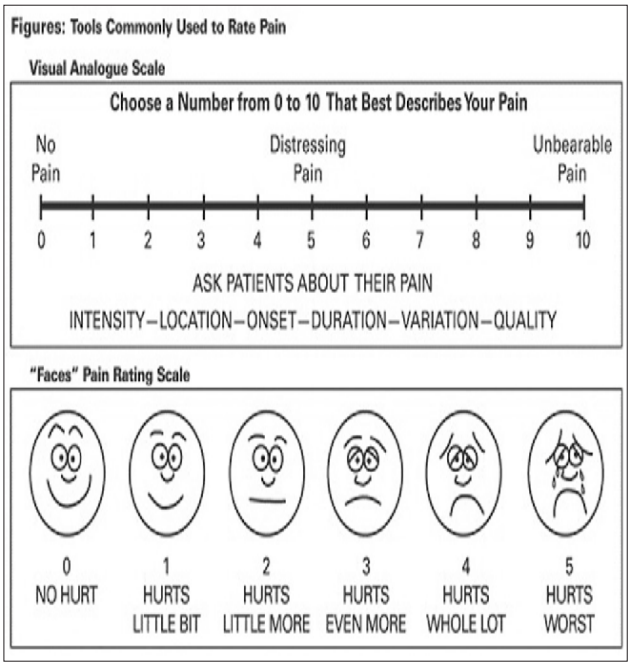

Fig. 1: Pain Scale. Figure taken from Ghaderi, Faezeh & Banakar, Shahin & Rostami, Shima. (2013). Effect of pre-cooling injection site on pain perception in pediatric dentistry: "A randomized clinical trial". Dental research journal. 10. 790-4. 10.4103/1735-3327.122486.

anesthesia evaluation. The patients were also questioned regarding the presence of pain, or any other unusual sensation in the lower extremities. Physical examination was also done to determine if there are any other abnormalities in the anatomic site supplied by the saphenous nerve.

Anesthetic Management: An anesthetic protocol routinely used in the Cardiovascular Anesthesia Division was implemented. No other interventions were done.

Surgical Technique: The attending surgeon determined the length of the saphenous vein grafts to be harvested, and harvesting technique to be done - one long incision, multiple short incisions, or endovascular technique. The harvest was done in such a say that injury to the saphenous nerve and its branches were prevented. After closure of the wounds, the lower extremities were compressed with elastic bandage.

Outcome Measurement: The NPRS scale was used to determine the presence of pain after receiving analgesics following CABG. Both the maximum and average pain score were asked from the participants on a 10-point NPRS scale, with 0 describing "no pain", and 10 signifying the "worst possible pain". Clinically significant pain will be marked for pain scores of 4 and above. Patients were again assessed on the 7th postoperative day by a health care personnel oriented by the investigator regarding the study. After discharge, participants were asked to answer telephone calls from the investigator of the research assistant for follow-up assessment every month, for 3 months. Each assessment session comprised of questions regarding the lower extremity involved in the saphenous vein graft harvest.

Participants were questioned about presence of pain, or any abnormal sensation in the lower extremity involved in the saphenous vein graft harvest. In order to exclude other possible causes of the leg pain, trauma or strenuous activities involving the use of lower extremities were asked. The following characteristics of pain associated with neuropathic apin were also inquired about: numbness, pricking, burning, or stabbing pain. Presence of dull and aching pain was determined as non-neuropathic. Participants were also questioned if the presence of pain affected their daily activities. The reply was noted as "yes" or "no".

Patients were labeled as having persistent leg pain associated with saphenous vein graft harvest if the pain is located within a specific anatomic distribution supplied by the saphenous nerve, with relation to the site of surgical trauma. Any pain, as described above, (1) which the patient continued to experience after discharge from hospital, and/or (2) which the patient experienced ONLY after discharge, --- both instances can be defined as persistent postoperative leg pain PROVIDED the patient reported a NPRS of 4 and above on follow-up.

Sample Size: Using G*Power 3.1.92, a minimum of 36 patients were required for this study based on 3.35 odds ratio of closure of leg wound in two layers, to have a chronic saphenous neuralgia,[71] 5% level of significance and 80% power.

Statistical Analysis: Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables, median and inter quartile range for non-normally distributed continuous variables, and mean and SD for normally distributed continuous variables. Odds ratio and corresponding 95% confidence intervals from binary logistic regression were computed to determine significant predictors of persistent leg pain. All statistical tests were two tailed test. Shapiro-Wilk will be used to test the normality of the continuous variables. Missing variables will neither be replaced nor estimated. Null hypotheses will be rejected at 0.05α level of significance. STATA 13.1 will be used for data analysis.

RESULTS

One hundred ninety-eight (198) patients underwent CABG with saphenous vein graft harvest during the study period. Of the 198 patients, 161 (81.3%) were excluded from the study due to their disqualification or unwillingness to take part in the study. The reasons for disqualification include the following: history of

surgery or trauma on the lower extremities, presence of peripheral vascular disease, diabetic neuropathies, and mental incapacity.

Thirty-seven patients (18.7%) were included in the study. 26 patients included in the study (78.4%) were followed-up until 3 months post-operatively. 11 patients (29.7%) were lost to follow-up, appealed not to be included further in the study, had stroke, or died.

Four patients (10.8%) from the 37 participants who were followed-up during the 3-month postoperative period had persistent leg pain of clinically significant severity. At the end of the 3-month follow-up period, 9 patients (34.3%) had persistent pain, but were labeled as not significant. 14 patients (37.8%) had no complaints of pain at the saphenous vein graft harvest site after discharge.

The feedback from participants that were initially included in the study (37 patients) were 95% (35), 70% (26), 70% (26), and 70% (26) after Day 1, Days 3-5, 1st month, 2nd month, and 3rd month postoperative respectively.

Between the incidence of persistent leg pain and the following variables, no noted significant difference was seen: age (OR, 0.94; 95% CI, 0.85–1.04; P-value, 0.216), female gender (OR,7; 95% CI, 0.34–144; P-value, 0.207), body mass index (BMI) (OR, 1.14; 95% CI, 0.82–1.57; P-value, 0.438), smoker (OR, 2.25; 95% CI, 0.20–25; P-value, 0.512), diabetes mellitus (OR, 1.1; 95% CI, 0.13–9.34; P-value, 0.930) and hypertension (OR, 2.25; 95% CI, 0.20–25; P-value, 0.512).

Table 2 shows the severity of pain 3 months post CABG in participants labeled as suffering from persistent leg pain. The median (IQR) worst pain scores before postoperative day 7 was 7.5 ± 1 (OR, 4.24; 95% CI, 1.19–15.05; P-value, 0.025), and the average pain score before postop day 7 was 5.75 ± 1.32 (OR3.99; 95% CI, 0.98–16.32; P-value, 0.054) respectively. For every 1 score increase in the Numerical Pain Scale score before post operative. Day 7, the odds of having persistent leg pain also increases by 4.24 times.

Table 3 shows that there is no significant difference between the incidence of persistent postoperative leg pain and these surgical factors: CPB duration, aortic cross clamp time, surgical time, SVG harvest time, and SVG harvest technique.

Table 4 shows that there is no significant difference between the incidence of postoperative leg pain and these anesthetic factors: total anesthesia time (OR, 1.01; 95% CI, 0.98–1.02; Pvalue, 0.860), anesthesia technique (OR, 1.5; 95% CI, 0.13–9.34; P-value, 0.930), intraoperative medication used such fentanyl bolus only or fentanyl bolus and drip, and IV postoperative pain medications.

Persistent pain 3 months after CABG surgery was rare, more so to be considered severe in pain intensity. Though individual rating of pain was subjective and diverse, pain score a day after the procedure were mostly rated as moderate. Mild saphenous vein graft harvest was noted to be common in 6 patients (17%). Moderate pain was noted in 12 patients (34%), and 7 patients (35%) had severe pain. 3 to 7 days CABG postoperative day, 3 participants (24%) complained of mild pain, 13 participants (3%) had moderate pain, and 1 participant (4%) complained of severe pain.

Table 1. Patient Characteristics

Variable	Total (n=26)	With Persistent Leg Pain (n=4)	No Persistent Leg Pain (n=22)	Odds Ratio (95% CI)	P Value
	Frequency (%); Mean ± SD				
Age (years)	60.81 ± 11.31	54.25 ± 13.28	62 ± 10.83	0.94 (0.85–1.04)	0.216
Gender					
Male	24 (92.31)	3 (75)	21 (95.45)	reference	-
Female	2 (7.69)	1 (25)	1 (4.55)	7 (0.34–144)	0.207
Weight	68.03 ± 10.23	73.25 ± 13.58	67.08 ± 9.60	1.06 (0.96–1.17)	0.276
Height	1.62 ± 0.08	1.64 + 0.09	1.62 + 0.09	35.58 (0.01–100)	0.604
BMI, kg/m^2	25.91 ± 3.23	27.06 + 2.71	25.70 + 3.33	1.14 (0.82–1.57)	0.438
Current Smoker	15 (60)	3 (75)	12 (57.14)	2.25 (0.20–25)	0.512
Comorbidities					
Diabetes Mellitus	12 (48)	2 (50)	10 (47.62)	1.1 (0.13–9.34)	0.930
Hypertension	18 (72)	3 (75)	15 (71.43)	1.2 (0.10–13.95)	0.884
Atrial Fibrillation	0	0	0	-	-
Dyslipidemia	0	0	0	-	-
Renal Impairment	0	0	0	-	-
History of ACS	22 (88)	4 (100)	18 (85.71)	-	-
Previous Cardiac Surgery	1 (4)	0	1 (4.76)	-	-
History of TIA	3 (12)	0	3 (14.29)	-	-
Preoperative EF <40%	1 (40)	0	1 (4.76)	-	-
NYHA Class III/IV	0	0	0	-	-

Data to be presented as mean (SD) or number (percentage). 95% confidence interval; ACS, acute coronary syndrome; BMI, body mass index; EF, ejection fraction; NYHA New York Heart Association, TIA, transient ischemic attack

Table 2. Extent of Painful Area and Severity of Pain 3 Months Postoperative Period after CABG in Patients Labeled as Having Persistent Leg Pain secondary to Saphenous Vein Graft Harvest

Variable	Total (n=26)	With Persistent Leg Pain (n=4)	No Persistent Leg Pain (n=22)	Odds Ratio (95% CI)	P Value
	Frequency (%); Mean ± SD				
Worst pain score before post-operative day 7	4.19 ± 2.65	7.5 ± 1	3.59 ± 2.40	4.24 (1.19–15.05)	**0.025**
Average pain score before postoperative day 7	3.10 ± 2.17	5.75 ± 1.32	2.61 ± 1.94	3.99 (0.98–16.32)	0.054

Data to be presented as number (%)

Table 3. Surgical Details

Variable	Total (n=26)	With Persistent Leg Pain (n=4)	No Persistent Leg Pain (n=22)	Odds Ratio (95% CI)	P Value
	Frequency (%); Mean ± SD				
CABG Procedure	26 (100)	4 (100)	22 (100)	-	-
Valve Replacement / Repair Done with CABG	1 (3.85)	0	1 (4.5)		
Emergent/Urgent	0	0	0	-	-
3 or More Coronary Vessels Grafted	25 (96.15)	4 (100)	21 (95.45)	-	-
CPB Duration	143.46 ± 64	157 + 62.98	141 ± 65.61	1.003 (0.99–1.02)	0.646
CPB Time > 120 mins	16 (61.54)	3 (75)	13 (59.09)	2.08 (0.19–23.3)	0.553
Aortic Cross Clamp Duration	115.92 ± 34	127 + 34.96	113.9 ± 34.55	1.01 (0.98–1.04)	0.480
Aortic Cross Clamping Time >75 mins	25 (96.15)	4 (100)	21 (95.45)	-	-
Hypothermia on CPB <30deg C	26 (100)	4 (100)	22 (100)	-	-
Surgical Time >240 mins	344.5 ± 88.84 25 (96.15)	358.5 + 84.09 4 (100)	341.95 ± 91.33 21 (95.45)	1.002 (0.99–1.01)	0.727 -
Harvesting of SVG Duration (mins)	63 (48–94)	65.5 (19.5–112)	64.5 (48–87)	0.99 (0.97–1.02)	0.729
SVG Harvest Technique					
One Long Incision	4 (15.38)	1 (25)	3 (13.64)	2.11 (0.16–27.58)	0.569
Multiple Short Incisions	22 (84.62)	3 (75)	19 (86.36)	(reference)	-
Endovascular Harvest	-	-	-	-	-
Closure of leg wound in 2 layers	26 (100)	4 (100)	22 (100)	-	-

Data to be presented as number (percentage). 95% confidence interval; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; SVG, saphenous vein graft

Table 4. Anesthetic Management Details

Variable	Total (n=26)	With Persistent Leg Pain (n=4)	No Persistent Leg Pain (n=22)	Odds Ratio (95% CI)	P Value
	Frequency (%); Mean ± SD				
Total Anesthesia Time	402 ± 81.96	408.5 ± 79.03	400.76 ± 84.34	1.01 (0.98-1.02)	0.860
Anesthetic Technique					
GETA	17 (68)	3 (75)	14 (66.67)	1.5 (0.13-17.18)	0.744
TIVA					
Intraoperative Medications Used:					
Fentanyl Bolus	13 (52)	2 (50)	11 (52.38)	1.1 (0.13-9.34)	0.930
Fentanyl Bolus and Drip	12 (48)	2 (50)	10 (47.62)	(reference)	-
IV Postoperative Pain Medications:					
Paracetamol	25 (100)	4 (100)	21 (100)	-	-
Tramadol	15 (60)	2 (50)	13 (61.90)	0.62 (0.07-5.28)	0.658
Oxycodone	10 (40)	2 (50)	8 (38.10)	1.63 (0.1–13.93)	0.658

Data to be presented as number (percentage). 95% confidence interval; GETA – General Endotracheal Anesthesia; TIVA – Total Intravenous Anesthesia; IV - Intravenous

DISCUSSION

The incidence of persistent leg pain, defined as the presence of clinically significant pain in the anatomic area supplied by the saphenous nerve 3 months and beyond after CABG surgery, was approximately 11%. Only the presence of clinically significant pain prior to postoperative day 7 presented as a significant risk factor in the presence of persistent leg pain.

The quality of life of a post-operative CABG patient can be significantly affected if he or she feels severe pain. Surgical damage to tissues can elicit a stress response that can result in several complications. Inadequate analgesia that causes unrestricted stress response may lead to the following: increased heart rate and oxygen consumption, cardiac dysrhythmias, hypertension, vasoconstriction, poor tissue perfusion, increased catabolism, immunosuppression, respiratory complications, and coagulation disorders, and increased hospital stay.[79] Poor pain control is also a possible cause for hospital admission after CABGsurgery.[80] Uncontrolled postoperative pain resulted to poor quality of life immediately during the postoperative period (two weeks after cardiac surgery).[81] 12 months postoperatively, these patients suffered from persistent and chronic pain.[82] In some patients, significant pain is still present 2 years after cardiac surgery.[83]

Postoperative pain after CABG surgery may be present after wound-healing has taken place, even after treatment with present-day analgesics. Because of this, a significant number of patients still suffer from chronic pain after planned surgery.[84,85] The incidence of persistent post operative pain after CABG surgery is estimated to be at 30-50%. Of this, the incidence of severe, disabling pain is 5-10%.[86-91] Persistent postoperative pain is related to subjective rating for poor health --- subjective rating for poor health was an independent predictor of mortality.[92]

Traditional technique for harvesting the Saphenous Vein involves long continuous open skin incision, involving the entire leg most of the time. Much attention has been paid to deep chest wound infection and mediastinitis because of the potential life-threatening effect. But in reality, Saphenous Vein harvest site infection is more common, which increases the morbidity, causes delayed discharge from the hospital, and increases the hospital costs.[93-95]

Other risk factors associated with saphenous vein harvest site complications include increased age, [96,97] female sex,[95,98-100] increased body mass index, [95,96,99-102] and comorbidities such as DM, [95,97-99,103] PVD,[97-99] low preoperative hemoglobin levels,[100] congestive heart failure, and chronic renal failure, whereas the perioperative factors include duration of surgery, open technique of harvesting,[104,105-108] harvesting from the leg with deep vein thrombosis, inappropriate use of electrocautery, and IABP use. However, our results showed that only the presence of severe postoperative pain until day 7 is the significant risk factor for the presence of persistent postoperative pain.

Surgical injury to nerves resulting to neuropathic pain and active inflammation are the probable causes of persistent postoperative pain.[109] Characteristics or neuropathic pain include sensory loss, hypersensitivity, and at times, paroxysmal pain. Patients are predisposed to persistent pain after cardiac surgery because of different mechanisms that may include damaged anatomical structures of the nervous system.

Most studies regarding post-operative pain after CABG refer to the post-sternotomy site. Limited literature can be found regarding complications at graft harvest sites. Impaired leg wound healing occurs in as many as 1-25% of patients.[96-97] Other factors that can prolong recovery include wound infections, hematomas, cellulitis, and saphenous neuropathy.[110] Difficulty in mobilization due to pain can impair a person's quality of life.[111,112] Presence of acute postoperative pain after cardiac surgery has been classified as mild in other studies. However, this is not true with persistent leg pain after surgery, which has a 21-56% prevalence rate.

Sensitivity disorders around surgical scars are believed to regress spontaneously within a few weeks to months after surgery,[113,114]

however, these alterations may persist. Accord ing to scarce literature, may concern up to 24% of the patient.[114] Numbness, paresthesia and/ ordysesthesia were still mentioned by an equal percentage (39%) of the interrogated patients at the saphenous vein harvest sites. Although this disorder is considered minor from a surgical point of view, its high frequency cannot be ignored, especially as it is persistently reported by patients after months or years after surgery has been completed.

One of the most important concern of the patient who will undergo cardiac surgery is adequate post-operative pain control.[115] This hinders the patient from further discomfort and suffering. One worthy motive of this study is to know the factors that will result to less surgical stress response and therefore, provide adequate pain control of patients who will undergo CABG surgery with saphenous vein graft harvest.

Studies of postoperative analgesia after CABG, especially of harvest-site pain, have been rare.[116] To prevent complications of opioids, paracetamol have been used for pain control after CABG.[117,118] Other modalities used to reduce opioid use include the use of local anesthesia infiltration, regional anesthesia procedures, and addition of additional medications as adjunct to opioid therapy.[118-121] Currently at the Philippine Heart Center, patient education and pharmacologic therapy have been given to patients for pain intervention.

CONCLUSION

Persistent leg pain after CABG surgery utilizing saphenous vein graft is common. The only risk factor identified in this study is the presence of severe pain prior to postoperative day 7. A larger sample size is needed to further validate these result using prospective cohort studies. A relevant implication for this findings is that attention to the pain status of the postoperative CABG patient should always be taken into consideration, and not just the hemodynamic and surgical status of the patient. This assessment can help in the prevention of having persistent leg pain.

REFERENCES

Accuracy of a Deep-Learning-Derived Artificial Intelligence Model in the Detection of Aortic Dissection in Contrast-Enhanced Chest and Abdominal CT Scans

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Background **---** Aortic dissection is the tearing of the intima of the aorta from its media anywhere from its origin at the aortic root to its bifurcation at the lower abdomen. Majority of these cases are emergencies, wherein the management relies on the immediate recognition. Studies using deep learning in the automatic detection and segmentation of aortic dissection has been done in the past, with a few studies already showing promising results with high sensitivity and specificity but those studies had a variety of limitations.The purpose of this study is to determine the accuracy of the use of a convolutional neural network model to screen for aortic dissections in contrast enhanced chest and abdominal CT scans.

Methods **---** This was a criterion reference based (validation) cross-sectional study in which a pretrained AI model, VGG-19, was retrained to classify axial CT slices as having or not having aortic dissection. This was then used to classify axial slices of CT scans of a sample size of 100 patients. Patients were then classified as test model-positive and test model-negative by using certain cutoff for the total number of positive images per patient. These results were then compared to the gold standard results established at the start of the study maneuver and statistical analyses was applied.

Result **---** The model obtained a sensitivity of 80.00%, specificity of 73.33%, positive predictive value of 50%, negative predictive value of 91.67%, positive likelihood ratio of 3.00, negative likelihood ratio of 0.27 and an area under the ROC curve of 0.752.

Conclusion **---** The use of retrained AI models may still be used as an automated screening for detecting aortic dissection cases with sensitivity and specificity values of 80% and 73%, respectively, despite being slightly lower than those obtained in previous studies. However, additional studies may be done to improve the parameters obtained. ***Phil Heart Center J 2022;25(2):75-80.***

Key Words: Aorta, dissection ■ CT Scan ■ Computed Tomography ■ Artificial Intelligence ■ cardiac computed tomography ■ machine learning ■ deep learning

Aortic dissection is the tearing of the intima of the aorta from its media anywhere from its origin at the aortic root to its bifurcation at the lower abdomen. Majority of these cases are emergencies, wherein the management relies on the immediate recognition.[1] Computed tomography (CT) scans have been the most commonly used modality in detecting dissection due to its high sensitivity and specificity coupled with availability and cost-effectiveness.[2] As the number of patients and studies performed increase over time for a multitude of indications, the need for early initial assessment of studies becomes more and more imperative. Radiologists need a way to prioritize studies that may have the need for more urgent or immediate intervention even before opening the studies. Researchers have now recently turned to computer-aided diagnosis with machine and deep learning to address this issue. Machine learning is the process by which a computer is trained to perform tasks like classification by learning patterns on its own from a large dataset rather than being meticulously programmed by humans.[3] Classically this method involves data scientists providing the

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algorithm with distinct features that the algorithm will use in its analysis. However, sometime experts do not always know the right features to define to optimally perform these tasks, hence the growth of popularity of deep learning. Deep learning is a subtype of machine learning where the algorithm learns a composition of features that reflect a hierarchy of structures in the data.

Studies using deep learning in the automatic detection and segmentation of aortic dissection has been done in the past, with a few studies already showing promising results with high sensitivity and specificity.[4-7] However, multiple studies showed a variety of limitations. Most studies concentrated on evaluating just the thoracic aorta for uniformity of the inputs. Other studies implemented segmentation of the aorta incorporated in the model, which while being useful in some instances, also puts in a substantial GPU-intensive process which may impede other tasks. Additionally, some of the studies showed increased false positive rates due to artifacts, degenerative aortic changes and even normal structures such as the aortic valve. Furthermore, the nature of deep learning allows for the utmost flexibility, theoretically offering innumerable possibilities in the number of parameters and layers it can assess, which may lead to a variety of results. It is with these issues that additional studies be conducted in this field to help radiologists as well as their clinician counterparts be more effective and efficient.

The purpose of this study is to determine the accuracy of the use of a convolutional neural network model to screen for aortic dissections in contrast-enhanced chest and abdominal CT scans.

METHODS

Study Design: The study design used was a criterion reference based (validation) cross-sectional study. This was conducted in the CT Scan Section of the Cardiovascular Radiological Sciences Division from June 2020 to July 2020 and from patients with studies in the PACS archive from December 2013 up to December 2019.

Included in the study are patients above 19 years old, who underwent contrast-enhanced CT scans of the chest and abdomen and had their images uploaded into the PACS archive were included in the study. While those excluded are patients who underwent surgical operations, endovascular operations on the aorta or mediastinum were excluded from the study. Patients with incomplete images in the PACS system were also excluded from the study.

Sample Size: A minimum of 100 images were required for the testing phase of the convolutional neural network based on 0.93 C-statistic of convolutional neural network to predict positive for aortic dissection,[2] 5% level of significance and 10% desired width of the confidence interval.

Study Maneuver: Post-contrast CT scans (chest and abdomen) that satisfied the same inclusion and exclusion criterias stated above were retrieved from the PACS, anonymized and included in the pre-study maneuver. All images were saved in a secure external hard drive. These images were then reviewed by two separate radiologists and determined the presence, classification and extent of the aortic dissection. Studies with disagreement on the presence of dissection were reviewed by both radiologists to determine a final result. Their final decisions were used as the gold standard or 'ground-truth' in this study. The DICOM images of the studies will be cropped to from 512x512 to 224x224, entered on the aorta. The axial images containing a portion of the dissection were labeled 'positive' while the rest of the images were labeled negative'. Using tensorflow and Keras, a pre-trained 2D convolutional neural network model, VGG19, was reappropriated using transfer learning. The model was retrained with the training set images to be able to classify something as having or not having aortic dissection. This fully retrained AI model was used in the study maneuver.

A total of 100 qualified patients satisfying the inclusion and exclusion criteria as stated above were included in the study. After satisfying the criteria, the post contrast CT images

of the patient were retrieved, anonymized and evaluated by two radiologists in a similar manner as in the pre-study maneuver. Using tensorflow and Keras, the images will them be evaluated by the AI model trained in the pre-study maneuver which will classify the images as 'positive' or 'negative'. Patients were then classified as test model-positive and test model-negative by using certain cutoff for the total number of positive images per patient. These results were then compared to the original gold standard results established at the start of the study maneuver and statistical analyses was applied.

Statistical Analysis: Descriptive statistics was utilized to summarize the demographic and clinical characteristics of the patients included. Frequency and proportion was used for categorical variables, median and inter quartile range for non-normally distributed continuous variables, and mean and SD for normally distributed continuous variables. Area under the receiver operating characteristics curve was used to determine the diagnostic model to be generated from convolutional neural network to predict positive for aortic dissection. Shapiro-Wilk test was utilized for testing the normality of the continuous variables. Missing values was neither be replaced nor estimated. Null hypotheses was be rejected at 0.05α-level of significance. STATA 13.1 program was utilized for data analysis.

Ethical Considerations: The study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki and National Ethical Guideline for Health and Health-related Research (2017). Prior to the study initiation, the protocol was reviewed and approved by the Philippine Heart Center Institutional Ethics Review Board (PHC IERB).

The investigator requested the waiver of informed consent for the following reasons: it is impracticable to obtain individual written consent since there is insufficient information to get up-to-date contact details of the research subjects; and the use of de-identified information might not achieve the research purpose. Once the data was collected, reasonable steps to de-identify the information was done. The investigator made sure that the anonymity of the subject was maintained. All data was encoded using a password-protected Excel spreadsheet. A code number was assigned for each patient. To maintain anonymity, a separate password protected spreadsheet that links the study code to the patient's name was made. Only the primary investigator had access to this file. After encoding, all data collection forms were kept in a secured cabinet by the researcher. After the House Staff has received clearance from the Clinical Trial and Research Division and the Institutional Ethics Review Board, the file that contains the link of the study code with the subject's identifiers will be deleted. The data collection form will then be shredded and disposed. The researchers adhered fully to the provisions of the Data Privacy Act of 2012.

RESULTS

A total of 100 samples were evaluated for this study and is described in Table 1. The majority of the sample as well as total positive cases were males, however, a higher proportion of the females in the sample were seen to have had aortic dissections (41%).

Table 2 describes the distribution of the different classifications of aortic dissection. Only two samples were diagnosed as Debakey 2, meaning only the ascending segment would exhibit findings of dissection. All other samples mostly showed long segment dissections majority of which involve the descending thoracic and abdominal segments.

Table 3 shows the accuracy of the retrained AI model in detecting the aortic dissection. Cut-off percentage that was used for the classification was 13% positive slices out of the total number of slices per patient. The model was able to classify 20 of the total number of true positive cases while missing 5 samples. Of the 11 Stanford A dissections, only 1 was not detected. Wide ranges of the confidence intervals are noted in the parameters calculated.

Table 1. Demographic Data

Characteristics (n=)	Mean ± SD or n (%)			
	With Aortic Dissection (n=25)	Without aortic dissection (n=75)	Total	P Value
Age (years)	53.3 ± 14.9	57.9 ± 16.8	56.8 ± 16.4	0.000651161
Gender				
Male	18 (18%)	58 (58%)	76 (76%)	0.588688
Female	7 (7%)	17 (17%)	24 (24%)	

Table 2. Distribution of aortic dissection based on Stanford and Debakey Classifications

Classification	(n (%)
Standford	53.3 ± 14.9
A	11 (44%)
B	14 (56%)
Debakey	
1	9 (36%)
2	2 (8%)
3	15 (56%)

Table 3. Accuracy of the retrained AI model in detecting aortic dissection

	(+) Aortic Dissection	(-) Aortic Dissection
Test-Positive	20	20
Test-Negative	5	55
Sensitiivity = 80.00% (59.30% to 93.17%)	Positive predictive value = 50% (39.57% to 60.43%)	
Specificity = 73.33% (61.86% to 82.89%)	Negative predictive value = 91.67% (65.34% to 83.12%)	
Positive Likelihood Ratio = 3.00 (1.96 to 4.58)	Negative Likelihood Ratio = 0.27 (0.12 to 0.60)	

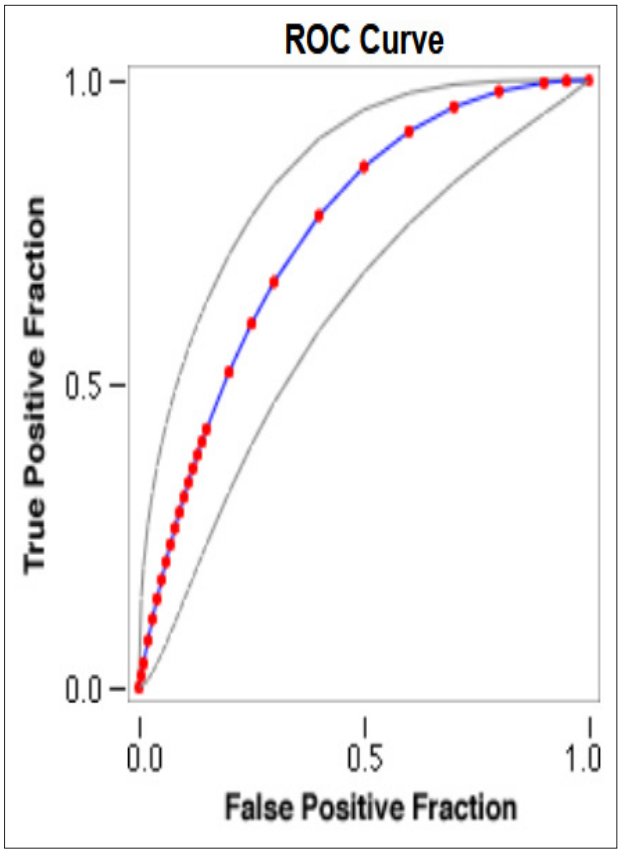

Fig. 1: Graph 1 - Area Underan ROC Curve. Fitted ROC Area: 0.752

DISCUSSION

Using our retrained model to classify positive and negative dissection cases, we obtained slightly lower sensitivity and specificity values than the previously noted studies measuring 80% and 73%, respectively. Compared to higher values from 82.2% sensitivity and 83.3% specificity and higher in the studies by Harris, Dehghan, Gayhart and Xu.[4,5,7] Despite being lower, 80% sensitivity still suggests that the use of retrained AI models may still be used as an automated screening for detecting aortic dissection cases, however, additional studies may be done to improve the parameters obtained.

In reviewing the 5 cases that were categorized as false negatives, two cases had short segment dissections involving only approximately 10-11 slices, which is not within the cutoff for the percent of slices used for the model to call a study positive. However, lowering the cutoff percentage would lead to an increase in the false negative cases. One false negative case showed motion artifacts at the level of the dissection.

In which may have contributed to the model interpretation. Another case showed a poorly attenuated false lumen, usually seen in early arterial phases where the contrast has not made its way into the false lumen. Representation of these images in the training set may have impacted the evaluation of this case by the model.

Among the 20 cases that were categorized as false positives, there were approximately 3 patients that were called in areas with atherosclerotic ulcer plaques, 8 patients with aneurysms and 1 patient with contained rupture. Seven patients were also flagged at the slices which included the heart.

One of the biggest contributing factors of any AI model is the amount of sample images as the output of the model is highly dependent on the data you initially feed the model during training.[3] For our pre-study model, we used a total of 23 negative patients with 12,534 images and 43 positive patients with 12,587 images with a total of 25,121 images used. The sensitivity and specificity seen in the literature this study was based on was from Harris et.al,[4] used a total of 57,074 images which is more the twice the number used for the present study. Moreover, these 57 thousand images were obtained from 475 unique patients, which is more than 7 times the number of patients used in the present study. A contributing factor to this is likely due to the fact that most of the newer patients were saved in the PACS system were reconstructed with thin slices (0.63 mm slices) leading to increased number of images per patient. This leads to multiple images within the training set that are very similar to each other. A consequence of an increased number of similar appearing thin slices is the probability of overrepresentation of these images during training, and extraneous variables in the images such as configurations of the partially visualized vertebral bodies, and other internal organs may influence the prediction model into thinking they may be important. Specific configuration of the dissection (straight or wavy, thick or thin, direction of flap, etc.) may also be exacerbated by multiple similar appearing images as more weight is given to them artificially during training in a phenomenon known as overfitting. In the same vein, a lower number of patients representing the positive cases leads to a decrease in the representation of other configurations of dissections which may not be recognized by the model. Overfitting may have led to the 6 patients, 1 false negative and 5 false positives with normal radiographic appearance of the aorta, being flagged by the model incorrectly, as the model may have been looking at other factors in the image.

Another contributing factor in the difference in sensitivity and specificity with the other studies reviewed were the use of annotated images during training. This is when the images are individually labeled with pixel coordinates indicating the location of the aorta and pathology, which may be the intimal flap of a dissection, the outpouching of an aneurysm or the bulk of a thrombus. These measures increase the accuracy of the model but manually annotating tens of thousands of images would require a large number of work hours and would likely only be feasible if with a huge team of researchers or if the work will be outsourced to a third party.

The area under the ROC curve showed a fitted area of 0.752. This is categorized as fair discrimination and is lower than the previously obtained AUC in other studies ranging from 0.857 to 0.979.[4,5] This finding is likely also due to the abovementioned factors.

Wide confidence intervals seen in this study suggests a need to increase the sample size to more accurately determine the true sensitivity and specificity when used for a higher population.

Multiple avenues are available for continuing this line of research. Increased sample size for the testing dataset will likely improve the wide confidence intervals noted in the present study. Training a model with higher quality training datasets in the future will likely provide a better trained and more accurate model for the purposes of detecting dissection. Higher quality training datasets will likely involve a much higher number of images, annotated/labeled images and images representing a majority of the configurations of dissection.

The use of different pretrained models with varying number of neurons and layers may provide different results. Training with 3D datasets (datasets with x, y and z dimensions as opposed to axial scans with only 2 dimensions) may likely provide a more accurate model but would also require a much higher number of patients to include in the training data. Also, one of the limitations of this study was not including the automatic detection of the classification of dissections and that could also be done with better labeled data.

CONCLUSION

The use of retrained AI models may still be used as an automated screening for detecting aortic dissection cases with sensitivity and specificity values of 80% and 73%, respectively, despite being slightly lower than those obtained in previous studies. However, additional studies may be done to improve the parameters obtained.

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Association of Epicardial Adipose Tissue Volume and Location-Specific Epicardial Adipose Tissue Thickness in the Assessment of Major Adverse Cardiovascular Events Among Patients Who Underwent Cardiac Computed Tomography

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Background **---** Cardiovascular diseases (CVDs) are considered to be the number one cause of mortality and morbidity globally. Recent evidence has implicated the presence of excessive epicardial adipose tissue (EAT) accumulation with increased risk for CVDs.[4] Over the last decade, several studies have reported a significant association between EAT and coronary artery stenosis,[5] coronary artery calcification,[6] myocardial ischemia[5] and major adverse cardiovascular events (MACE).[7] This study aims to determine the association of EAT volume and location-specific EAT thickness and MACE.

Methods **---** MACE, demographic data and clinical profiles of the study participants were collected from the PHC patient database using the MEDTRAK. EAT volume and location-specific epicardial adipose tissue thickness from the cardiac computed tomography scans were also retrieved and reviewed. Data collected were statistically analyzed.

Result **---** For mm increase in EAT thickness in the right and left ventricular wall, the odds of having MACE decreased by 33.12% (odds ratio= 0.71, 95% confidence interval= 0.50-1.00, p-value=0.03) and 34.55% (odds ratio= 0.65, 95% confidence interval= 0.44-0.95, p-value=0.02), respectively. For each unit increase in systolic and diastolic blood pressures, the odds of having MACE are decreased by 2.56% and 6.99%, respectively. Participants using ACE inhibitors were found to be 67.1% less likely to have MACE.

Conclusion **---** Findings of this study show that there was no association of epicardial adipose tissue volume in the assessment of MACE and there was association of epicardial adipose tissue thickness with MACE, particularly the right and left ventricular wall. ***Phil Heart Center J 2022;25(2):81-90.***

Key Words: epicardial adipose tissue (EAT) ■ epicardial adipose tissue thickness ■ location-specific epicardial adipose tissue thickness ■ major cardiovascular adverse events (MACE) ■ cardiac computed tomography

Cardiovascular diseases (CVDs) are considered to be the number one cause of mortality and morbidity globally. In 2016, the World Health Organization estimated a total of 17.9 million deaths due to CVDs, accounting to 31% of all global deaths.[1] Ischemic heart diseases (diseases of the heart and of the blood vessels) make up the greatest proportion of those deaths.[2] Similarly, ischemic heart diseases were the leading cause of death in the Philippines in 2017.[3]

Recent studies have shown growing evidence regarding the role of epicardial adiposity on cardiometabolic risk. Excessive epicardial adipose tissue (EAT) accumulation has long been associated with increased CVDs.[4] Over the last decade, several studies have reported a significant association between EAT and coronary artery stenosis,[5] coronary artery calcification,[6] myocardial ischemia[5] and major adverse cardiovascular events (MACE).[7] There are many plausible mechanisms that could account for

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this, including changes in blood pressure, blood glucose regulation, lipid metabolism, and overall systemic inflammation.[8]

Recent developments in non-invasive diagnostic imaging such as such as multi-detector computed tomography (MDCT), echocardiography, and cardiac magnetic resonance (CMR) imaging has permitted increasing accuracy in the measurement and quantification of epicardial fat. There is an increasing attention on the location-specific EAT thickness as a potential predictor in cardio-metabolic disease because of uneven regional distribution of EAT around the heart.[9-11]

Recent studies have suggested the use of location-specific EAT thickness at the left AV groove as a new marker in predicting cardiometabolic risk with the use of 2D CT or MR measurement.[11-14] Epicardial fat volume has prognostic value for adverse cardiac events. Several studies have investigated the prognostic value of EFV using non-contrast CT and cardiac CT angiography. Furthermore, there is increasing evidence that EFV gives incremental but not redundant predictive value above previously reported cardiovascular risk factors.[15-17]

Therefore, this study aims to determine the association of epicardial adipose tissue volume and location-specific adipose tissue thickness in the assessment of major adverse cardiovascular events among patients who underwent cardiac computed tomography at the Philippine Heart Center from January 01, 2016 to December 31, 2018.

The objective of the study is to determine the association of epicardial adipose tissue volume and location specific epicardial adipose tissue thickness in the assessment of major adverse cardiovascular events. While its specific objectives are: (1) to determine the epicardial adipose tissue volume; (2) determine the location-specific EAT thickness; (3) determine the association between epicardial adipose tissue volume and the major adverse cardiovascular events; (4) determine the association between the location-specific EAT thickness and the major adverse cardiovascular events; and (5) determine the socio-demographic characteristics of the study participants.

METHODS

The research design used in this study was an analytical cross-sectional study design to determine the association of epicardial adipose tissue volume and location-specific epicardial adipose tissue thickness in the assessment of major adverse cardiovascular events in accordance with the accepted standards of the Philippine Heart Center Institutional Ethics Review Board.

This study was conducted at the Philippine Heart Center, a hospital specializing in the treatment of heart ailments located in Quezon City, Philippines. The study commenced from July 2020 to December 2020. Included in the study were adult patients (above 18 years old) who underwent cardiac computed tomography from January 01, 2016 to December 31, 2018. While excluded are those study participants who underwent cardiac computed tomography but lost to follow up.

Study Maneuver: Major adverse cardiovascular events (any severe or acute cardiovascular condition including acute MI, angina pectoris, coronary insufficiency, CVA, TIA, intermittent claudication, CHF, CV death, late percutaneous or surgical revascularization and coronary revascularization), demographic data and clinical profiles of the study participants were retrieved from the PHC patient database using the MEDTRAK.

Epicardial adipose tissue volume and location-specific epicardial adipose tissue thickness were retrieved from the cardiac computed tomography scans. The epicardial adipose tissue volume was obtained using a semi-automated volumetric software. Manual delineation of the chest area to be used for epicardial measurement was done, including slices 1 cm above the origin of the left main coronary artery to the cardiac apex. The pericardium is outlined manually at each cross section. Computer software identifies the delimited area, defined by density between

-30 and -200 HU. The sum of the volume of all sections provides the overall epicardial fat volume. Location-specific epicardial adipose tissue thickness is the echo-free space in the right and left ventricular walls and the grooves between the atria and ventricles.

Definition of Outcomes: The collected data in the MEDTRAK and measurements of epicardial adipose tissue volume and thickness in cardiac computed tomography scan for each study participants were tabulated using a Microsoft excel. Statistical analysis was done on the study results, which were then presented in tables.

Sample Size: Using G*Power 3.1.9.2, a minimum of 80 patients were required for this study based on 3.1 odds ratio of epicardial fat volume and thickness to predict MACE, 5% level of significance and 95% power.

Statistical Analysis: The demographic and clinical characteristics were described. Frequency and proportion were used for categorical variables and mean and SD for normally distributed continuous variables. Independent Sample *T*-test and Fisher's exact test were used to determine the difference of mean and frequency, respectively, between patients with and without MACE. Odds ratio and corresponding 95% confidence intervals from binary logistic regression were computed to determine significant factors of MACE. All statistical tests used two tailed test. Shapiro-Wilk was used to test the normality of the continuous variables. Missing variables were neither replaced nor estimated. A 0.05 αlevel of significance was used for the rejection of null hypotheses. STATA 13.1 was used for data analysis.

Table 1. Demographic and clinical profile of the patients

	MACE		P Value
	With	Without	
	Frequency (%) (%); Mean + SD		
TOTAL: 80	(67.00)	(33.00)	
Demographics			
Age	49.32+17.13	51.43+20.24	0.61
Sex			
Male	(58.00)	(73.33)	0.23
Female	(42.00)	(26.67)	
Height (cm)	38 (42)	1 (14.3)	15 (68.2)
Weight (kg)	156.9+9.14	156.9+10.73	0.72
BMI (kg/m^2)	61.2+10.18	62.06+10.57	0.71
Blood pressure			
Systolic	115+17.17	126.33+26.19	0.02
Diastoloc	71.6+10.17	79.33+10.48	0.001
Lipid Profile			
Total Cholesterol	159.53+47.85	179.26+51.65	0.12
LDL	97.27+34.01	103.56+37.99	0.49
HDL	46.16+13.02	48.65+14.86	0.48
Triglycerides	134.09+71.63	121.13+53.60	0.44
Medications			
Statins	(40.00)	(60.00)	0.16
Beta-blockers	(32.50)	(67.50)	0.32
Diuretics	(22.50)	(77.50)	0.58
Angiotensir R blockers	(11.25)	(88.75)	0.72
Calcium channel blockers	(13.75)	(86.25)	1.00
ACE inhibitors	(23.75)	(76.25)	0.05

Table 2. Epicardial adipose tissue profile of the patients

	MACE		P Value
	With (50)	Without (30)	
	Frequency (%) (%); Mean + SD		
TOTAL: 80			
EAT volume	106.91 ± 15.87	113.73 ± 19.78	0.09
EAT thickness (all)	8.84 ± 1.76	9.35 ± 1.92	0.23
EAT in all grooves	11.86 ± 1.83	12.69 ± 2.17	0.07
EAT in IV groove	11.78 ± 2.25	12.75 ± 11.72	0.09
EAT left AV groove	12.42 ± 1.76	13.15 ± 2.18	0.10
EAT right AV groove	11.42 ± 1.74	12.01 ± 2.29	0.20
EAT in ventricular walls	3.66 ± 0.92	4.43 + 1.99	0.02
EAT in the right ventricular wall	3.69 ± 1.00	4.53 ± 2.44	0.03
EAT in the left ventricular wall	3.61 ± 0.95	4.35 ± 1.75	0.02

Table 3. Factors associated with MACE

Parameters	Odds Ratio	95% CI	P Value
Blood Pressure			
Systolic	0.97	0.95-0.99	0.02
Diastolic	0.93	0.88-0.97	0.001
ACE inhibitors	0.32	0.11-0.94	0.05
EAT in ventricular walls	0.66	0.46-0.97	0.02
EAT in the right ventricular wall	0.71	0.50-1.00	0.03
EAT in the left ventricular wall	0.65	0.44-0.95	0.02

It can be gleaned in Table 1 that among the 80 subjects, 67% have major adverse cardiovascular events (MACE) and 33% without MACE. Subjects identified with MACE had the mean age of 49.32 ± 17.13 composed of 58% males and 42% females, while without MACE is 51.43 ± 20.24 composed of 73.33% males and 26.67% females. Among patients with MACE, the mean Systolic Blood Pressure (SBP) was at 115 ± 17.17 and mean Diastolic Blood Pressure (DBP) was at 71.6 ± 10.17 while those without MACE, the mean Systolic Blood Pressure (SBP) was at 126.33 ± 26.19 and mean Diastolic Blood Pressure (DBP) was at 79.33 ± 10.48. The systolic and diastolic blood pressure of the subjects were significantly associated in the assessment of MACE with p-value of 0.02 and 0.001, respectively. There was no significant association found between the lipid profile and medications of the subjects except for those taking ACE inhibitors with a p value of 0.05. Among those subjects taking ACE inhibitors, 23.75% have MACE and 76.25% are without MACE.

It can be noted on Table 2 that the mean value of EAT volume in subjects identified with MACE is 106.91 ± 15.87 while without MACE is 113.73 ± 19.78. EAT thickness in subjects with MACE had a mean value of 8.88 ± 1.76 and without MACE is 9.35 ± 1.92. There was no significant association of EAT volume and EAT thickness in the assessment of MACE except for EAT thickness in the ventricular walls. For those who have MACE, the mean EAT in the ventricular walls was 3.66 ± 0.92 with mean EAT in the right ventricular wall at 3.69 ± 1.00 and mean EAT in the left ventricular wall at 3.61 ± 0.95 while for those who did not have MACE, the mean EAT in the ventricular walls was 4.43 ± 1.99 with mean EAT in the right ventricular wall at 4.53 ± 2.44 and EAT in the left ventricular wall at 4.35 ± 1.75.

Table 3 shows the factors that were significantly associated in the assessment of MACE. Blood pressure both SBP and DBP logistic regression analysis showed that increase in systolic and diastolic pressures could decrease MACE (systolic BP: odds ratio= 0.97, 95% confidence interval= 0.95-0.99, p-value=0.02; diastolic BP: odds ratio= 0.93, 95% confidence interval= 0.95-0.99, p-value =0.001). There was significant association found with the use of ACE inhibitors in the assessment of MACE (odds ratio= 0.33, 95% confidence interval= 0.11 - 0.95, p-value=0.05). There was also significant association of EAT thickness in the ventricular walls particularly the right ventricular wall (odds ratio= 0.71, 95% confidence interval = 0.50-1.00, p-value=0.03) and left ventricular wall (odds ratio= 0.65, 95% confidence interval= 0.44-0.95, pvalue=0.02) in the assessment of MACE.

DISCUSSION

There are three findings in this study. For unit increase in systolic and diastolic blood pressures, the odds of having MACE decreased by 2.56% and 6.99%, respectively. Subjects using ACE inhibitors were 67.1% less likely to have MACE. For mm increase in EAT in the right and left ventricular wall, the odds of having MACE decreased by 33.12% and 34.55%, respectively.

Granger, et al. proposed the Global Registry of Acute Coronary Events (GRACE) risk prediction tool which considered systolic blood pressure as one of the nine factors that independently predicted death and the combined end point in the initial 6 months after admission. For every 20-mmHg reduction in SBP, the odds ratio for hospital mortality increases by 1.4.[16-19] Additionally, several studies have previously demonstrated the inverse link between increasing SBP and the risk of adverse cardiovascular outcome.[20-23]

In the study conducted by Bergmark et. al,[44] they showed a population with established CV disease or multiple CV risk factors U-shaped relationships between blood pressure CV events.

SBP was found to have U-shaped relationships with MACE, CV death, and hospitalization due to heart failure, while DBP with MACE, MI, and hospitalization due to heart failure. The associations established between these variables proved to be robust even across multiple strategies which addressed residual confounding. Additionally, the association between low blood pressure and reduced risk for ischaemic stroke provides assurance that low blood pressure was not simply a marker of overall frailty in this population. There is consistency of findings in this research and that of the study of Bergmark et al. where persistent association between low DBP, elevated troponin, and MI is notable. This study also revealed that there is an inverse association between of DBP and occurrences of MACE. This inverse association may be explained by basic physiological concepts. Coronary filling is dependent on central aortic pressure, largely during diastole, and this observation may support concern for low DBP as a cause of insufficient coronary perfusion, subclinical myocardial injury, and MI, as has been hypothesized by others.[45-46]

It is important to keep in mind, however, that these data are observational and do not support inference of a causal relationship. From this perspective, low DBP may for many patients be a marker of arterial stiffness, a risk factor for atherothrombotic events.

We cannot causally link lower blood pressure to increased risk of MACE in this, but we rigorously demonstrate the association between low DBP and risk, which may be due to underlying causes or blood pressure lowering therapy. While the underlying mechanisms of the associations reported here ultimately cannot be resolved in this analysis, the findings do show a robust association between low DBP and MACE that deserves further attention in randomized trials.

Subjects using ACE inhibitors were 67.1% less likely to have MACE. Angiotensin Converting Enzyme (ACE) inhibitors have been shown convincingly to reduce the risk of cardiovascular (CV) death, myocardial infarction (MI), and stroke in a wide range of patients, including those with impaired systolic function, heart failure, and vascular disease with preserved ventricular function.[24-31] The benefit of using ACEI in MACE as a major finding of this research is also consistent with the meta-analysis of Ong et al. (2013)[47] that ACEI reduced stroke, nonfatal MI, and cardiovascular and total mortality in high-risk patients, while ARB only modestly reduced stroke and did not reduce the risk of nonfatal MI or cardiovascular and total mortality. The meta-analysis conducted aimed in seeking to answer the question of whether ACEI or ARB therapy is able to reduce adverse cardiovascular outcomes in patients at high risk. They analyzed only the prospective, randomized, placebo-controlled trials that actually addressed this issue and excluded ONTARGET and similar trials that had no placebo arm but compared active ACEI therapy with ARB or their combination.

Their meta-analysis has shown that ACEI and ARB are not equivalent in their effect on clinical outcomes. Results showed that the use of ACEI significantly reduced total mortality, cardiovascular mortality, nonfatal MI, and stroke in high-risk populations compared to placebo. It also shows that in high-risk patients, when compared to placebo, ARB treatment has no significant effect on cardiovascular or total mortality, as well as nonfatal MI. Determination of the number needed to treat (NNT) enables comparison of ACEI and ARB in terms of of reducing risk of stroke. The modest reduction in stroke risk by ARB (5.84% versus 6.45%; NNT 164) is smaller than the benefit provided by ACEI therapy (3.43% versus 4.58%; NNT 87). Thus, ARB is shown to be inferior to the ACEI and cannot be considered an equivalent treatment alternative in reducing the risk for adverse cardiovascular outcomes in high risk patients. This is unlike the significance of ARB in heart failure, where it is may be used as an alternative to ACEI. Thus, in patients at high risk of coronary events, ACEI should be offered before ARB, which should be used only in those intolerants of ACEI.

Epicardial adipose tissue (EAT) is a visceral adipose tissue around the heart that is particularly deposited around subepicardial coronary vessels.[32] In physiological conditions, the fat tissue consists about 20% of the heart volume, and there is no fascia between muscular tissue of the heart and epicardial fat.[33-35] The composition of EAT might play an important role in the development of high-risk plaque features increasing the risk for MACE. The epicardial fat is more prominent in the atrioventricular and interventricular grooves and right ventricular lateral wall. Epicardial adiposity can be measured using the thickness at a single point or using volume calculation. Prior research has demonstrated that increased EAT volume is independently related to adverse cardiovascular events.[36-38] Study of Markus Goeller et al, showed that in comparison to patients without MACE, subjects who experienced cardiac death or MI were found to have higher epicardial fat volume and lower epicardial fat density. In multivariable Cox analysis adjusted for CCS and ASCVD risk score, EAT volume >125 cm^3 was the only variable independently associated with MACE. Echocardiographic studies have suggested that EAT was neither strongly associated with the incidence of major adverse cardiovascular events in patients with CAD, nor associated with coronary artery stenosis.[39-41] More recently, a meta-analysis by Xu et al.,[41] of 15 case–control studies and one case sectional study (N=2872 patients) found a positive association between EAT thickness and volume and the presence of CAD. However, in this present study conducted, it could not reveal the association of EAT volume and thickness in the assessment of MACE. This is consistent with the study conducted by Pandey et al,[48] which sought to investigate the association between volume and attenuation of epicardial fat and presence of obstructive coronary artery disease (CAD) and high-risk plaque features (HRPF) on CT angiography (CTA) in subjects who presented with atypical chest pain and whether such an association,

if present, can be identified as independent factors in relation to traditional risk factors and coronary artery calcium score (CACS). Subjects under clinical suspicion for CAD and atypical chest pain who underwent coronary CTA were included in the study. Determination of CACS, epicardial fat volume (EFV) and epicardial fat attenuation (EFat) was done using the non-contrast CT images. The angiographic study was assessed for coronary artery stenosis and HRPF. Of the 255 patients included in the study, CAD, obstructive CAD and CTA-derived HRPFs was present in 133 (52.2%), 37 (14.5%) and 82 (32.2%) patients respectively. In comparison to patients without coronary artery stenosis, patients with obstructive CAD were shown to have significantly lower EFat (−86HU [IQR:−88 to −82 HU] vs −84 [IQR:−87 HU to −82 HU]; p = 0.0486). Lower Efat values were also seen in patients with HRPF compared to those without (−86 HU [IQR:−88 to −83 HU] vs −83 HU [−86 HU to −81.750 HU]; p < 0.0001). Thus, EFat showed significant association with obstructive CAD and HRPF. However, EFV was not found to be significantly associated with obstructive CAD or HRPF. Adding EFat to conventional coronary risk factors and CACS in the pre-test probability models increased the area-under curve (AUC) for prediction of both obstructive CAD (AUC[95% CI]: 0.76 [0.70–0.81] vs 0.71 [0.65–0.77)) and HRPF (AUC [95% CI]: 0.92 [0.88–0.95] vs 0.89 [0.85–0.93]), although not reaching statistical significance. It was concluded in their study that epicardial fat attenuation (EFat) but not epicardial fat volume (EFV), is an independent predictor of obstructive CAD and HRPF. These suggest that EFat is a clinically significant characteristic of epicardial fat as it describes "quality" of adipose tissue, considering the effects of brown-white fat transformation and fibrosis. This characterization of epicardial fat gives additional value in comparison to mere adipose tissue quantification using EFV. Their study pointed out that epicardial fat attenuation (EFat) is a better predictor of obstructive CAD and HRPF than EFV. Therefore, the result of my study agrees to their study and can thus explain the inconsistent association of increased epicardial fat volume (EFV) alone with CAD as part of MACE.

Another notable finding in this research study is that for 1-mm increase in EAT in the right and left ventricular wall, the odds of having MACE decreased by 33.12% and 34.55%, respectively. However, several studies have shown that the thickness of epicardial adipose tissue (EAT) was reported to be highly associated with the incidence of MACE. A study by Chu et al,[49] analyzed the utility of EAT thickness in predicting adverse cardiovascular (CV) events by using echocardiographic assessment with EAT thickness determination in 190 patients with persistent AF. CV events included CV mortality, heart failure hospitalization, MI and stroke. The multivariable analysis demonstrated that chronic heart failure, increased left ventricular (LV) mass index and the ratio of transmitral E-wave velocity to early diastolic mitral annulus velocity, decreased body mass index, and increased EAT thickness (per 1-mm increase, odds ratio 1.224, 95% confidence interval [CI] 1.096-1.368, P < 0.001) were associated with adverse CV events.

Also, this study cannot conclude reasons that increasing EAT thickness on left and right ventricular walls will greatly decrease MACE since there may be different factors to consider and EAT thickness varies according to ethnic group. Several studies have shown that ethnicity affects the distribution of visceral adipose tissue. Willens et al,[50] showed that non-Hispanic white males have larger epicardial fat thickness than African-American men, independently of age, weight, and BMI. These differences might be attributed to inherited and non-genetic factors. However, the identities of genes that underlies population variation in adipose tissue development in humans needs to be properly understood in separate studies.

This research study submits the recommendation focusing on furthering research on investigating reasons on the inferences and possible physiologic and clinical mechanisms that an increased SBP, DBP and EAT thickness on right and left ventricular walls can decrease the occurrences of major adverse cardiovascular events (MACE).

The strength of this research study is the analysis for MACE when EAT measurements are collected at different anatomical references. The present study has some limitations inherent to an observational study where data are observational and do not support inference of a causal relationship. The potential for confounding by measured or unmeasured variables cannot be ruled out and major limitations of the present study includes: first, potential selection bias because patients were recruited with and without MACE; second, no survival analysis at different time points for MACE's was performed; third, this study doesn't intend to scale the incidence of MACE; and fourth, MACE includes a lot of disease entities ranging from any severe or acute cardiovascular condition including acute MI, angina pectoris, coronary insufficiency, CVA, TIA, intermittent claudication, CHF, CV death, late percutaneous or surgical revascularization and coronary revascularization.

CONCLUSION

EAT is the true visceral fat deposit of the heart, as it exists directly on the epicardial surface of the myocardium and is contained entirely within the pericardial sac. As the coronary arteries and their major branches are embedded in this fat, this creates a perfect environment for a local interaction between a metabolically active EAT and the coronary vessels it surrounds. In this research, it was noted that EAT volume was not significant in the assessment of MACE. Despite the capacity of different methods to assess EAT, including cardiac CT, there is currently no rationale for its primary use as a risk stratification device as it is unclear if it provides any greater prognostic benefit than currently employed techniques. The future application of EAT thickness location specific quantification may be found to add to the prognostic benefit of pre-existing risk risk stratification techniques and screening MACE.

We cannot causally link lower blood pressure to increased risk of MACE in this but we rigorously demonstrate the association between low DBP and risk. The findings do show a robust association between low DBP and MACE that deserves further attention in randomized trials.

ETHICAL CONSIDERATION

The study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki and National Ethical Guideline for Health and Health-related Research (2017). Prior to the study initiation, the protocol was reviewed and approved by the Philippine Heart Center Institutional Ethics Review Board (PHC IERB). The investigator requests for the waiver of informed consent for the reason of difficulty in obtaining individual written authorization since the last contact with research subjects.

The risk to the subject's privacy is minimal and no sensitive information was obtained. The investigator ensured that the subject's anonymity was maintained. All data were encoded using a password-protected Excel spreadsheet. A code number was assigned for each patient. To maintain anonymity, a separate password protected spreadsheet that links the study code to the patient's name was made. Only the primary investigator had an access to this file. After encoding, all data collection forms were kept in a secured cabinet. The researchers intend to adhere fully to the provisions of the Data Privacy Act of 2012.

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The ***Introduction*** should describe the purpose of the study and its relation to previous work in the field. It should not include an extensive literature review. The description of the ***Methods*** should be concise, but sufficiently detailed to permit repetition by other investigators. ***Results*** should present positive and relevant negative findings of the study, supported when necessary by reference to tables and figures. The ***Discussion*** should interpret the results of the study, with emphasis on their relation to the original hypothesis and to previous studies.

Abbreviations or acronyms such as CAD, AMI, LVH may be used after the terms are spelled out once each in the abstract and text followed by the abbreviation or acronym in parentheses. All measurements should use the International System (SI) of units. Alternative units may be indicated in parentheses if necessary.

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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.

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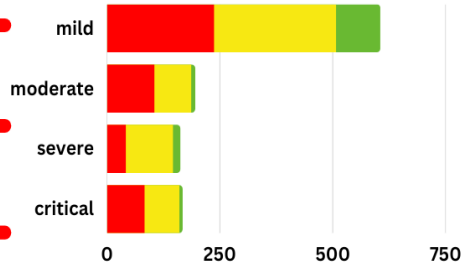

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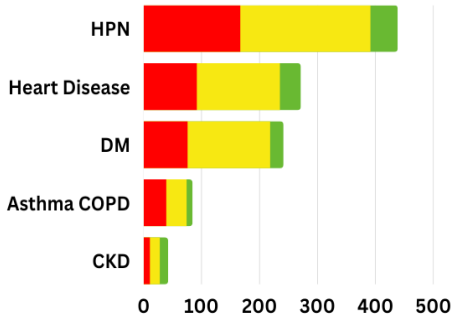

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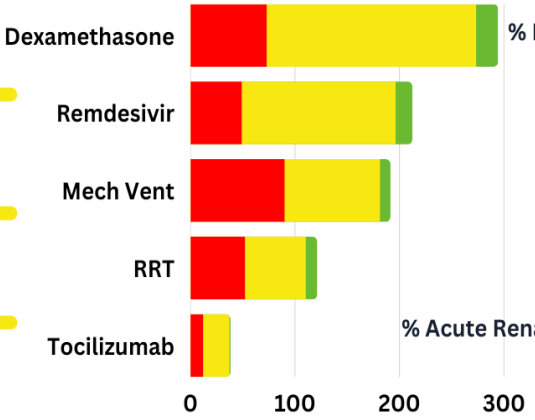

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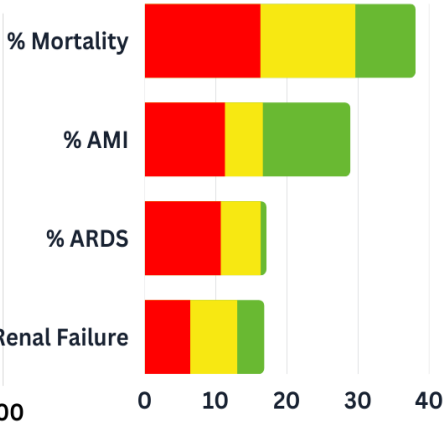
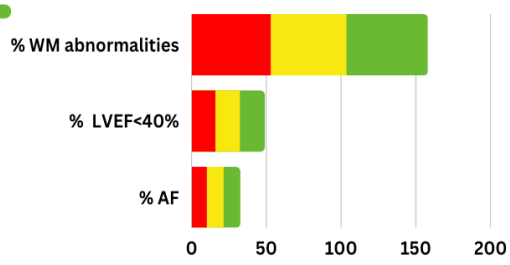
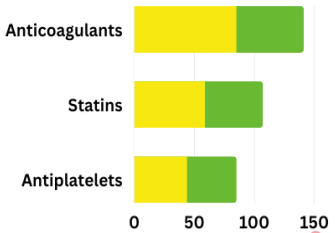


CARDIOVASCULAR TEST ABNORMALITIES



CARDIOVASCULAR DRUGS*



- Data not available in 2020

References

COVID REGISTRY TRENDS and PATTERNS
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