Association of Erectile Dysfunction and Extent of Coronary Vessel Involvement by Syntax Score in Coronary Artery Disease Patients Undergoing Coronary Angiography at Perpetual Succour Hospital from October 2014 – September 2015

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Abstract

Introduction: Erectile dysfunction (ED) has numerous links to cardiovascular disease. Numerous studies show the severity of ED is strongly associated with atherosclerosis and endothelial dysfunction implicated in the pathogenesis of coronary artery disease (CAD). These common vascular pathways have led to evidence that ED onset may be used as a marker of the severity of CAD as well as a pre-clinical marker of early onset-CAD. The researchers aim to determine the association of ED and CAD in terms of prevalence, clinical presentation and severity and extent of vessel involvement by SYNTAX score among CAD patients undergoing coronary angiography.

Methods: This is a prospective, cross sectional, analytical study design set at Perpetual Succour Hospital – Cebu Heart Institute, a private, tertiary hospital with cardiac specialty units located in Cebu City. This study includes all Filipino patients admitted at Perpetual Succour Hospital suspected to have coronary artery disease based on symptoms of angina, dyspnea or other anginal equivalent with indications to undergo coronary angiography during the period of October 1, 2014 to September 30, 2015 were included.

Results: A total of 160 patients were included in the study. The mean age is 57.23 years with most of the patients admitted for stable ischemic heart disease (SIHD) of 54.7%, non-ST elevation acute coronary syndromes (NSTEACS) 33.5% and ST-elevation myocardial infarction (STEMI) 11.8% with multiple cardiovascular risk factors like hypertension, diabetes mellitus, smoking and dyslipidemia. Eighty-two percent complained of ED symptoms with a mean International Index of Erectile Function (IIEF) score of 15.15. Most ED patients identified had mild to moderate ED (31.7%), mild ED (21.7%), moderate ED (17.4%) and severe ED (11.8%). There were only 17.4% of patients who had undergone coronary angiography for CAD complaints that had no ED symptoms on admission. Per clinical presentation, there was a significant association between patients presenting with severe ED, moderate ED and mild to moderate ED with those presenting with SIHD and ACS-NSTEMI on admission, moderate ED and mild to moderate ED. ED was significantly associated with obstructive CAD (p=0.001) and correlated directly with the number of vessels involved (p<0.01) and inversely related to SYNTAX scores (p<0.001). ED symptoms were noted to precede CAD diagnosis by 4.9 to 5.9 years.

Conclusion: In conclusion, there is a high prevalence of ED among CAD patients and its existence is significantly associated with obstructive CAD varying directly with extent and number of vessel involvement. There is a significant inverse relationship with severity of ED and SYNTAX scores. The existence of ED was present in all subsets of CAD patients, regardless of presentation of admission and preceded CAD symptoms and diagnosis by four to five years.

Keywords: erectile dysfunction, coronary artery disease, syntax score

Introduction

Erectile dysfunction (ED) is defined as the inability to reach or maintain erection sufficient for satisfactory sexual performance.[1] It has come to worldwide attention because of its prevalence in half of men beyond 40 years of age and significantly impacts the quality of life of the individual and his partner. Aging accounts for a great majority of ED cases, however, studies have established ED as having a vascular pathology sharing extensive links with atherosclerosis and endothelial dysfunction, as well as sharing cardiovascular risk factors like diabetes mellitus, hypertension, cigarette smoking, dyslipidemia, obesity and the metabolic syndrome, and peripheral arterial disease.[2] Its presence may also herald the onset of other diseases like coronary artery disease (CAD) and cerebrovascular disease.

The knowledge on the incidence of ED in the Philippines, and Asia in general, is limited. This is due to the lack of epidemiological studies of ED among Filipino males. The present data on ED in Asia has been derived largely from foreign studies involving Asian populations where the reported incidence among Filipinos ranged from 33% to 65%.[3,4] These figures may be underestimated due to

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the aforementioned lack of structured studies and the differences in cultural taboos and personal factors.

The pathophysiologic link between ED and CAD has been described as a spectrum of atherosclerosis and artery-size theory on one end and endothelial dysfunction on the other.[1,5] Prevalence of ED in established CAD is as high as 75%.[6] Because ED and cardiovascular disease share common etiologies and pathophysiology, as well as mounting evidence that severity of ED correlates with the severity of cardiovascular disease,[7] it has been concluded that ED may be a sentinel symptom in asymptomatic CAD, thus the need to determine the burden of disease in the Filipino male population and its association with CAD presentation and severity.

To date, there is paucity of data regarding the burden of ED in CAD patients in the community. In Cebu Heart Institute – Perpetual Succour Hospital, cardiovascular disease remains one of the top reasons for admission annually with CAD contributing a significant fraction of the total cardiovascular burden.

Erectile dysfunction is common, as several epidemiologic studies worldwide show a high incidence and prevalence in over 150 million men.[8] ED increases with age and is present in two-thirds of men 70 years and older. As reported in the Massachusetts Male Aging Study (a large community-based observational survey of men aged 40-70 years old), the prevalence was 52% and graded as minimal in 17.2%, moderate in 25.2%, and complete in 9.6%.[2,7] In a European study by Braun et al., the prevalence ranged from 19%-35% in men aged 18 to 75 years old. The burden of disease will only increase as the world's aging population grows, and is expected to be as high as 300 million men worldwide by the year 2025.[9,10]

Among three important epidemiologic studies in published internationally that included Asian subjects: the Global Study of Sexual Attitudes and Behaviors (GSSAB) subgroup study in Asian countries,[11] the Asian Men's Attitudes to Life Events and Sexuality Study[12] and the Asian Survey of Aging Males,[13] the Philippines has the highest incidence of erectile dysfunction in the region ranging from 33% to 65%. This number may even be more as this health problem is often not consulted with physicians due to sexual attitudes influence by cultural influences, religious dogmas and economic concerns. Therefore, the true incidence of ED is largely underreported.

The link between erectile dysfunction and cardiovascular disease have been documented in several studies with shared risk factors like age, smoking, diabetes, atherosclerosis, depression, hypertension, obesity and hyperlipidemia, and sedentary lifestyle.[10] This has led to the propagation of the theory that ED is largely vascular in origin, seen either as a functional manifestation exemplified by the impairment of the nitric oxide pathway resulting in endothelial dysfunction[5] or a structural abnormality in the form of atherosclerosis and a high plaque burden affecting the penile circulation.

As proposed by Montorsi, et al., atherosclerosis, being a systemic disorder, should affect all major vascular beds with uniform extent.[14] However, consequences of an extensive atherosclerotic burden do not manifest at the same time. This may be due to the varying sizes of arteries supplying the affected vascular beds, whereby a significant obstruction in a smaller vessel as exemplified by the penile arteries (1.00-2.00 mm in diameter) may be better accommodated in larger arteries like the coronary (3.00-4.00 mm) and femoral arteries (6.00-8.00 mm).

Endothelial dysfunction also plays a key role in linking ED and CAD. It contributes to pathogenesis of atherosclerosis, myocardial ischemia and acute coronary syndromes in patients with angiographically-defined CAD and those with normal coronary vessels. Evidence shows that men with ED and concomitant CAD have blunted endothelium-mediated vasodilator responses and endothelial injury may be an independent predictor of future prothrombotic events.[1,15]

Currently, diagnosis of ED is made with a comprehensive medical and sexual history and scored by a validated 15-item questionnaire, the International Index of Erectile Function (IIEF). This self-administered questionnaire has been used as a de facto "gold standard" in the diagnostic evaluation of ED severity and has been used as the primary endpoints in most clinical trials for ED.[16] It meets the psychometric criteria for test validity, has a high sensitivity and specificity and correlates well with treatment outcomes.[17] The dynamic penile Doppler evaluation has been found to be of some help in ED diagnosis. Conventionally, patients who show a peak systolic velocity (PSV) <35 cm/s after intracavernosal injection with a vasoactive agent have an impaired vascular response of the penile circulation.[1,14] Penile doppler has not been recommended as a first-line non-invasive diagnostic tool for ED because its sensitivity (67%) and specificity (57%) are moderate at best, but has found its niche as a rule out test given its high negative predictive value (87-98%). Hormone level measurements (i.e. testosterone, prolactin) may also be done, however this is not routinely recommended.

Most patients with ED also have ongoing treatment for other established cardiovascular factors like diabetes mellitus, hypertension and dyslipidemia. These subjects may be on certain drugs that are associated with ED or exacerbation of existing ED like beta blockers, thiazide diuretics, calcium channel blockers, statins. Though there may be an association between certain drugs in CAD with ED, there has been little evidence to support the increased risk of these drugs causing ED per se. The ED may be a result of the underlying cardiovascular pathology rather than drug intake especially if symptoms develop more than four weeks after initiating therapy.

Thompson, et al.[10] submits that due to the shared etiologies of ED and cardiovascular disease combined with the correlation of ED with disease severity, the former may be a harbinger of cardiovascular pathology, particularly coronary artery disease. Patients with coronary artery disease frequently describe symptoms of preexisting erectile dysfunction and has been found to precede it by three to five years.[6] The identification of ED in the asymptomatic male population with CAD would allow a more aggressive approach to diagnosis and treatment of risk factors, as well as, earlier intervention thereby possibly further reducing mortality and morbidity.

The researchers aim to determine the association of erectile dysfunction with coronary artery disease in terms of prevalence, clinical presentation and extent of coronary vessel involvement by SYNTAX score in patients undergoing coronary angiogram at Cebu Heart Institute–Perpetual Succour Hospital (CHI-PSH) from October 2014 - September 2015. More specifically;

1. To determine the prevalence of erectile dysfunction among coronary artery disease patients undergoing coronary angiogram at CHI-PSH
2. To describe the clinical and epidemiological characteristics of patients with ED among CAD patients undergoing coronary angiogram at CHI-PSH
3. To describe the association of ED and clinical presentation of CAD (acute coronary syndromes and chronic stable angina) patients undergoing coronary angiogram at CHI-PSH
4. To establish the association of ED and extent of coronary vessel involvement based on number of vessels involved and SYNTAX scoring among CAD patients undergoing coronary angiogram at CHI-PSH.
5. To determine the chronologic interval between ED onset and CAD diagnosis among CAD patients undergoing coronary angiogram at CHI-PSH

Methods

This is a prospective, cross-sectional analytic study set at Cebu Heart Institute–Perpetual Succour Hospital, a private, 250-bed capacity, tertiary hospital with a cardiac specialty unit located in Cebu City, Philippines.

The study included all Filipino male patients admitted at Cebu Heart Institute - Perpetual Succour Hospital suspected to have coronary artery disease based on symptoms of angina, dyspnea or other anginal equivalent with indications to undergo coronary angiography during the period of October 2014 to September 2015 were included. On the other hand, patients who did not consent, who had prior percutaneous or surgical myocardial revascularization procedures were not be included in the study. Patients with diseases that could alter sexual activity, such as liver cirrhosis, renal failure with GFR <30 mL/min or on dialysis, thyroid disease (hypo- and hyperthyroidism on replacement treatment), major depression on long-term pharmacological treatment, and spinal cord injuries, and those with previous pelvic, penile, urethral, or prostate trauma or surgery were excluded.

Sample size computed was between 43 to 1488 to achieve 90% power to detect an effect size (W) of 0.1000-0.05000 using a one-degree of freedom chi-square test with a significance level (alpha) of 0.01000.

Definition of terms

- Erectile dysfunction (ED) - the inability to reach or maintain erection sufficient for satisfactory sexual performance
- International Index of Erectile Function (IIEF) – a validated self-administered 15-item questionnaire to assess the presence and severity of ED from five domains of sexual function: erectile function, orgasmic function, sexual desire, intercourse and overall satisfaction.[16, 17] (See Appendix A.)
- No erectile dysfunction – a score of 22 – 25 on the IIEF questionnaire
- Mild erectile dysfunction – ED with a score of 17 – 21 on the IIEF questionnaire
- Mild to moderate erectile dysfunction – ED with a score of 12 – 16 on the IIEF questionnaire
- Moderate erectile dysfunction – ED with a score of 8–11 on the IIEF questionnaire
- Severe erectile dysfunction – ED with a score of less than 8 on the IIEF questionnaire
- Coronary artery disease (CAD) - a condition that results when the coronary arteries are narrowed or occluded by atherosclerotic deposits of fibrous and fatty tissue
- Insignificant or nonobstructive CAD - <50% coronary artery diameter narrowing of the left main coronary artery and <70% coronary artery diameter narrowing by visual estimate of the left anterior descending artery, left circumflex artery, right coronary artery and other branches
- Significant or obstructive CAD - >50% diameter narrowing of the left main coronary artery and >70% diameter narrowing by visual estimate of the left anterior descending artery, left circumflex artery, right coronary artery and other branches.
- SYNTAX scoring system – grading of the severity of CAD based on the narrowing of the coronary lumen on coronary angiography[18] (Appendix B)
- Unstable angina (UA) - defined as angina or anginal equivalent occurring at rest or minimal exertion usually lasting >20 minutes occurring with a crescendo pattern not relieved with nitrates with normal cardiac biomarkers
- Non-ST elevation myocardial infarction (NSTEMI) – presence of typical angina, rise and fall in cardiac markers and usually associated with ST segment depression on at least two contiguous leads
- Non ST-elevation acute coronary syndromes (NSTEACS) – denotes both unstable angina and non-ST elevation myocardial infarction acute coronary syndromes.
- ST elevation myocardial infarction (STEMI) – requires

the presence of at least two of the following for the diagnosis of myocardial infarction: characteristic angina, ST elevation on at least two contiguous leads on ECG and a typical rise and fall in cardiac markers

- Stable ischemic heart disease (SIHD) or chronic stable angina (CSA) - typically manifests as poorly localized chest or arm discomfort (rarely described as pain), reproducibly precipitated by physical exertion or emotional stress, and relieved within five to 10 minutes by rest or sublingual nitroglycerin.

All adult male patients (>18 years old) admitted at CHI-PSH that fulfilled the inclusion criteria and underwent coronary angiogram to evaluate for coronary artery disease, regardless of presentation (ACS and SIHD) from October 2014 to September 2015 were screened. The subjects were informed of the study objectives and their consent were obtained (see Appendix C). The demographic profile were noted including age, sex, smoking history, BMI and co-morbidities such as hypertension, diabetes mellitus, dyslipidemia, maintenance medications as well as the diagnosis on admission were entered in the data sheet (see Appendix D). Routine diagnostic results such as electrocardiogram and echocardiogram findings were also noted and entered in the data sheet.

Coronary angiographies were done by interventional cardiologists. Significant coronary artery disease was considered in 50% or more stenosis of the left main coronary artery and 70% or more stenosis of the major coronaries such as the left anterior descending, left circumflex and right coronary arteries. They were classified as having significant/obstructive CAD or insignificant/nonobstructive CAD. The number of vessels involved were also noted as 1, 2, 3 and 3-vessel disease with left main (LM) accordingly. The coronary angiograms were later reviewed and the severity of CAD was determined based on SYNTAX scoring system by a single interventional cardiologist blinded to the study and this investigator. SYNTAX scoring was done with the use of the online SYNTAX calculator 2.1 on www.syntaxscore.com. The SYNTAX score increases with increasing complexity of obstruction and variations in anatomy.

Erectile function was evaluated by the erectile function domain of the International Index of Erectile Function (IIEF-EFD) a validated 15-item guided questionnaire. Erectile function is specifically addressed by six questions that form the so called 'erectile function domain' of the questionnaire. Each question is scored one to five. ED is defined as any value <26 and the lesser the IIEF score, the worse the ED. IIEF questionnaire was administered to patients after a mean time interval of three (two to five) days since the admission to the hospital. Review of their in-patient charts was done.

Ethics approval from the Perpetual Succour Hospital – Institutional Ethics Board (PSH-IERB) was sought prior to the conduct of the study. (Appendix E)

The data gathered was encoded in Microsoft Excel 2013 spreadsheet. Patient profiles, which were categorical types, were expressed using frequency and percentage distribution while those which were of continuous nature were presented in mean, standard deviations and absolute ranges. In testing associations between patient profiles (categorical variables) and their levels of ED, Chi-square test of independence with appropriate contingency tables was utilized. Moreover, in testing correlation between SYNTAX and ED scores, Pearson-r product moment correlation was used. Also, ED scores as stratified by SIHD or CSA, NSTE-ACS (UA and NSTEMI) and STEMI, were compared using one-way ANOVA. Any associated p-values lesser than 0.05 alpha were considered significant. IBMSPSS 21 was used as the statistical software in the processing of data.

Results

There were a total of 173 male patients who underwent coronary angiogram from October 1, 2014 to September 30, 2015 in our institution. Applying the inclusion and exclusion criteria, only 160 patients (92.5%) were included in the final analysis. There were six patients who refused, three patients who were post coronary artery bypass graft surgeries, two patients who only underwent angiography in preparation for valve surgery, one patient with renal failure on hemodialysis, one patient on chronic drug treatment for post-traumatic stress disorder. (Table I)

The mean age was 57 years old with an average BMI of 27.26 and majority had an admitting diagnosis of stable ischemic heart disease (SIHD) or chronic stable angina (CSA) (55%). This was followed by non-ST elevation myocardial infarction (NSTEMI) at 18%, unstable angina (UA) at 15.6%, both collectively called the non-ST elevation acute coronary syndromes (NSTEACS), and ST-elevation myocardial

Table I. Clinical and demographic profile (n=160)

Patients' demographics	Descriptive
Age, years ± SD	57.23 ±11.54
BMI	27.26 ± 3.27
Diagnosis on admission, f(%)	
CSA or SIHD	88 (55)
NSTEMI	29 (18.1)
STEMI	19 (11.9)
UA	25 (15.6)
Co-morbidities, f(%)	
Non-insulin dependent diabetes mellitus	45 (28.1)
Insulin-dependent diabetes mellitus	9 (5.6)
Hypertension, controlled	121 (75.6)
Hypertension, poorly controlled	18 (11.3)
Current smoking	37 (23.1)
History of smoking	53 (33.1)
Dyslipidemia	32 (20)
Family history of CAD	33 (20.6)
Chronic kidney disease, non dialysis	5 (3.1)
Lifestyle, f (%)	
Cigarette smokers	107 (66.9)
Pack-years	23.12 ± 17.12
Alcohol drinkers	125 (8.1)

infarction (STEMI) 11.9%. Most common co-morbidities were controlled hypertension (75.6%), cigarette smokers (33.1%), with non-insulin dependent DM (28.1%), a family history of CAD (20.6%), and dyslipidemia (20%). (Table I)

Sixty-six percent (66.9%) of patients were cigarette smokers, and averaged of 23.12 pack-years. Seventy-seven percent (78.1%) were alcohol drinkers, 72% of which classified their drinking as occasional. (Table I)

Most patients were on an ARB or ACEI prior to admission (57.5%), along with statins (54.4%), and antiplatelet therapy with both clopidogrel (41.3%) and aspirin (33.8%) and diuretics (21.9%). Beta blockers, which show a high usage rate in the country due to its relatively low cost and notoriously associated with ED were being taken in 33.1% of patients used for a mean of four years. (Figure 1)

There were 133 patients (83.1%) complaining of ED with an average IIEF score of 15.15, ranging from five to 25, with an average onset prior to CAD diagnosis of 5.70 years, ranging from as early as four months to 40 years. In terms of patients' coronary profiles, their mean SYNTAX score is 21.56±12.59 with 70.6% having obstructive CAD and 30% had non-obstructive or insignificant CAD. (Table II)

Most CAD patients identified had mild to moderate ED (31.9%), mild ED (21.9%), moderate ED (17.5%) and severe ED (11.9%). There were only 17.5% of patients who had undergone coronary angiography for CAD complaints who had no ED symptoms on admission. (Figure 2)

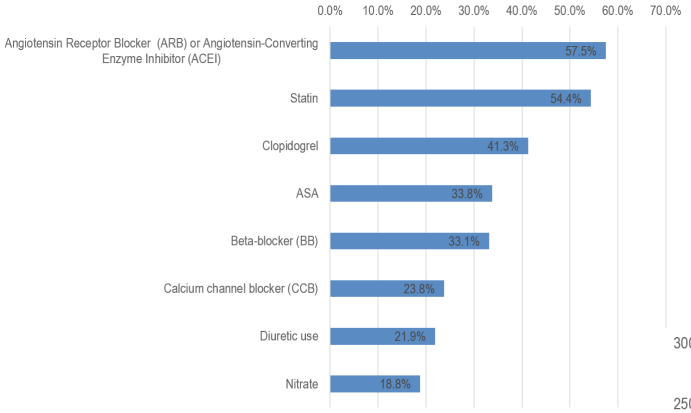

Figure 1. Prehospital Medications (n=160)

Table II. Erectile dysfunction severity, SYNTAX Scores and CAD

ED profiles	Descriptive
ED incidence, f (%)	133 (83.1)
ED score	
mean(SD)	15.15 ± 5.26
range	5-25
Years onset before CAD diagnosis	
mean(SD)	5.7 ± 5.62
range	0.3 - 40
SYNTAX Score	21.56 ± 12.59
CAD Type, f (%)	
Obstructive CAD	113 (70.6)
Nonobstructive CAD	47 (30)

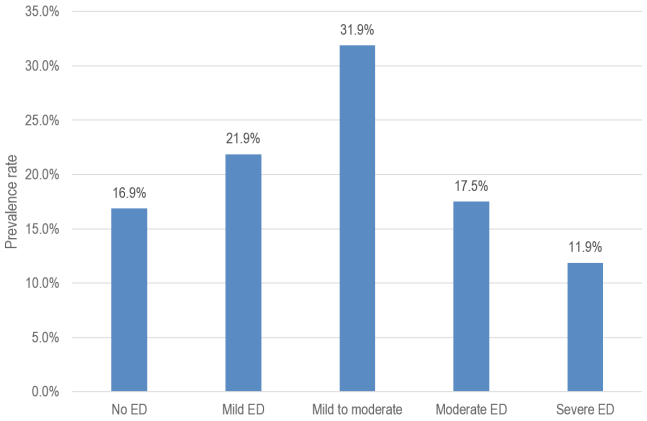

Figure 2. Severity of ED among CAD patients (n=160)

There was a significant number of patients with severe ED among those who presented with CSA (47%) and NSTEMI (26%) on admission, as well as with moderate ED and mild to moderate ED. Patients with UA and STEMI had lower rates of severe ED. The association was statistically significant (p=0.017). (Figure 3)

Among patients with ED, there was no association found between the any of the medications taken (e.g. beta blockers, nitrates, statins, calcium channel blockers) and the different levels of ED (p>0.05). (Figure 4)

ED was found to be statistically associated with obstructive CAD (p=0.001) especially mild to moderate ED (92%), moderate ED (93%) and severe ED (100%). (Figure 5)

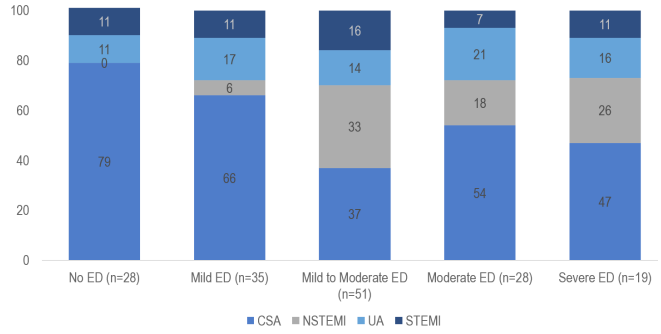

Figure 3. Association of ED levels with CAD diagnosis on admission

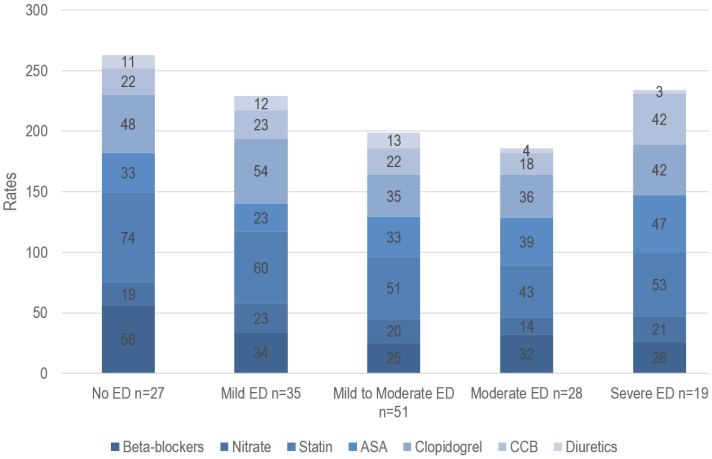

Figure 4. Association of ED levels with medications taken on admission

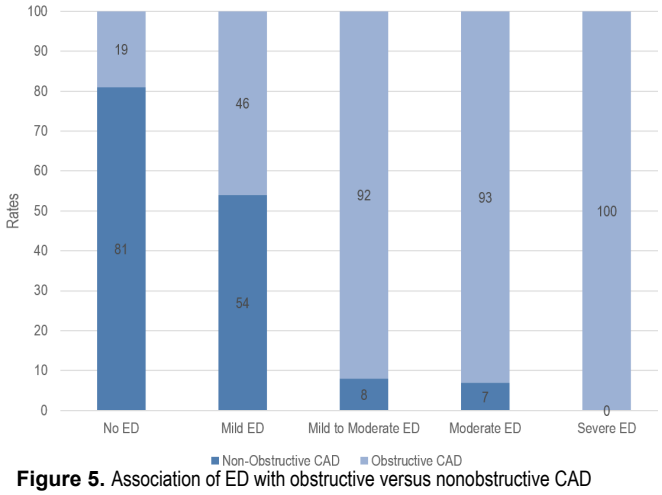

Figure 5. Association of ED with obstructive versus nonobstructive CAD

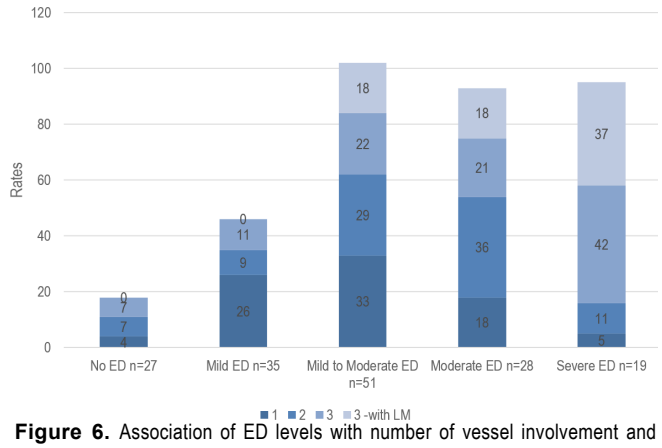

Figure 6. Association of ED levels with number of vessel involvement and obstructive CAD

In patients with obstructive CAD, there was a significant association with ED severity and the number of vessels involved (p<0.04 alpha). This is especially true among patients with three-vessel disease with LM involvement (p<0.01). (Figure 6)

There is a significant inverse correlation between SYNTAX scores and ED scores, wherein, the higher the SYNTAX score, the more severe the ED, and vice versa (r = (-0.454), p<0.001). (Figure 7)

Subjects were diagnosed within 4.91 to 5.90 years from ED onset to CAD diagnosis across the different entities in the spectrum of CAD. (Table III)

Discussion

Evidence shows that ED and CAD are manifestations of a common pathophysiologic process. The links to atherosclerosis and endothelial dysfunction as final common pathways to the vascular disease process are well founded with several retrospective association studies.[2,6,9] In this study, the presence of ED was established in 82.6% of patients undergoing coronary angiography for complaints attributable to CAD. This is higher than the reported prevalence in European (19-35%)[2] and American (52%)[9] data.

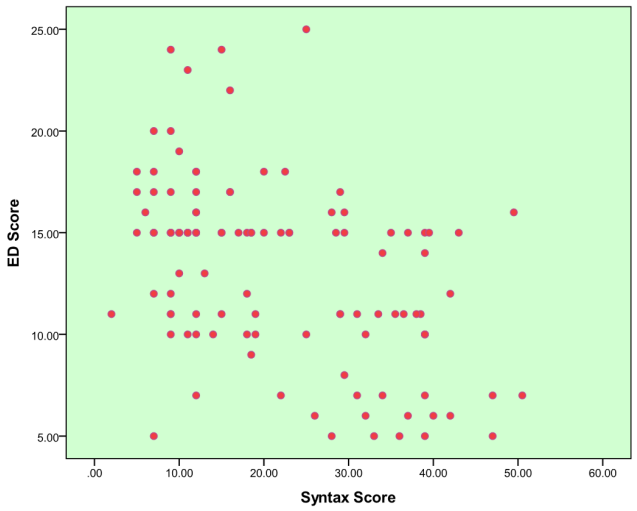

Figure 7. Correlation of ED severity with SYNTAX scores

Table III. ED onset from CAD diagnosis by angiography

	ED Onset (years)
Groups	Mean
CSA/SIHD	5.90
NSTE-ACS	5.59
STEMI	4.91
Total	5.66

The paucity of Asian epidemiological studies make it difficult to declare the actual prevalence in the country and the region, but this study's data will support the literature that Filipino males included in foreign epidemiologic studies have the region's highest prevalence at approximately 33-65%.[11,12,13]

In agreement with other studies, the clinical and epidemiologic profiles of patients were consistent with the most ED cases occurring in the 50-60 year old range (mean, 57 years old) mostly mild to moderate in severity in a population with common cardiovascular risk factors like diabetes mellitus, smoking, dyslipidemia, and hypertension. With the strength of evidence linking these risk factors with ED and CAD, aggressively treating these may provide improvement in both cardiovascular and sexual functions. Given the notoriety of medications being a cause of ED in this population of CAD patients, this study shows that patients on full treatment regimens for CAD, which included beta blockers, statins, nitrates, ACEI and ARB's, were not sginficantly associated with an increased risk of ED. This finding is consistent with studies by Jackson, et al. and Ko, et al.[8,19]

In the COBRA trial by Montorsi, et al.,[6] ED rate significantly differed across patients with established CAD according to coronary clinical presentation and atherosclerotic burden. It was low in patients with acute coronary syndromes and high in those with SIHD. In this study, this is not as clear cut as there are a significant number of patients with severe ED, moderate ED and mild to moderate ED with SIHD and ACS-NSTEMI. There were lower rates of severe ED among those with ACS-UA and STEMI, suggesting a more uniform

distribution of ED across the spectrum of ACS and SIHD. This is seen in the relationship of progressively worsening ED function with obstructive CAD (p=0.001) and with the greater the number of vessels involved (p<0.01). This study established the inverse relationship between SYNTAX scores and ED severity, whereby the greater the complexity of anatomy and severity of obstruction, the more severe the ED (p<0.001).

In line with the vessel-size and endothelial dysfunction theories, ED frequently comes before the onset of CAD symptoms and eventual diagnosis. This has led to several studies like that of Montorsi et al. and Inman et al. to describe ED as a "sentinel of the heart," acting as a surrogate marker prior to clinical onset of CAD.[2,5,6] Most published studies report that ED precedes CAD symptoms by at least three years, giving an important clinical window for directed work-up, appropriate intervention, and aggressive treatment. This study's findings show that in our patient population, ED preceded CAD diagnosis by four to five years.

Conclusion

In conclusion, there is a high prevalence of ED among CAD patients who underwent coronary angiography at our institution. The existence of ED in these patients were significantly associated with obstructive CAD and varies directly with extent and number of vessel involvement. There is a significant inverse relationship with severity of ED and SYNTAX scores. The existence of ED was present in all subsets of CAD patients, regardless of presentation of admission and preceded CAD symptoms and diagnosis by four to five years.

Given the strong correlation of ED and CAD and its chronologic appearance prior to overt CAD symptoms and CAD diagnosis, this provides a clinical window for appropriate diagnostics and aggressive treatment of CAD risk factors.

Recommendations

This study recognizes the imperfect method of determining ED severity by means of intermittent questioning of patients and that the employment of adjuncts to ED diagnosis in the CAD population with penile Doppler studies and serum testosterone determinations may support the primary ED impression by means of the IIEF validated questionnaire.

This study recommends the follow-up of the patients in this study, in particular those with ED and no CAD, and whether this subset population actually do develop a coronary event in the future.It is also the recommendation of the investigators to study measures to evaluate endothelial dysfunction and its significance in the link between ED and CAD.

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APPENDIX A: The International Index Of Erectile Function (IIEF) 5 Questionnaire

Please encircle the response that best describes you for the following five questions:

Over the past 6 months					
1. How do you rate your confidence that you could get and keep an erection?	Very Low 1	Low 2	Moderate 3	High 4	Very High 5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never 1	A few times (much less then half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always or always 5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?	Almost never or never 1	A few times (much less then half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always or always 5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Extremely difficult 1	Very difficult 2	Difficult 3	Slightly difficult 4	Not difficult 5
5. When you attempted sexual intercourse, how often was it satisfactory to you?	Almost never or never 1	A few times (much less then half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always or always 5

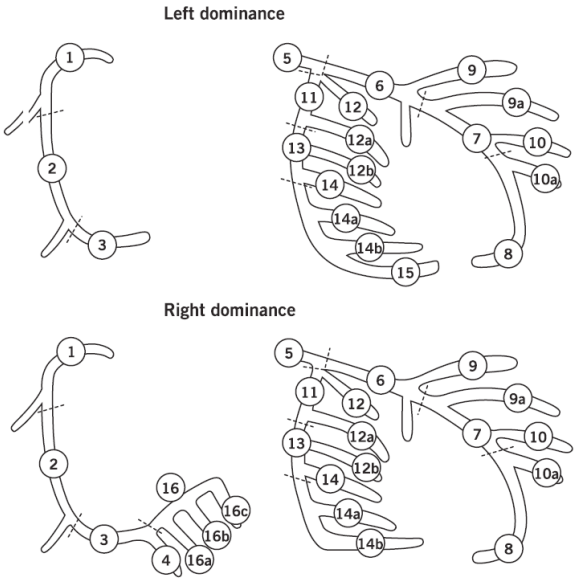
Total Score

1-7 Severe ED 8-11 Moderate ED 12-16 Mild to moderate ED 17-21 Mild ED 22-25 No ED

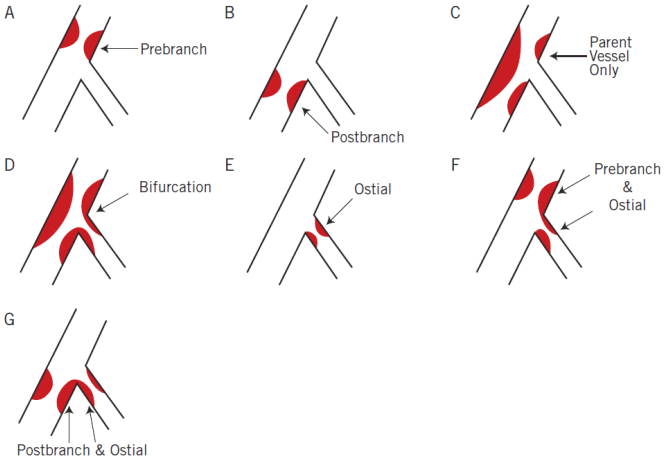
APPENDIX B. SYNTAX Scoring tool

The SYNTAX score is an angiographic grading tool to determine the complexity of coronary artery disease. It is the sum of the points assigned to each individual lesion identified in the coronary tree with >50% diameter narrowing in vessels >1.5mm diameter. The coronary tree is divided into 16 segments according to the AHA classification (Figure 1). Each segment is given a score of 1 or 2 based on the presence of disease and this score is then weighted based on a chart, with values ranging from 3.5 for the proximal left anterior descending artery (LAD) to 5.0 for left main, and 0.5 for smaller branches (Table 1). The branches <1.5 mm in diameter, despite having severe lesions, are not included in the SYNTAX score. The percent diameter stenosis is not a consideration in the SYNTAX score, only the presence of a stenosis from 50–99% diameter, <50% diameter narrowing or the total occlusion. A multiplication factor of 2 is used for non-occlusive lesions and 5 is used for occlusive lesions, reflecting the difficulty of PCI.

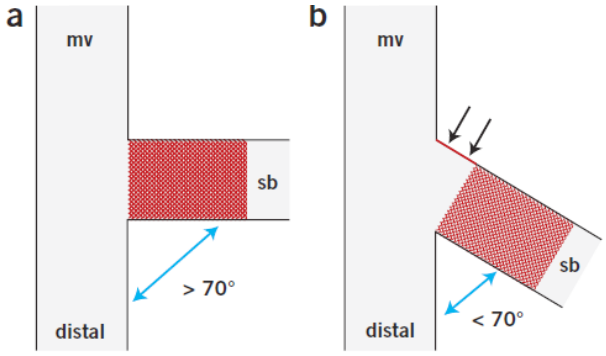
Further characterization of the lesions adds points. For example, a total occlusion duration >3 months, a blunt stump, a bridging collateral image, the first segment visible beyond the total occlusion, and a side branch >1.5 diameter all receive one point. For trifurcations, one diseased segment gets three points, two diseased segments get four points, three diseased segments get five points, and four disease segments get six points. For bifurcation lesions, one point is given for types A, B, and C; two points are given for types D, E, F, and G (Figure 2); and one point is given for an angulation >70 degrees (Figure 3). Additionally, an aorto-ostial lesion is worth one point, severe tortuosity of vessel is worth two points, lesion length greater than 20 mm is worth one point, heavy calcification is worth 2 points, thrombus is worth 1 point, and diffuse disease or small vessel is at 1 point per segment involvement (Table 2). For multiple lesions less than three reference vessel diameters apart, these are scored as a single lesion. However, at greater distance than three vessel diameters, these are considered separate lesions. Segments in which bifurcations are evaluated are those involving the proximal LAD and left main, the mid LAD, the proximal circumflex, mid circumflex, and crux of the right coronary artery. With regard to trifurcation lesions, these also are additive in number of segments involved. The SYNTAX score algorithm then sums each of these features for a total SYNTAX score (Table 3). A computer algorithm is then queried and a summed value is produced.



Appendix B. (Fig 1) Scout film of the abdomen shows dilated bowel loops with diffusely thickened small intestinal wall



Appendix B. (Fig 2) Bifurcation classification (modified from Duke and ICPS classifications systems)



Appendix B. (Fig 3) Bifurcation lesion

SYNTAX Scoring Tool

Appendix B (Table I). Segment Weighing Factors

Segment Number	Segment	Right Dominance	Left Dominance
1	RCA proximal	1	0
2	RCA mid	1	0
3	RCA distal	1	0
4	Posterior descending artery	1	Na
16	Posterolateral branch from the RCA	0.5	Na
16a	Posterolateral branch from the RCA	0.5	Na
16b	Posterolateral branch from the RCA	0.5	Na
16c	Posterolateral branch from the RCA	0.5	Na
5	Left Main	5	6
6	LAD proximal	3.5	3.5
7	LAD mid	2.5	2.5
8	LAD apical	1	1
9	First diagonal	1	1
9a	First diagonal	1	1
10	Second diagonal	0.5	0.5
10a	Second diagonal	0.5	0.5
11	Proximal circumflex artery	0.5	2.5
12	Intermediate / Anterolateral artery	1	1
12a	Obtuse marginal	1	1
12b	Obtuse marginal	1	1
1.513	Distal circumflex	0.5	1.5
14	Left posterolateral	0.5	1
14a	Left posterolateral	0.5	1
14b	Left posterolateral	0.5	1
15	Posterior descending artery	Na	1

Appendix B (Table II). Lesions Adverse Characteristic Scoring

Diameter Reduction	
Total Occlusion	x 5
Significant Occlusion (50-99%)	x 2
Total Occlusion (TO)	
Age of > 3 months or Unknown	+ 1
Blunt stump	+ 1
Bridging	+ 1
First segment visible beyond TO	+ 1 per nonviable visible segment
Side branch (SB) – Yes, SB < 1.5 mm	+ 1
Yes, both SB < and > than 1.5 mm + 1	
Trifurcations	
1 diseased segment	+ 3
2 diseased segments	+ 4
3 diseased segments	+ 5
4 diseased segments	+ 6
Bifurcations	
Type A, B, C	+ 1
Type D, E, F, G	+ 2
Angulation < 70 degrees	+ 1
Aorto ostial stenosis	+ 1
Severe tortuosity	+ 2
Length > 20 mm	+ 1
Heavy calcifications	+2
Thrombus	+1
Diffuse disease / Small vessels	+ 1 per segment number

Appendix B (Table III). The SYNTAX Score Algorithm

1. Dominance
2. Number of Lesions
3. Segments involved per lesion

Lesion Characteristics

4. Total occlusion
   a. Number of segments involved
   b. Age of the total occlusion (> 3 months)
   c. Blunt stump
   d. Bridging collaterals
   e. First segment beyond the occlusion visible by antegrade or retrograde filling
   f. Side branch involvement
5. Trifurcation
   a. Number of segments diseased
6. Bifurcation
   a. Type
   b. Angulation between distal main vessel and the side branch less than 70 degre
7. Aorto-ostial lesion
8. Severe tortuosity
9. Length > 20 mm
10. Heavy calcification
11. Thrombus
12. Diffuse disease / Small vessels
    a. Number of segements of diffuse disease / small vessels

APPENDIX D: DATA COLLECTION SHEET

I. DEMOGRAPHICS:

Name	<Family Name, First Name, M.>			**Admission Date**		**Chief Complaint**	
Case #		**Rm #**		**Managed by**	□IM □Cardio □Others:_____		
Age		**Hosp #**			**Address**		

II. DIAGNOSIS

Diagnosis on Admission	Cardiac Diagnosis: □STEMI □NSTEMI □UA □CSA □Others Non-Cardiac Diagnosis:

III. PRE-HOSPITALIZATION DATA

Prior Interventions	□PCI □CABG □Valvular Surgery □Valvular Percutaneous □Pacemaker □ICD		
Co-Morbidities	□Hemorrhagic Stroke □Non-Hemorrhagic Stroke □TIA □Documented CAD (#V:____) □Suspected CAD □History of ACS (Year: _____) □PAD	□DM, Non-Insulin Dependent □DM, Insulin Dependent □HPN, Controlled □HPN, Poor-Control □Current Smoking □History of Smoking □Thyroid Disorder	□Dyslipidemia □Family History of CAD □Chronic Lung Disease □CKD (Non-HD) □CKD (On HD) □Others
Smoking	Pack-Years		
Alcohol	Bottles and Frequency		
Family History of CAD	□Yes □No		

Prior Medications	Date Started	Dose	Compliance

IV. CLINICAL PRESENTATION ON ADMISSION

Place of Admission	□ER □ Ward □ER □ ICU □ Ward □ICU	
Chief Presentation	□Dyspnea □Syncope □Near-Syncope □Orthopnea □PND □Edema □Cardiac Arrest □Angina □Nausea □Palpitations □Arrhythmia □Fatigue □Others:	
ECG:	□STEMI, Location _____ □Ischemia, Location _____ □NSSTTWC _____ □Others _____	**Precipitating Factors** □None □Myocarditis □ACS □Pregnancy □Arrhythmia □Dietary Indiscretion □Endocarditis □Non-Compliance □Pneumonia □Drugs / Toxins □UTI □Electrolytes □Other Infection □ Anxiety □Thyrotoxicosis □Unknown □ Trauma □Others: □ Hypoxemia □ Anemia
Admission Vital Signs	BP: HR: RR: O_2Sat:	
Measurements	Height (cm): Weight (kg): BMI:	
Functional Class	□I □II □III □IV	
Edema	□I □II □III □IV	
Crackles	□< 50% LF (Mild) □≥ 50% LF (Severe)	
Other Pertinent PE:		
IIEF – EFD Score		
How long ago would you say this started?		

V. TESTS

Echocardiogram (Date:_____)

2DED	
Hypokinesia	□Yes □No
Location	
EF	
Teicholz	
Simpsons	

Flow-Mediated Vasodilatation (Date:_____)

FMD	
	□Yes □No

Ankle-Brachial Index (Date:_____)

ABI	
	□Yes □No

Coronary Angiogram (Date:_____)

Angiogram	
LAD	
LCX	
RCA	
LM	
SYNTAX	

V. IN-HOSPITAL MANAGEMENT

Medications Started:

Medications *	Dose	Date Started	Date Discontinued **	Adverse Effect
Beta blockers				
ACEI/ARBs				
Inotropes				
CCB				
ASA				
Clopidogrel				
Statin				
Diuretic				
Nitrates				
Anti-diabetes				

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APPENDIX E. ETHICS APPROVAL FROM INSTITUTIONAL ETHICS AND REVIEW BOARD

INSTITUTIONAL ETHICS AND REVIEW BOARD
Room 501, SPC – Medical Specialty Center
Perpetual Succour Hospital
Gorordo Avenue, Cebu City

NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD:
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Institutional Ethics and Review Board
Room 501, SPC – Medical Specialty Center
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PSH-IERB CODE: **PSH2014-039**
PROTOCOL TITLE: **Association of Erectile Dysfunction and Coronary Artery Disease: Prevalence, Clinical Presentation and Extent of Coronary Vessel Involvement in Coronary Artery Disease Patients Undergoing Coronary Angiogram at Perpetual Succour Hospital from October 2014-October 2015**

This is to inform you that your responses to the queries for the above-mentioned study has been reviewed and is hereby granted final approval by the PSH Institutional Ethics and Review Board

(Note: All subsequent communications will have to include the PSH-IERB code aside from the sponsor assigned protocol no.)

The Perpetual Succour Hospital – Institutional Ethics and Review Board is organized and operates according to ICH-GCP and applicable laws and regulations.

Ellie May B. Villegas, MD
Co-chair