Undiagnosed chronic obstructive pulmonary disease is highly prevalent in patients referred for dobutamine stress echocardiography with shortness of breath

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Undiagnosed chronic obstructive pulmonary disease is highly prevalent in patients referred for dobutamine stress echocardiography with shortness of breath.

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Abstract

Purpose: Shortness of breath (SOB) is a common symptom referral for dobutamine stress echocardiography (DSE). Patients with SOB and a normal DSE have worse long-term outcome than the general population. This suggests multiple aetiologies are involved. The purpose of this study was to assess the prevalence and clinical significance of undiagnosed COPD amongst patients referred for a DSE with SOB.

Methods: We prospectively studied 114 patients referred for DSE with SOB without prior evidence of lung disease (mean age 64.9±18.5 years, 60 male). Respiratory function testing using spirometry was performed on all patients on the day of their DSE. The study end-points were cardiac events and total mortality.

Results: Respiratory function testing and DSE was performed in all patients and COPD was highly prevalent (n=93). Multivariate Cox regression analysis was used to estimate the effect of dyspnoea on non-fatal cardiac events (NFCE) and all-cause mortality. Over a mean follow-up of 4.5±2.6 years, the composite end-point of NFCE and all-cause mortality occurred in 62.7% and 16.7% patients, respectively. COPD (HR 1.27;95%CI 1.17-1.93), previous myocardial infarction (HR 1.84;95%CI 1.06-3.2), myocardial ischaemia (HR 2.56;95%CI 1.48-4.43), peak wall motion score index (HR 4.66;95%CI 2.26-9.6) and mitral E/E' (HR 1.21;95%CI 1.1-1.33) were significantly associated with a NFCE. Myocardial ischaemia (HR 4.43;95%CI 1.24-15.81) was the only independent predictor of all-cause mortality.

Conclusions: Undiagnosed COPD is highly prevalent and independently associated with worse outcome amongst patients with SOB referred for DSE. Symptom presentation is therefore an important consideration when interpreting DSE results.

Introduction

Shortness of breath (SOB) or laboured breathing (dyspnoea), is characterised by a subjective experience of breathing discomfort [1], which intensifies on exertion. SOB is a common symptom in patients with cardiac and respiratory disease and is a strong predictor of mortality [1], even in the general population [2]. The causes of SOB are often multifactorial and this often results in variation of practice amongst clinicians concerning diagnostic testing.

Dyspnoea is an important and common symptom among patients with suspected and known coronary artery disease (CAD). The stimulus and aetiology is complex; however, among patients with dyspnoea and CAD, the risk of death from cardiac cause is four times greater compared to asymptomatic patients and more than twice the risk compared to patients with typical angina [3]. As such, dyspnoeic patients are frequently referred for dobutamine stress echocardiography (DSE) to evaluate cardiac structure, function and the presence or absence of myocardial ischaemia. Several studies have demonstrated associations between dyspnoea and all-cause and cardiovascular disease (CVD) mortality [4]. However, the prevalence and clinical significance of undiagnosed respiratory disease amongst dyspnoeic patients referred for a DSE is unknown. Therefore, the aim of this study was to prospectively assess respiratory function in a cohort of unselected dyspnoeic patients without accompanying chest pain referred for DSE, and ascertain the prevalence of respiratory disease, myocardial ischaemia and adverse events.

Methods

Study Cohort

We prospectively recruited 114 patients undergoing clinically indicated DSE for the evaluation of dyspnoea between April 2015 and December 2016 in the outpatient setting. Exclusion criteria included patients referred with typical or atypical chest pain, unstable angina, age <18-years, inability to consent, severe aortic stenosis, pulmonary hypertension and asymptomatic patients awaiting non-cardiac surgery. In addition, patients with an active or recent (<6 weeks) infection and recent surgery or condition that may affect patients performing forced expiration were excluded. Clinical characteristics were recorded at the time of the patients DSE. Follow-up data was obtained by investigators blinded to all results and was collated by contacting patients or a family member, general practitioners, and reviewing hospital records, to enquire about interim hospital admissions, outpatient diagnosis of cardiovascular events, and deaths. The date of the last review or consultation was used to calculate the duration of follow-up through to March 2020.

This investigation conformed to the Declaration of Helsinki principles. All patients provided informed consent before testing, and the local research ethics committee approved the study.

Dobutamine Stress Echocardiography

At baseline, all patients recruited underwent a full cross-sectional transthoracic echocardiogram with measurements recorded as recommended by current guidelines [5]. All patients then underwent DSE using a commercially available ultrasound machine (Vivid E95,

GE Healthcare, Milwaukee, Wisconsin). The image quality obtained was interpretable in all patients (36 [31.6%] requiring contrast) and the entire cohort was used in data analysis. DSE was performed according to a standard protocol [6] with images acquired in the standard parasternal long- and short-axis and apical 2-, 3-, and 4-chamber views. The left ventricle (LV) was divided into a 17-segment model for qualitative analysis [7] and wall motion was scored on a 4-point scale (1, normal wall motion; 2, hypokinesis; 3, akinetic; and 4, dyskinetic) as is standard [6]. In patients with resting akinetic segments a biphasic response was used to indicate ischaemia. LV ejection fraction was calculated using biplane Simpson's technique. Results were classified as a normal response with an overall increase in wall motion or abnormal response. An abnormal response was described as the occurrence under stress of hypokinesia, akinesia or dyskinesia in one or more resting normal segments and/or worsening of wall motion in one or more resting hypokinetic segments [8]. In this way patients were categorised as non-ischaemic or ischaemic. The extent and location of inducible ischaemia were evaluated and a wall motion score index (WMSI) was calculated, both at rest and during stress. Patients were further categorised with low (1-3 ischaemic LV segments) or high (>3 ischaemic LV segments) ischaemic burden [9]. Non-viable myocardium was defined as severely dysfunctional myocardium without change during DSE [10] and referred to as fixed wall motion abnormalities (WMA). Two experienced operators, who were blinded to all other test results, interpreted all echocardiographic data.

Respiratory Function Testing

Lung function was assessed using a validated spirometer (Microlabs™ 3000 portable spirometer) and performed on a single occasion prior to each patient's DSE by the same qualified researcher. Each patient had a one-to-one explanation, observed a demonstration of

the correct technique and had a practice opportunity in order to prepare for spirometry. After preparation, in the seated position, each patient performed a minimum of three (maximum of eight) spirometry manoeuvres with an ideal repeatability criterion of 150 mls as per guidelines [11]. The time between attempts was 1-2 minutes and real-time visual displays of the spirograms were used as a visual aid to help patients complete each manoeuvre as accurately as possible. The data was recorded electronically and as printed graphs for subsequent analysis. Predicted values were calculated using ECCS reference values [12]. A separate researcher blinded to all other results interpreted the spirometry (printed and electronic) curves and confirmed that both forced expiration volume in 1-second (FEV_1) and forced vital capacity (FVC) met American Thoracic Society/European Respiratory Society criterion [11]. A classification of COPD was defined by an FEV_1/FVC ratio <0.7 [13].

End point definition

The principal end-point of interest for this analysis was non-fatal cardiac events (NFCE) and secondarily death from any cause, with patients censored at the time of the last follow-up. A NFCE was defined as hospitalisation for myocardial infarction, ischaemic chest pain with an elevation of cardiac enzymes with or without electrocardiographic changes, and time to coronary angiography, with or without revascularisation procedures (defined either as coronary artery bypass graft surgery or percutaneous coronary intervention). Hospitalisations were identified by means of the principle discharge diagnosis. For patients with multiple events, only the first event was considered.

Data analysis

Continuous variables are expressed as mean±SD and categorical variables as n (%). Multivariable adjusted Cox proportional hazard models were constructed to ascertain predictors of NFCEs and all-cause mortality. For model building, demographic, clinical history, medication, respiratory and echocardiographic parameters were evaluated for their association with NFCE and mortality. Age and gender were included in all models. Forward stepwise selection procedures were used to compare models for goodness-of-fit and a *P*-value <0.1 was used for retention in the final model. The final multivariate model consisted of 7 variables for NFCE and 5 variables for all-cause mortality. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) are reported.

Kaplan-Meier survival curves were constructed and compared using the log-rank test and a *P* value <0.05 was used to report statistical significance. The survival curves were stratified first according to the presence or absence of COPD and, second, by the presence or absence of myocardial ischaemia. All analyses were conducted using the statistical package for social sciences (SPSS 23 release version of SPSS for Windows; SPSS Inc., Chicago IL, USA).

Results

All 114 patients referred for DSE with SOB were included in our final analysis. The patients' mean age was 65.3 ± 16.1 years with an almost equal male to female ratio (52.6% vs 47.4%, respectively). The prevalence of hypertension, dyslipidaemia and diabetes were 73.7%, 70% and 45.6%, respectively. Thirty-seven (32.5%) patients had a prior myocardial infarction, 61 (53.5%) had prior coronary revascularisation, 52 (45.6%) had a positive family history of CVD, and 50 (43.9%) were current smokers. Table 1 provides the characteristics of COPD negative and positive patients. Patients with COPD had a significantly greater prevalence of previous myocardial infarction and diabetes. There were no significant differences in cardiac medication between COPD positive and negative patients. None of the patients required intravenous ß-blocker to reverse the effects of dobutamine or treat arrhythmias.

Spirometry

Respiratory function was successfully performed in all 114 patients. Ninety-three (81.6%) patients with SOB had COPD defined by spirometry and confirmed by a consultant respiratory physician. These patients had a chest radiograph to exclude other pathologies. In total, 16 (17.2%) patients had mild COPD, 71 (76.3%) moderate COPD and 6 (6.5%) severe COPD [13]. Patients with COPD had a significantly lower forced expiratory volume in 1-second ($p<0.001$) and forced vital capacity ($p<0.001$) compared to COPD negative patients (see Table 2).

DSE and COPD

DSE was completed in all patients and the level of agreement, kappa, between the two sonographers was 0.91. Consensus was obtained in discordant cases. In total, 1,938 left ventricular segments were analysed. COPD patients had a significantly lower LVEF ($p<0.001$), E/A ratio ($p=0.017$), septal and lateral E' ($p=0.048$ and $p=0.04$, respectively), E/E' septal, E/E' lateral and E/E' average ($p=0.021$, $p=0.046$ and $p=0.02$, respectively), and significantly greater left atrial size ($p=0.03$) and peak wall motion score index ($p=0.049$) compared to COPD negative patients (Table 3).

In total, 49 (43%) patients developed a new or worsening wall motion abnormality (WMA) and 23 (20.2%) had fixed WMAs. Of the patients with fixed WMAs, 17 (73.9%) developed a new or worsening WMA during DSE. However, there was no significant difference in the proportion of COPD positive (n=40) and COPD negative (n=9) patients who had ischaemia on DSE ($p=0.938$). Of the 49-patients who had myocardial ischaemia, 29 (59.2%) underwent coronary angiography during the follow up period. Of these patients, 22 (75.9%) were COPD positive and 7 (24.1%) were COPD negative. Coronary angiography results demonstrated that 7 (31.8%) of the 22 COPD patients with myocardial ischaemia had significant coronary disease that required revascularization. Of the remaining patients, 1 (4.5%) had moderate double vessel disease, 5 (22.7) had moderate single vessel disease and 9 (40.9%) had no visible or luminal coronary artery abnormalities. Of the 7 COPD negative patients with myocardial ischaemia who underwent coronary angiography, 6 (85.7%) patients had significant coronary disease that required revascularization and 1 (14.3%) patient had moderate double vessel disease.

In total, 49 (43%) patients underwent coronary angiography and there was no significant difference in the proportion of COPD positive (n=42) and COPD negative (n=7) patients (p=0.323). However, there was a significant difference in the proportion of COPD positive (28.6%) and COPD negative (85.7%) patients who underwent coronary revascularization (p=0.004) for significant coronary artery disease.

Clinical outcomes

During a mean follow-up period of 4.5 ± 2.6 years, the composite end-point of NFCE and all-cause mortality occurred in 55 (62.7%) and 19 (16.7%) patients, respectively. There was a significant difference in the proportion of COPE positive (n=50/53.8%) vs COPD negative (n=5/23%) patients presenting with NFCE (p=0.013). However, there was no significant difference in the proportion COPE positive (n=17/18.3%) vs COPD negative (n=2/9.5%) patients for all-cause mortality (p=0.331). There was a significant difference in the proportion of ischaemic (n=34/69.4%) vs non-ischaemic (n=22/33.8%) patients presenting with NFCE (p=0.013) and all-cause mortality (n=13/27.1% vs n=6/9.1%, respectively; p=0.042).

In addition, a significantly greater proportion of patients presenting with NFCE had a previous MI (n=25/45.5% vs n=12/20.3%; p=0.004) and previous revascularisation (n=30/54.5% vs n=19/32.2%; p=0.016), as well as a significantly greater peak WMSI (1.27 ± 0.3 vs 1.1 ± 0.2; p=0.002) and E/E' (15.4 ± 7 vs 9.5 ± 3.2, p=0.001), and significantly lower left ventricular ejection fraction (50.5 ± 13% vs 55.8 ± 10.4%, p=0.018) and septal E' (0.06 ± 0.2 $m \cdot s^{-1}$ vs 0.08 ± 0.03 $m \cdot s^{-1}$, p=0.046). A greater proportion of all-cause mortality patients had a previous MI (n=10/52.6% vs n=27/28.4%; p=0.004).

The unadjusted Kaplan-Meier curves for the cumulative incidence of NFCE and all-cause mortality, dichotomized according to the presence or absence of COPD and the presence or absence of myocardial ischaemia, are presented in Figure 1 and Figure 2, respectively. After multivariable adjustment, parameters significantly associated with NFCE were previous myocardial infarction (HR 1.84; 95% CI 1.06 to 3.2; p=0.03), COPD (HR 1.27; 95% CI 1.17 to 1.93; p=0.038), myocardial ischaemia (HR 2.56; 95% CI 1.48 to 4.43; p=0.001), peak WMSI (HR 4.66; 95% CI 2.26 to 9.6; p<0.001) and E/E' average (HR 1.21; 95% CI 1.1 to 1.33; p<0.001). Myocardial ischaemia (HR 4.43; 95% CI 1.24 to 15.81; p=0.022) was the only independent predictor of all-cause mortality (Table 4).

Discussion

Undiagnosed COPD is highly prevalent amongst patients with SOB referred for DSE. These patients have greater LV systolic dysfunction, higher estimated LV filling pressures and higher ischaemic burden. Prior research has consistently demonstrated that dyspnoeic patients referred for cardiac stress testing have worse outcome compared to patients with chest pain [3, 14-16]. Our results support previous work with 62.7% and 19% of our patients experiencing a NFCE and all-cause mortality, respectively, over a 4.5-year follow-up period. Symptom presentation is therefore an important consideration when interpreting DSE results. However, our work extends prior research, since we performed spirometry to determine if patients had underlying respiratory disease. Indeed, patients characterised with COPD on spirometry had a >2-fold increased frequency of NFCE's compared to dyspnoeic patients with a negative diagnosis of COPD. The diagnosis of COPD exacerbates adverse outcomes in an already high CVD risk population. This is a novel finding and on the basis of our results it may be appropriate for all patients with SOB referred for cardiac stress testing to undergo lung function testing simultaneously. In addition, the presence of myocardial ischaemia in this group of dyspnoeic patients was an important determinant of NFCE and all-cause mortality, which has significant clinical implications.

Few studies have investigated the clinical outcome of dyspnoea in patients referred for non-invasive evaluation of myocardial ischaemia. Bergeron et al.[15] reported that unexplained dyspnoea was associated with a high probability of myocardial ischaemia and increased cardiac events in dyspnoeic patients referred for exercise echocardiography. In their cohort of 443 patients, dyspnoea was associated with twice the incidence of myocardial ischaemia and greater incidence of MI, cardiac death and all-cause mortality. Similar to our study, WMSI

index (an indicator of the extent of myocardial ischaemic), EF and previous MI were independent predictors of cardiac events. However, compared to the current study, the reported adverse outcomes (MI, coronary revascularisation or death) was lower (23%). A possible explanation is the patients performed exercise echocardiography and are therefore likely to be a healthier cohort. In addition, our cohort have a greater prevalence of co-morbidity and prior CVD. Bernheim et al.[14] reported that in a large cohort of patients referred for DSE, dyspnoea was independently associated with worse outcome, and ischaemic risk was similar to that of asymptomatic patients; however, adverse outcome was not associated with any DSE parameters indicative of myocardial ischaemia. Interestingly, pulmonary disease was an independent predictor of all-cause mortality; however, objective measures of pulmonary function was not performed. Argulian et al.[17] reported conflicting results, where the incidence of stress induced ischaemia was low in patients referred for stress echocardiography with exertional dyspnoea. However, the authors did not report predictors of adverse outcome and included a mixed cohort (high proportion of patients with obesity, diabetes and traditional CVD risk factors) and included patients who could undergo exercise echocardiography.

In the large outcome studies investigating the impact of dyspnoea in patients referred for cardiac stress testing [3, 14, 15], the major limitations reported is the lack of information on cardiac diastolic function. Despite the high prevalence of COPD in our cohort, dyspnoea may be a manifestation of increased cardiac filling pressures, which is an important contributor to heart failure, even in the presence of normal systolic function and is associated with a poor prognosis, even when symptoms are mild [18]. Our results demonstrate that estimated filling pressure is an independent predictor of NFCE's and further highlights the complex aetiology and clinical management of this patient cohort. Indeed, dyspnoea with and without a

diagnosis of COPD may represent a more advanced state of heart disease. In addition, this is the first study to perform spirometry and report objective respiratory disease in patients referred with dyspnoea for DSE. Previous research demonstrated that pulmonary function testing provided independent predictive information in apparently healthy men undergoing ETT [19]. Our study demonstrates that COPD is an independent predictor of NFCE's.

The relationship between coronary artery disease (CAD) and COPD is more complex than a simple coexistence of both diseases in the same individual. Although the precise mechanism linking CAD and COPD is not fully known, systemic inflammation, oxidative stress and hypoxemia are recognised factors [20, 21]. Systemic inflammation as a factor is supported widely in the research literature, and COPD is associated with low grade inflammation, which may 'spill-over' [22] and accelerate atherosclerotic processes. Indeed, Topsakal et al.[23] demonstrated that inflammation and oxidative stress in COPD are associated with the intensity and severity of atherosclerosis in patients with CAD through unfavourable effects on endothelial function. Importantly, Enriquez et al.[24] reported that COPD patients undergoing percutaneous coronary intervention (PCI) had a greater mean number of significant coronary lesions. However, the lesions were shorter and less likely to cause total occlusion (diffuse disease) compared to patients without COPD and therefore less treatable with PCI, which may be associated with adverse prognosis.

Limitations

This was a relatively small sample size and single centre study. Patients did not perform post-bronchodilator spirometry to confirm the diagnosis of COPD; however, for most individuals spirometric reversibility testing is not necessary. We performed follow-up on patients for

NFCE and all-cause mortality only and did not track change in the clinical management of patients based on their spirometry. Although not significantly different between groups, patients with COPD were older, which may have impacted the results. In addition, heart failure data was not recorded, which may have impacted patient outcomes. Future research should closely follow the clinical management of patients, since early management of COPD with and without the presence of myocardial ischaemia may optimise outcomes.

Conclusion

This study highlights that patients who self-report with dyspnoea represent a high-risk population and underlying COPD is highly prevalent. In the later cohort, the rate of adverse outcomes is significantly greater and based on our results these patients require aggressive diagnostic and therapeutic workup.

Conflicts of Interest: None

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Table 1: Characteristics of COPD negative and positive patients

Parameter	COPD Negative (n=21)	COPD Positive (n=93)	P Value
Demographics			
Age (y)	58.7 ± 25.7	66.3 ± 16.3	0.087
Height (cm)	167.7 ± 7.4	166.7 ± 9.6	0.683
Weight (kg)	83.4 ± 24.8	77.6 ± 14.6	0.167
History			
Previous MI	3 (14.3)	34 (36.6)	0.049
Previous PCI	4 (19)	32 (34.4)	0.171
Previous CABG	2 (9.5)	23 (24.7)	0.128
Diabetes	4 (19)	48 (51.6)	0.007
Hypertension	13 (61.9)	71 (76.3)	0.175
Dyslipidaemia	16 (76.2)	64 (68.8)	0.592
Family History CVD	7 (33.3)	45 (48.4)	0.196
Smoker	11 (52.4)	48 (51.6)	0.949
Cardiac Medication			
Beta Blocker	10 (47.6)	46 (49.5)	0.701
ACE	7 (33.3)	32 (34.4)	0.795
Diuretic	5 (23.8)	21 (22.6)	0.996
CCB	7 (33.3)	25 (26.9)	0.656
Nitrate	4 (19)	20 (21.5)	0.715
Warfarin	4 (19)	10 (10.8)	0.394
Aspirin	9 (42.9)	55 (59.1)	1
Statin	14 (66.6)	71 (76.3)	0.164
Clopidogrel	2 (9.5)	17 (18.3)	0.449
ARB	4 (19)	22 (23.7)	0.565

Note: COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; CVD = cardiovascular disease; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker.

Table 2: Respiratory function results for COPD negative and positive patients

Parameter	COPD Negative (n=21)	COPD Positive (n=93)	P Value
FEV_1 (L/min)	1.9 ± 0.6	1.54 ± 0.6	<0.001
FVC (L)	2.3 ± 0.9	2.49 ± 0.8	<0.001
FEV_1/FVC ratio	0.80 ± 0.7	0.64 ± 0.8	0.358
PEF (L/min)	313 ± 117	287 ± 116	0.362

Note: COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; PEF = peak expiratory flow.

Table 3: Resting and stress echocardiographic results for COPD negative and positive patients

Parameter	COPD Negative (n=21)	COPD Positive (n=93)	P Value
Heart rate ($b \cdot min^{-1}$)	73.6 ± 11	75 ± 15	0.698
Peak heart rate ($b \cdot min^{-1}$)	136 ± 16	135 ± 17	0.773
Baseline sBP (mmHg)	145 ± 20	136 ± 24	0.093
Peak sBP (mmHg)	146 ± 30	145 ± 27	0.883
Baseline dBP (mmHg)	81 ± 13	74 ± 12	0.019
Peak dBP (mmHg)	79 ± 17	71 ± 15	0.062
LVEF (%)	58.2 ± 7.7	53.2 ± 11.9	<0.001
Left atrial size (cm)	3.8 ± 1.1	4.1 ± 1.1	0.03
Ascending aorta diameter (cm)	3.1 ± 0.6	3 ± 0.5	0.378
LVPWd (cm)	0.96 ± 02	0.96 ± 0.2	0.959
LVIDd (cm)	4.6 ± 0.8	4.7 ± 0.7	0.829
IVSd (cm)	0.97 ± 0.2	0.97 ± 0.3	0.978
LVIDs (cm)	3.09 ± 0.8	3.12 ± 0.9	0.883
MV E velocity ($m \cdot s^{-1}$)	0.9 ± 0.3	0.8 ± 0.3	0.254
MV E deceleration time (ms)	207 ± 78	200 ± 53	0.627
E/A ratio	1.56 ± 1.1	1.09 ± 0.6	0.017
E' septum ($m \cdot s^{-1}$)	0.09 ± 0.04	0.07 ± 0.02	0.048
E/E' septum	10.2 ± 2.8	14.8 ± 3.1	0.021
E' lateral ($m \cdot s^{-1}$)	0.12 ± 0.02	0.09 ± 0.02	0.04
E/E' lateral	9.5 ± 2.6	11.3 ± 2.1	0.046
E/E' average	10.1 ± 4.5	12.4 ± 6.1	0.02
Baseline WMSI	1.06 ± 0.2	1.12 ± 0.3	0.06
Peak WMSI	1.12 ± 0.2	1.18 ± 0.3	0.049
Ischaemic	9 (42.9)	40 (43)	0.938

Note: COPD = chronic obstructive pulmonary disease; sBP = systolic blood pressure; dBP = diastolic blood pressure; LVEF = left ventricular ejection fraction; LVPWd = left ventricular posterior wall thickness diastole; LVIDd = left ventricular internal diameter diastole; IVSd = interventricular septal wall thickness diastole; LVIDs = left ventricular internal diameter systole; MV = mitral valve; WMSI = wall motion score index.

Table 4. Multivariable Predictors of NFCE and All-Cause Mortality

	NFCE		All-Cause Mortality	
Parameter	Hazard Ratio (95%) Confidence Interval)	P Value	Hazard Ratio (95%) Confidence Interval)	P Value
Age	0.99 (0.96 - 1.03)	0.831	0.98 (0.96 - 1)	0.063
Gender	0.97 (0.27 - 3.45)	0.958	1.18 (0.42 - 3.34)	0.758
MI	1.84 (1.06 - 3.2)	0.03	2.62 (0.99 - 6.96)	0.053
COPD	1.27 (1.17 - 1.93)	0.038	-	-
Ischaemia	2.56 (1.48 - 4.43)	0.001	4.43 (1.24 - 15.81)	0.022
PWMSI	4.66 (2.26 - 9.6)	<0.001	1.74 (0.98 – 5.04)	0.076
E/E' Average	1.21 (1.1 – 1.33)	<0.001	-	-

Note: MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; PWMSI = peak wall motion score index.

Figure Legends

Figure 1: Kaplan-Meier curve for COPD positive and negative patients for the cumulative freedom from A) Non-fatal cardiac events and B) All-cause mortality.

Figure 2: Kaplan-Meier curve for ischaemic and non-ischaemic patients for the cumulative freedom from A) Non-fatal cardiac events and B) All-cause mortality.