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Impacts of valve intervention on the Functional REServe of the Heart: The FRESH-valve pilot study

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ABSTRACT

Purpose: Severe valve lesions require corrective interventions to avoid progression to heart failure (HF) and premature demise. We tested the hypothesis that despite operative risks, corrective valvular interventions will lead to significant improvements in overall cardiac pump function, especially before the onset of cardiac decompensation.
Methods: We compared the cardiopulmonary exercise performance and non-invasive haemodynamics of 46 consecutive patients with severe valvular disease before and after valvular intervention with reference to 101 healthy male and 139 female controls without cardiovascular disease. Cardiac and physical functional reserves were measured with standard respiratory gas analyses and CO_2 rebreathing to measure cardiac output non-invasively during peak treadmill exercise. Data are given as mean ± SD and statistical significance accepted at $P < 0.05$.
Results: The entire patient cohort showed no significant improvement in peak O_2 consumption ($\dot{V}O_{2max}$, $P = 0.74$) or in peak cardiac power (CPO_{max}, $P = 0.34$) after valvular intervention, but we found instead a dichotomous outcome depending on preoperative cardiac function: (i) the pre-operative cardiac decompensatory subgroup (LoW, $n = 26$) showed increased CPO_{max} (2.63 ± 0.67 to 3.42 ± 0.98 W, $P < 0.0001$) and $\dot{V}O_{2max}$ (1.38 ± 0.55 to 1.56 ± 0.59 $L \cdot min^{-1}$, $P < 0.01$); and (ii) the pre-operative non-decompensatory subgroup (HiW) showed reduced CPO_{max} (4.58 ± 0.96 to 3.84 ± 0.92 W, $P < 0.001$) and $\dot{V}O_{2max}$ (2.29 ± 0.72 to 1.97 ± 0.75 $L \cdot min^{-1}$, $P < 0.01$). Changes in NYHA class were found to be discrepant with these objective measurements.
Conclusion: This investigation found an unexpected finding that valvular interventions performed in routine clinical practice do not consistently improve cardiac function, especially in those without pre-operative cardiac decompensation. Assessing cardiac functional gains would open up new avenues for future trials of valvular interventions.

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In chronic valvular affection the symptoms only arise where exhaustion of the heart muscle sets in. The symptoms due to exhaustion appear at varying periods after the damage has been done to the valves, and the time of the appearance of these symptoms depends on the degree of embarrassment offered to the heart's work by the damaged valve, on the condition of the muscle-wall, and on such accessory factors as tend to exhaustion, as over-exertion, ….

[*Sir James Mackenzie, 1908* [1], (first modern cardiologist) [2]]

A prevailing conviction in modern cardiological thinking is that a damaged valve, either causing significant stenosis or regurgitation, must be functionally worse for the heart than a non-stenotic or non-regurgitant prosthetic valve. There are on-going debates about the optimal timing for valvular interventions [3–7], but the opposing sides share a common hope and expectation that the valvular intervention would lead to normalisation of cardiac function thereby improving the quality and quantity of life of valve disease patients [8].

Current clinical practice relies predominantly on imaging criteria such as cardiac chamber enlargement, reduction in ejection fraction or elevation of pulmonary artery systolic pressure to determine evidence of cardiac decompensation. The assessment of symptoms relies predominantly on subjective tools such as the NYHA classification. However, studies from heart failure populations have shown us that changes in structural measures or contractility measured at rest often show poor correlation with more direct indicators of cardiac function measured during exercise [e.g. 9,10]. We also know that, apart from near-perfect repair of regurgitant mitral valves, replacements of any faulty valve inevitably introduce distortions which render the eventual subunits somewhat inferior to normally functioning natural valves [11]. Surrogate indicators of successful interventional outcomes, such

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as an absence of regurgitation or stenosis, NYHA class, reverse ventricular remodelling, improved exercise ability and peak oxygen consumption have been reported with varying success [12–16]. The introduction of cardiopulmonary exercise testing (CPX) adds a new advantageous dimension to the assessments of patients with valvular heart diseases, by providing objective functional information to the structural information obtainable from imaging techniques. However, as shown in Appendix B [17], there are many factors which influence the eventual peak O_2 consumption and other respiratory gaseous exchange variables measured during CPX and these correlate with cardiac reserve if the other factors are controlled or invariant. The direct consequences of valvular lesions are primarily on cardiac function, and secondarily on peak O_2 consumption, other CPX variables and exercise capacity. To date, no investigator has reported whether corrective valvular interventions actually improve overall cardiac function by directly measuring pump function during peak exercise.

We therefore set out to conduct a pilot study to evaluate the effects of valve interventions on the heart's ability to fulfil its work maintaining the circulation [18,19] during severe exertion [1], which has been shown to be the strongest predictor of prognosis in heart failure patients [20,21]. We set out to test the hypotheses that (i) the overall cardiac function of patient show significant improvement after valvular interventions despite operative risks, and (ii) those who had subnormal pre-operative cardiac reserve indicative of cardiac decompensation would gain less physical and cardiac functional benefits than those with preserved cardiac function represented by pre-operative cardiac reserve still within the normal range of healthy sedentary controls.

1. Method

1.1. Study populations

In order to reflect standard clinical practice, we studied unselected consecutive patients, with severe valve disease diagnosed along standard local and international guidelines, who underwent non-invasive haemodynamic evaluation during CPX stress testing in our tertiary cardiology referral centre before and after valvular interventions. The CPX tests were requested by the patients' clinicians. The diagnosis and management of valvular disease in each case was established by the physicians in charge of the patients according to standard UK practice. The decision when to intervene rested entirely on the cardiologists and cardiac surgeons in charge of the patients according to current practice and guidelines. Sedentary healthy male (n = 101) and female (n = 139) controls (C) spanning the active adult ages (2nd to 8th decades) who were free of known cardiovascular diseases, on no medication, normotensive, non-smokers as reported previously [22] provided the reference CPX and exercise haemodynamic data, against which the data from valve patients were compared. Patients in NYHA functional class IV, or with angina as the limiting symptom for exercise, serious uncontrolled arrhythmias, severe lung diseases or serious systemic diseases were not included in this study. Since the CPX tests were requested by the referring physicians for clinical indications and no patient identifiable information has been included in this report, in accordance with the ethical guidelines of the 1975 Helsinki declaration, our local ethics committee has exempted this investigation from the need to apply for ethical approval.

1.1.1. Cardiopulmonary exercise tests

These were conducted as described in previous reports [23,24]. Symptom-limited exercise tests on a treadmill (Trackmaster TMX425 Full Vision Inc. 3017 Full Vision Drive Newton, KS 67114, USA) were performed using the Bruce or modified Bruce protocol with continuous ECG recording to monitor and measure breath-by-breath rates of ventilation, O_2 consumption ($\dot{V}O_2$), CO_2 production ($\dot{V}CO_2$), beat-by-beat heart rate (HR) and exercise duration, using a MedGraphics Cardio$_2$ equipment (Medical Graphics Corporation, St Paul, U.S.A.). Systolic and diastolic blood pressures (SBP, DBP mm Hg) were measured using manual cuff sphygmomanometry. A second peak single-stage exercise test, targeted for approximately the peak workload attained during the prior incremental test, was then performed to measure cardiac output using CO_2 re-breathing technique [25].

1.2. Data analyses

Respiratory exchange ratio (RER = $\dot{V}CO_2/\dot{V}O_2$) and O_2 consumptions normalised by body mass ($\dot{V}O_2$/kg) were calculated using conventional equations. The ventilatory (anaerobic) threshold was determined using the V-slope method [26]. Cardiac output ($CO = \dot{Q}\ L \cdot min^{-1}$) was calculated using the indirect Fick method and at least two measurements were taken in order to calculate an average. Mean arterial pressure (mm Hg) was calculated from the standard equation, MAP = DBP + 0.412 ∗ (SBP − DBP) [27]. The cardiac power output (watts) was calculated from the equation: CPO = cardiac work done per second = $\dot{W}$ (watts) = (CO × MAP) × K, where K is the conversion factor into watts (2.22×10^{-3}) [28]. The systemic vascular resistance ($dyn \cdot s \cdot cm^{-5}$) was calculated using the equation: SVR = (MAP / CO) × 80.

1.3. Statistics

All data were analysed using SPSS. Data are presented as mean ± standard deviation, or as counts with proportions. Univariate comparisons were made with Student's paired, two-tailed t-test for continuous variables pre- and post-valve interventions. Comparisons between patients and controls were made using Student's unpaired, two-tailed t test. Categorical data were analysed using the Chi-squared test and Fisher's exact test (when n < 5). A P value of <0.05 was considered to be statistically significant, and a non-significant difference denoted as NS.

2. Results

2.1. Demographics

Forty six patients (32 males, age 59.6 ± 15.1 (SD) years) with valvular disease were found to have completed CPX testing with non-invasive hemodynamic evaluations both before and an average of 15 months after their valvular interventions. The male patients had similar heights as the male controls (176.6 ± 6.1 cm, C: 176.6 ± 7.1 cm, P = 0.97), but they were non-significantly heavier (85.6 ± 15.9 kg, C: 81.1 ± 10.6 kg, P = 0.15). The female patients were also of similar height compared to female controls (161.3 ± 7.9 cm, C: 162.7 ± 6.3 cm, P = 0.54) but non-significantly lighter (62.1 ± 14.3 kg, C: 67.4 ± 10.7 kg, P = 0.19). The mean body mass index (BMI) of male (Pts: 27.5 ± 5.5 $kg \cdot m^{-2}$, C 26.0 ± 3.1 $kg \cdot m^{-2}$, P = 0.14), and female (Pts: 23.8 ± 5.1, C: 25.5 ± 3.9 $kg \cdot m^{-2}$, P = 0.24) patients were similar to male and female controls, respectively. The severe valvular diseases intervened upon comprised: 25 patients with mitral regurgitation, 9 with mitral stenosis, 8 with aortic stenosis, 7 with aortic regurgitation, 3 with significant tricuspid regurgitation and some with multiple defects. The interventions undertaken were: 15 mitral valve replacements, 11 MV repairs, 8 mitral valvuloplasties, 15 aortic valve replacements and 3 tricuspid annuloplasties. Comorbidities that required concomitant interventions included AF ablation therapy (4), ASD closure, antibiotics for infective endocarditis, coronary bypass grafting (5) and structural ventricular reconstruction. The use of angiotensin converting enzyme inhibitors/angiotensin II receptor antagonists (ACEI/ARB) did not differ following intervention in either group, nor was there a difference in their use within either group in the pre-operative or post-operative period.