Physiological cardiac reserve: development of a non-invasive method and first estimates in man

G A Cooke, P Marshall, J K Al-Timman, D J Wright, R Riley, R Hainsworth, L B Tan

Abstract

***Objective*—To investigate whether physiological cardiac reserve can be measured in man without invasive procedures and whether it is a major determinant of exercise capacity.**

***Design*—Development of method of measurement and an observational study.**

***Setting*—A regional cardiothoracic centre.**

***Subjects*—70 subjects with a wide range of cardiac function, from heart failure patients to athletes.**

***Methods*—Subjects underwent treadmill, symptom limited cardiopulmonary exercise tests to measure aerobic exercise capacity (represented by $\dot{V}O_2$max) and cardiac reserve. Cardiac output was measured non-invasively using the CO_2 rebreathing technique.**

***Results*—Cardiac power output (CPO_{max}) at peak exercise was found to be significantly related to aerobic capacity: CPO_{max} (W) = 0.35 + 1.5$\dot{V}O_2$max (l/min), r = 0.87, $p < 0.001$. It also correlated well with exercise duration (r = 0.62, $p < 0.001$), suggesting that cardiac reserve is a major determinant of exercise capacity. In the study, cardiac reserve ranged from 0.27 to 5.65 W, indicating a 20-fold difference between the most impaired cardiac function and that of the fittest subject.**

***Conclusions*—A non-invasive method of estimating physiological cardiac reserve was developed. The reserve was found to be a major determinant of exercise capacity in a population of normal subjects and patients with heart disease. This method may thus be used to provide a clearer definition of the extent of cardiac impairment in patients with heart failure.**

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Keywords: cardiac reserve; cardiac power output; oxygen consumption; congestive heart failure

Institute for Cardiovascular Research, University of Leeds and Yorkshire Heart Centre, Leeds General Infirmary, Great George Street, Leeds LS1 3EX, UK
G A Cooke
P Marshall
J K Al-Timman
D J Wright
R Riley
R Hainsworth
L B Tan

Correspondence to:
Dr Tan.

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In the field of heart failure, it has been a long held belief that haemodynamic indicators of cardiac function do not correlate with exercise ability and clinical status.[1–3] This raises a curious paradox that while superior cardiac function is required by athletes to sustain their physical prowess, the extent of dysfunction of a failing heart is considered to be irrelevant to exercise intolerance in patients. A likely explanation for this paradox is that there has been a misapplication of performance variables because aspects of cardiac function were used in the evaluation that were irrelevant (for example, resting haemodynamic values to predict exercise responses) or incomplete (for example, assessing flow generating capacity while ignoring pressure generating capacity). It is therefore essential to find a more representative and comprehensive indicator of cardiac function and dysfunction. For this reason the concept of cardiac reserve and pumping capability was introduced.[4 5]

When a heart begins to fail, compensatory mechanisms will be activated in order to maintain the resting cardiac performance within as normal a range as possible. Its pumping capability (peak performance) is, however, compromised and presumed to be diminished. It is this diminution that represents the extent of its failure and needs to be measured. Observations made in patients with heart failure indicated that the most important aspect of cardiac dysfunction in heart failure was not the depressed cardiac performance noted at basal resting states, but rather the loss of cardiac reserve.[6] The loss of cardiac reserve leads to poor prognosis[6 7] and inability to cope with stress, such as exercise[5] or septicaemia.[8] An important objective of treating heart failure is to preserve and if possible improve cardiac reserve. To achieve this, more information needs to be gathered on factors that affect cardiac reserve. It is therefore essential to develop a non-invasive method to allow serial measurements of cardiac reserve.

In previous studies involving evaluation of cardiac reserve,[6–8] the haemodynamic variables were measured invasively using Swan-Ganz catheters and arterial lines. Cardiac stimulation was also achieved pharmacologically, using incremental dobutamine infusion. Clearly, such invasive assessment precludes long term serial determination of cardiac reserve. Although the pharmacologically determined cardiac reserve provides valuable information, it is not necessarily indicative or representative of physiological cardiac reserve.

The ultimate function of the heart is to maintain an adequate circulation, especially during severe stress. The commonest and probably the most demanding stress for the circulation is severe exertion (involving large muscle groups and producing limiting symptoms within a few minutes). For some time, it has been recognised that the heart is the limiting factor for severe exercise in normal healthy humans,[9 10] and this must be all the more true in patients with cardiac failure. It is therefore vital to investigate to what extent and in what way cardiac reserve is limited, and how the reserve contributes to the maintenance of the circulation during exercise. We propose that the first step towards this objective is the need to develop a method for measuring physiologi-

cal cardiac reserve directly and non-invasively, and to test the hypothesis that this reserve is correlated with exercise capacity.

Methods

EXPERIMENTAL SUBJECTS

For the purpose of this study, it was felt that a wide range of cardiac performance and pathology should be included in order to explore the general applicability of the concept and results in clinical practice. Seventy subjects (ranging from normal individuals to patients with New York Heart Association (NYHA) grade IIIb heart failure) were therefore included in this study. Eight subjects were healthy normal volunteers with no known cardiac or pulmonary disease. Forty two subjects were consecutive outpatients who underwent cardiopulmonary exercise testing as part of their clinical evaluation, with various diagnoses including heart failure (n = 22, NYHA class II-III), angina (6), hypertension (4), valvar diseases (7), and conditions without cardiac mechanical dysfunction (3). Twenty of the remaining subjects were heart failure patients (NYHA IIIb) who were being screened for cardiac transplantation and had cardiopulmonary exercise testing as part of the overall evaluation.

Twelve of the heart failure patients (NYHA II-III) recruited from outpatient clinics took part in the reproducibility study. These subjects repeated their cardiopulmonary exercise tests and measurements of exercise cardiac reserve while taking the same drugs and being in the same clinical condition, as far as could be ascertained. It is these repeat tests that constituted the evaluation of the reproducibility of measurements.

PROTOCOL

All subjects were exercised at least two hours after any food or drink. They were instructed not to drink ethanol or caffeine containing beverages before the tests. The tests were performed at an ambient room temperature maintained at about 20°C. The subjects performed symptom limited exercise and the limiting symptoms were recorded, unless the exercise test had to be terminated for reasons such as exercise induced hypotension, significant arrhythmia, or other clinical end points indicating compromised safety of continued exercise.

The exercise tests were performed in two stages. The first stage was an incremental test to determine the maximum oxygen consumption and the anaerobic threshold. A second constant maximum workload stage was used to make the cardiac output measurements in line with previous investigators.[11 12] This enabled more than one cardiac output measurement to be made at maximum workload. All tests were performed using a treadmill, adjustable for incline and speed.

The incremental exercise protocols were either a standard Bruce protocol or a modified Bruce protocol, selected according to the perceived fitness of the subjects. The duration at each stage was three minutes. The modified Bruce protocol contained two preliminary three minute stages of 2.7 kph at 0% incline and 2.7 kph at 5% incline. It then followed the standard Bruce protocol.

A 12 lead ECG was monitored and the heart rate derived from it. Blood pressure was measured using a sphygmomanometer before starting the test, two minutes into each stage, at peak exercise, and immediately after stopping exercise. Oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), end tidal partial pressure of carbon dioxide ($ETPCO_2$), tidal ventilation (V_t), and respiratory rate were measured and recorded breath by breath using the Medgraphics Cardio2 cardiopulmonary exercise test system (Medical Graphics Corporation, St Paul, Minnesota, USA). The respiratory exchange ratio ($RER = \dot{V}CO_2/\dot{V}O_2$), minute ventilation ($V_E = V_t \times$ respiratory rate), and $\dot{V}O_2$/kg ($\dot{V}O_2$/body weight in kg) were calculated from the above variables. The anaerobic threshold was determined using a V-slope method.[13] The exercise test was considered to be submaximal if the subject failed to reach the cardiopulmonary limits as indicated by failure to exceed the anaerobic threshold or an RER value of 1.10.

The subject then rested for at least 40 minutes until the heart rate, $\dot{V}O_2$, and $\dot{V}CO_2$ were within 5% of the initial resting values and stable for five minutes. Baseline cardiac output measurements were made using the carbon dioxide rebreathing method[14 15] to estimate the mixed venous PCO_2. The end tidal partial pressure of CO_2 was used as a measure of arterial PCO_2.[16] The partial pressures were then converted into concentrations using carbon dioxide dissociation tables stored in the computer.[17] The indirect Fick equation was then used to give the cardiac output. At least three measurements of resting cardiac output were made in each test.

A constant maximum workload exercise test was then performed. The treadmill speed and incline were initially set to the level of the highest completed or nearly completed stage of the incremental protocol. The speed and incline of the treadmill were then increased or decreased slightly to enable the subject to sustain the exercise for at least five minutes and a $\dot{V}O_2$ of at least 90% of the maximum attained during the incremental test. Two or three cardiac output measurements were made using the CO_2 rebreathing method at this workload. The blood pressure was measured using a sphygmomanometer after each determination of cardiac output.

All aspects of this investigation conform to the principles outlined in the declaration of Helsinki. Approval to conduct the study was granted by the local ethics committee and informed consent was obtained from each subject.

CALCULATIONS

The mean arterial pressure was calculated by the standard equation:

$$MAP = (SBP + 2DBP)/3,$$

where SBP is the systolic blood pressure and DBP is the diastolic blood pressure in mm Hg. The cardiac power output was calculated from

Table 1 Means of variables measured at rest and during peak exercise

	Mean (SEM)	*Correlation with $\dot{V}O_2$max*		*Correlation with Ex time*	
		r	*p*	*r*	*p*
Heart rate (beats/min)					
Rest	82.5 (1.61)	0.245	0.026	0.089	0.432
Exercise	144.5 (2.54)	0.316	0.002	0.447	< 0.001
Mean arterial pressure (mm Hg)					
Rest	89.6 (1.28)	0.300	0.345	0.100	0.367
Exercise	102.3 (1.51)	0.221	0.025	0.161	0.146
Cardiac output (l/min)					
Rest	5.33 (0.11)	0.374	< 0.001	0.200	0.063
Exercise	12.6 (0.43)	0.922	< 0.001	0.678	< 0.001
Stroke volume (ml)					
Rest	67.5 (2.27)	0.412	< 0.001	0.173	0.074
Exercise	84.1 (2.88)	0.632	< 0.001	0.387	< 0.001
Systemic vascular resistance (kPa.s.l^{-1})					
Rest	138.8 (3.34)	0.265	0.009	0.224	0.035
Exercise	69.3 (1.74)	0.762	< 0.001	0.600	< 0.001
LV stroke work index (10^{-3} J/m^2)					
Rest	423.1 (13.9)	0.316	0.094	0.152	0.094
Exercise	606.9 (22.5)	0.582	< 0.001	0.481	< 0.001
Cardiac power output (W)					
Rest	1.07 (0.03)	0.332	0.002	0.264	0.445
Exercise	2.88 (0.12)	0.872	< 0.001	0.625	< 0.001
Exercise time (s)	755.8 (27.9)	0.707	< 0.001	–	–

the averaged cardiac output and mean arterial pressures by the following equation: CPO = (CO × MAP) × K, where CPO is the cardiac power output in watts, CO the cardiac output in l/min, MAP the estimated mean arterial pressure in mm Hg, and K the conversion factor (= 2.22×10^{-3}).

STATISTICAL ANALYSIS

Statistical analysis was performed using standard statistical software. The relations between maximum $\dot{V}O_2$ and cardiac output and power output were determined by using a least squared fit regression equation. For the reproducibility study the analysis of Bland and Altman[18 19] was employed.

Results

Eighty two tests on 70 subjects have been conducted using the described protocol. The average age of the subjects was 56 years (range 15 to 79). Results were obtained in all of the tests. This cohort of patients did not include those with NYHA class IV symptoms who were unable to perform the two requisite exercise tests. The range of data obtained therefore did not contain those with very low cardiac reserve or exercise capacity. Thirteen subjects were tested using the standard Bruce protocol, while the remainder underwent tests with the modified Bruce protocol. The former subjects exercised for an average duration of 621 seconds (range 260 to 1185 seconds) and were assumed to be able to exercise an additional 360 seconds were they to exercise using the modified Bruce protocol, while the latter exercised for an average of 704 seconds (range 106 to 1090 seconds). The mean $\dot{V}O_2$max at the end of the incremental test was 1789 ml/min (range 759 to 4518 ml/min) for all the subjects.

The haemodynamic variables at rest and during exercise are shown in table 1, and the correlation of each with aerobic exercise capacity or with exercise duration is also shown. As expected, the correlation between aerobic capacity and exercise duration was reasonably good ($p < 0.001$), with a correlation coefficient of $r = 0.71$.

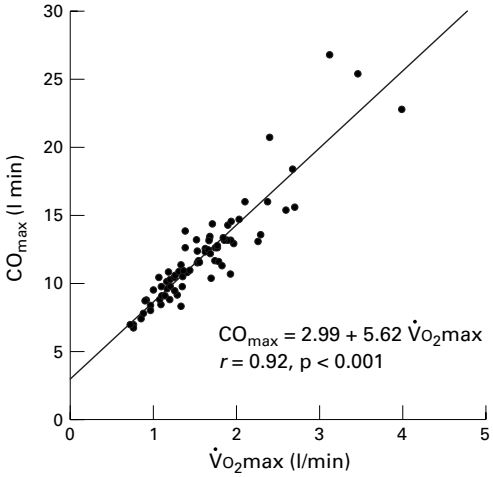

Figure 1 A plot of cardiac output during peak exercise (CO_{max}) against an indicator of aerobic exercise capacity, $\dot{V}O_2$max (peak oxygen consumption).

The correlations between haemodynamic variables measured *at rest* and aerobic capacity were generally poor, with low correlation coefficients ($r < 0.50$). Similarly, none of these variables measured at rest correlated with peak cardiac power output or cardiac reserve. In contrast, the variables measured *during peak exercise*, notably cardiac output ($r = 0.92$), stroke volume ($r = 0.63$), stroke work index ($r = 0.582$), systemic vascular resistance ($r = 0.76$), and cardiac power output ($r = 0.87$) all had reasonably good correlation with $\dot{V}O_2$max.

The average cardiac output at rest (CO_{rest}) was 5.33 l/min (range 3.35 to 7.47 l/min) while that during maximum exercise (CO_{max}) was 12.0 l/min (range 6.75 to 26.8 l/min). The average cardiac power output at rest (CPO_{rest}) was 1.07 W (range 0.56 to 1.93 W) and that during maximum exercise (CPO_{max}) it was 2.74 W (range 1.21 to 7.13 W). The cardiac reserve, as represented by the difference between cardiac power output at rest and at maximum exercise, ranged from 0.27 to 5.65 W, indicating that there was a 20-fold difference between the reserve of the patient with the most impaired cardiac function and that of the fittest subjects in the study.

Using the $\dot{V}O_2$max as an indicator of aerobic exercise capacity, the cardiac output during peak exercise (CO_{max}) was plotted against $\dot{V}O_2$max as shown in fig 1. This was not a plot of cardiac output against $\dot{V}O_2$ throughout the exercises, but the values during the highest exercise levels that the subjects could sustain to allow measurements to be made. There was a good correlation and the equation of the regression line was $CO_{max} = 2.99 + 5.62\dot{V}O_2$max ($r = 0.92$, $p < 0.001$).

Figure 2 shows the relation between cardiac power output during peak exercise (CPO_{max}) and $\dot{V}O_2$max. CPO_{max} was found to be significantly related to aerobic capacity: CPO_{max}(watts) = 0.35 + 1.5$\dot{V}O_2$max (l/min), $r = 0.87$, $p < 0.001$. It also correlated well with exercise duration (table 1; $r = 0.62$,

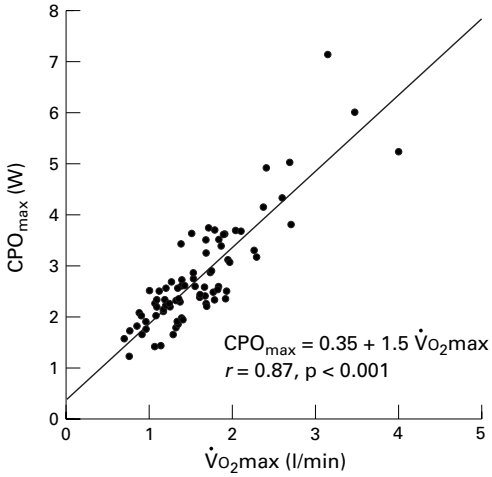

Figure 2 A plot of cardiac power output during peak exercise (CPO_{max}) against aerobic exercise capacity, $\dot{V}O_2max$.

p < 0.001), suggesting that cardiac reserve is a major determinant of exercise capacity. Patients who had higher measured maximum cardiac power output and therefore greater cardiac reserve had greater aerobic exercise capacity.

REPRODUCIBILITY STUDY

The exercise tests were repeated on 12 subjects under the same conditions at least four weeks apart to investigate the repeatability of the tests and measurements. Analysis was done with the Student *t* test.

There was no significant difference between the maximum oxygen consumption (p = 0.10), the cardiac output at peak exercise (p = 0.44), and the maximum cardiac power output (p = 0.45) in the two tests. Regression analysis was performed on both tests, correlating cardiac output and oxygen consumption. For the first test the regression equation was cardiac output = 2.83 + 0.00549$\dot{V}O_2$ (r = 0.91, p < 0.05) and in the second test cardiac output = 2.60 + 0.00594$\dot{V}O_2$ (r = 0.96, p < 0.001), indicating this relation was also repeatable.

The analysis of Bland and Altman[18 19] was used, giving the graphs shown in fig 3A–C. For $\dot{V}O_2$max (fig 3A), the mean difference between the first test and the second test was 15.8 ml/min (range −87 to 173). The standard deviation of repeated measurements was 40.8 ml/min, the coefficient of variation was 4.7%, the repeatability coefficient was 81.6 ml/min, and the limits of agreement were −25.0 to 55.6 ml/min.

For cardiac output at maximum exercise (fig 3B), the mean difference between the two tests was -0.15 l/min (range −2.33 to 1.27). The standard deviation of repeated measurements was 0.57, the coefficient of variation was 7.08%, the repeatability coefficient was 1.13 l/min, and the limits of agreement were −1.28 to 0.98 l/min.

For cardiac power output at maximum exercise (fig 3C), the mean difference between the two tests was −0.04 W (range −0.77 to 0.40). The standard deviation of repeated measurements was 0.16, the coefficient of variation was 9.08%, the repeatability coefficient was 0.316 W, and the limits of agreement were −0.35 to 0.28 W.

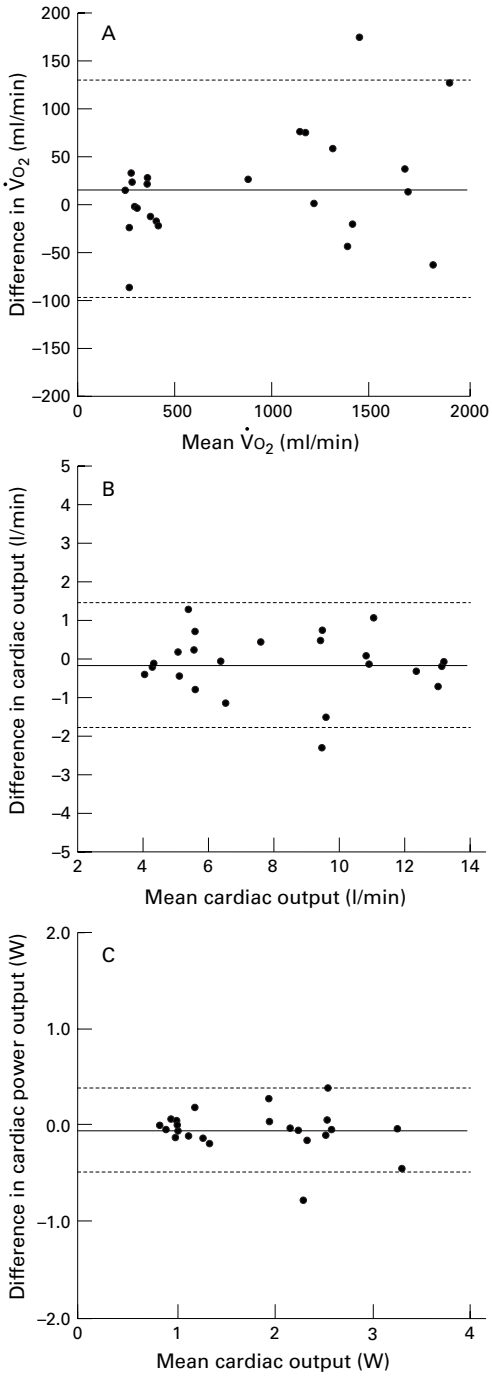

Figure 3 Bland and Altman plots[18 19] of the differences against the means of repeated measurements of (A) maximum oxygen consumption ($\dot{V}O_2max$), (B) cardiac output (CO_{max}), and (C) cardiac power output (CPO_{max}) during peak exercise, to indicate reproducibility of measurements (means and ± 2 SD limits indicated). See text for details.

Discussion

In this study, haemodynamic indices of cardiac function measured at rest did not correlate well with exercise capacity or cardiac reserve. This finding is consistent with previous reports[12 20] and is not surprising, because it is apparently

too optimistic to presume that resting variables can have any bearing on exercise performance, except when the resting cardiac function is so severely impaired that the patient is unable to perform any exercise. Cardiovascular compensatory mechanisms operate in an attempt to maintain resting cardiac function as much as possible within normal limits. Based on this finding we would concur with other investigators that an index of cardiac function measured at rest is a poor discriminator of the extent of cardiac impairment. Discarding evaluation at rest should not, however, imply that all haemodynamic evaluation of cardiac function should be abandoned, because the presumed diminution of peak pumping ability of failing hearts, if measured, would provide important information about the extent of functional impairment.

This study is the first to show that it is possible, even in patients with severe heart failure, to measure physiological cardiac reserve directly and non-invasively. The results showed that there was a greater than 20-fold difference in cardiac reserve between patients with severe heart failure and fit healthy subjects. There was a strong correlation between the diminution of cardiac pumping capacity with the reduction in aerobic exercise capacity, implying that in general those with the most impaired hearts and least cardiac reserve were also the ones with the greatest exercise intolerance. Recent results in our laboratory have also shown that, when the cardiac performance was depressed pharmacologically, the reduction in exercise capacity was secondary to the diminution in cardiac reserve (manuscript in preparation). Together these lead to the suggestion that exercise intolerance in our heart failure patients was to a large extent due to inadequate cardiac reserve.

We opted to use the treadmill as the exercise mode because walking is a familiar form of exercise to all subjects and tends to produce higher oxygen consumption during exercise than with bicycle ergometers.[21] The Bruce and modified Bruce protocols were adopted as they are the most well established and widely used protocols, and tend to provide a reasonable length of test for all types of subjects, ranging from patients with severe left ventricular dysfunction to athletes. Unfortunately, the use of treadmill and Bruce protocols does not allow us to quantify the workload without making assumptions. $\dot{V}O_2$max, the peak aerobic exercise capacity, was therefore adopted as the generalised measure of functional capacity.

It has been shown that there is a linear relationship between cardiac output and the $\dot{V}O_2$[22 23] and previous workers have used this equation to validate their measurements.[24] Our equation of $CO_{max} = 3.0 + 5.6\dot{V}O_2max$ was in close agreement with that of Jones,[11] who obtained cardiac output = $4.0 + 6.0\ \dot{V}O_2$. Compared with the relations obtained by Astrand and colleagues,[25] our equation was comparable to that obtained for their male subjects, cardiac output = $3.07 + 6.0\ \dot{V}O_2$, who performed exercise at intensities which produced $\dot{V}O_2$ equivalent to the values obtained in our study. The cardiac outputs in Astrand's study were measured by the standard dye dilution technique. It may be concluded that the techniques of measurement employed in our study produced results which are consistent with the results of other investigators.

The results from the reproducibility study obtained from the subgroup of subjects who underwent repeated tests showed that the coefficients of variation for the variables analysed were all below 10%, suggesting a high degree of repeatability. The equations relating the cardiac output to the $\dot{V}O_2$ in these two repeated tests were consistent with each other and also with the equation obtained for all study subjects. Because $\dot{V}O_2$ was measured breath by breath, whereas cardiac output could only be measured at discrete intervals using the CO_2 rebreathing method, it was not unexpected that the $\dot{V}O_2$ measurement had better reproducibility. Coupled with the variability of blood pressure measurement using cuff manometry, the repeatability of cardiac power output measurement was understandably inferior to that of cardiac output. Nevertheless, with a coefficient of variation of only 9.1%, this non-invasive method of measuring cardiac power output at rest and during exercise suggests that it can be adopted into clinical practice to provide meaningful results.

A major limitation of this study is the technological shortcoming of being unable to measure cardiac power output continuously. This shortcoming is similar to the early days of measuring $\dot{V}O_2$, when only discrete measurements at relatively large time intervals was achievable, whereas nowadays it is possible to measure breath by breath oxygen consumption, as in this study. Although it was possible to measure blood pressure continuously by intra-arterial cannulation, this was deemed to be too invasive. Automated non-invasive techniques of measuring blood pressure were used during preliminary investigations, but none of these were found to be reliable. Major technological advances are required before we can measure cardiac power output during exercise continuously. The prospect of monitoring cardiac power output continuously would make it possible to investigate whether the power output reaches a plateau at extreme exercise, which would further support the claim that cardiac pumping reserve is a major determinant of exercise limitation, not only in heart failure patients but also in healthy subjects, as suggested in a previous analysis.[5]

Another limitation of this study was the time required to perform repeated CO_2 rebreathing to obtain readings of cardiac output, because it takes about 15 seconds to perform the rebreathing of CO_2 but it requires approximately 1.5 to 2 minutes for the washout of the CO_2. Because of this, it was impossible to obtain the minimum of two cardiac output estimation at peak exercise workload during the incremental exercise test. It was therefore necessary to conduct a single stage exercise test, after a period of rest, which the subject was able to sustain at near maximum workload for about four to six minutes. This extra test was also necessary to obtain a clear reading of

$\dot{V}O_2$max during the incremental exercise test, because during the CO_2 rebreathing phase, $\dot{V}O_2$ estimation was temporarily halted. Because of this, the readings for $\dot{V}O_2$max and CPO_{max} were not simultaneous and, due to the need to sustain the single stage exercise for at least four minutes, the workload was therefore slightly below maximal (the peak $\dot{V}O_2$ during this was about 5% lower than during the incremental exercise test). The values obtained for CPO_{max} were therefore a slight underestimate of the true CPO_{max}. Given the technological limitations, this technique provides the closest estimate of physiological cardiac reserve hitherto achievable.

An ideal that is probably unattainable at present is the possibility of measuring physiological cardiac reserve independently of exercise performance. One reason for this is that it is impossible to be completely certain that the patient has performed the exercise to the absolute cardiac limit, unless a plateau is identified for peak $\dot{V}O_2$max or CPO_{max}. In some subjects there was a plateau at peak $\dot{V}O_2$, but they were in the minority. To stimulate cardiac performance to its maximum, it is essential to maximise the heart rate in sinus rhythm without conduction defects, to maximise the preload without causing pulmonary oedema, to maximise the inotropy without compromising lusitropy, and to optimise the ventricular afterload. None of this can be achieved without being invasive. Pharmacological means, using sympathomimetic and other inotropic agents, tend to reduce the preload, and their positive inotropic and chronotropic effects are not as potent as that obtained through direct sympathetic activation during exercise. The reserve values obtained thereby tend to be lower than cardiac reserve measured during maximum large muscle exercise.

The clinical implications of the availability of a method for measuring cardiac reserve non-invasively are manifold. Not only is cardiac reserve a strong indicator of prognosis, as previously shown,[6–8] but we have shown in this study that it is a major factor influencing aerobic exercise capacity. A few important clinical inferences can be drawn from this. First, we believe that it is no longer reasonable to assume that haemodynamic measurement of cardiac function is unimportant in the management of patients with heart failure. Second, cardiac reserve is probably the best available objective indicator of the overall mechanical cardiac function, in that it can distinguish a good from a poorly functioning heart. Third, treatment should be aimed at the long term preservation and if possible the improvement of cardiac reserve.

In conclusion, we have shown that cardiac power output can be measured non-invasively and reasonably reproducibly during peak exercise, and it was found to correlate well with aerobic exercise capacity in subjects with a wide range of exercise ability and cardiac pathophysiology. This method of assessing cardiac function may therefore be used to examine the functional extent of overall cardiac impairment in patients with heart failure, thereby complementing currently available techniques of evaluating the mostly morphological aspects of cardiac dysfunction. The clinical application of the concept and measurement of cardiac reserve in the management of patients with various heart diseases will require further study.

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