

# Regional blood flow in chronic heart failure: the reason for the lack of correlation between patients' exercise tolerance and cardiac output?

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## Abstract

**Background**—In patients with chronic heart failure there is no relation between cardiac output and symptom limited exercise tolerance measured on a bicycle or treadmill. Furthermore, the increase in cardiac output in response to treatment may not be matched by a similar increase in exercise tolerance. More important in determining exercise capability is blood flow to skeletal muscle. This implies that the reduction in skeletal muscle blood flow is not directly proportional to the reduction in cardiac output and that there are regional differences in blood flow in patients with heart failure.

**Methods**—Cardiac output and regional blood flow measured in 30 patients with chronic heart failure were compared with values obtained from 10 healthy controls. Measurements were made at rest and in response to treadmill exercise and were all made non-invasively.

**Results**—Cardiac output was lower in the patients at rest and during exercise. Blood flow in the superior mesenteric and renal arteries was also lower in the patients and represented a different proportion of cardiac output than in the controls. In response to exercise the increase in blood flow to the calf and therefore to skeletal muscle, was reduced in the patients. In the patients there was no correlation between resting cardiac output and blood flow in the superior mesenteric artery, renal artery, or calf.

**Conclusions**—Because blood flow to skeletal muscle and to the kidneys is likely to be important in determining patients' symptoms this factor may explain why central haemodynamic variables do not correlate with the exercise tolerance in patients with chronic heart failure.

therefore increased but because this is a measure of the summation of changes in all vascular beds it provides no information about local differences in arterial tone or regional blood flow.

One of the more interesting aspects of chronic heart failure is that the extent of cardiac dysfunction estimated from central haemodynamic variables bears no relation to the symptomatic impairment of patients assessed by treadmill exercise testing.<sup>2</sup> To explain this it has been suggested that the major cause of the limited exercise tolerance of patients is reduced blood flow to skeletal muscle.<sup>3,4</sup> Another vascular bed that is likely to be important in determining patients' symptoms is that of the kidneys. Control of salt and water excretion, and therefore plasma volume and tissue oedema, is intimately linked to both the perfusion pressure and blood flow to the kidneys.

If, as seems likely, the combination of cardiac output and arteriolar tone controls regional blood flow, knowledge of this would help in our understanding of heart failure and its response to treatment. The distribution of cardiac output has been described in healthy people and patients with heart failure.<sup>5,6</sup> These studies confirmed that there was a significant reduction in regional blood flow in the patients and the proposal was that this reduction in flow was in proportion to the reduction in cardiac output. However, the measurements were made with invasive techniques, which in themselves may alter haemodynamic variables.<sup>7</sup> This and the fact that the dye dilution measurements of regional blood flow cannot be readily repeated limit their usefulness in assessing patients' response to treatment. The purpose of this study was to investigate with non-invasive techniques cardiac output and regional blood flow at rest and in response to exercise in patients with chronic heart failure and compare the results with values obtained in healthy controls.

## Patients and methods

### PATIENTS

Thirty patients with chronic heart failure (New York Heart Association grade II-III) were studied. All had been in heart failure for at least six months. Their mean (SEM) age was 67 (2) years and 27 were men. Heart failure was caused by ischaemic heart disease

Peripheral vasoconstriction is well recognised in patients with chronic heart failure.<sup>1</sup> Venous vasoconstriction helps to maintain cardiac output by the Starling mechanism, while arterial vasoconstriction helps to maintain blood pressure in the face of a reduced cardiac output. Total systemic vascular resistance is

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in 23 patients, rheumatic heart disease with mitral regurgitation and impaired left ventricular function in four patients, and three patients had a dilated cardiomyopathy. All the patients were treated with at least 80 mg of frusemide daily and the mean dose was 156 mg (range 80–750 mg). In addition seven of the patients were taking captopril in a dose of at least 25 mg three times daily.

Ten volunteers with a mean (SEM) age of 49 (4) years were studied as healthy controls. Eight were men. All denied symptoms of heart failure and none had clinical evidence of heart failure. All had normal resting and exercise 12 lead electrocardiograms. None was taking any cardiovascular medication.

#### METHODS

Both the patients and controls were fully familiarised with the techniques on at least two occasions before being studied. Measurements of cardiac output and regional blood flow were then made after an overnight fast and at least 30 minutes of supine rest in a temperature controlled laboratory (23–24°C). Measurements were also made during a sub-maximal treadmill exercise test: the speed and slope of the treadmill were increased after four minutes at each of the following stages:

	Stage		
	I	II	III
Speed (km/h)	2.7	2.7	2.7
Slope (°)	0	1.3	2.6

#### Cardiac output

Cardiac output was measured by the indirect Fick principle and respiratory gases were monitored with a mass spectrometer (VG Medicals). Carbon dioxide was the indicator. Carbon dioxide production was calculated from minute ventilation and mixed expired carbon dioxide concentration, the partial pressure of carbon dioxide in pulmonary venous (systemic arterial) blood was derived from end tidal carbon dioxide concentration, and the partial pressure in mixed venous blood was measured after a rebreathing manoeuvre. These three variables were used to solve the Fick equation. The method has been shown to correlate closely with cardiac output measured by thermodilution.<sup>8</sup>

Cardiac output was measured with the patients sitting, standing, and at fixed submaximal workloads during the treadmill exercise test, at the end of stages I, and (if the patients were capable) at the end of stage III.

#### Blood flow in the superior mesenteric and renal arteries

Blood flows in the superior mesenteric artery<sup>9,10</sup> and right renal artery<sup>11</sup> were measured by transcutaneous Doppler ultrasound with a 5 kHz curvilinear ultrasound probe or with a sector scanner with an offset 2 kHz Doppler probe (Doptek). The vessels were identified by ultrasound and the sample volume of the pulsed Doppler system was adjusted to the size of the vessel being interrogated. Doppler spectral analysis was

recorded onto a video tape with the subjects' breath being held in mid-inspiration. Mean values of time averaged velocity were taken from at least 10 Doppler waveform complexes. For patients in atrial fibrillation, the time averaged velocity was calculated from a minimum of 25 Doppler waveform complexes. The vessel diameter was calculated as the mean of four values. Measurements and Doppler signals were made from the proximal portion of each vessel. Blood flow was calculated as ml/min<sup>12</sup>

$$\frac{(\pi \times D^2 \times TAV \times 60)}{4}$$

where D is the vessel diameter and TAV the time averaged velocity.

#### Calf blood flow

Calf blood flow was measured by venous occlusion plethysmography with mercury in silastic strain gauges.<sup>13</sup> Measurements were made with the patients resting and from three to 13 minutes after a second exercise test. The workload was identical for both patients and controls.

#### Intraobserver variability

Within subject variability for all of the variables both in patients and controls was assessed by repeated measurements over the course of three weeks. All measurements were performed by the same investigator (AFM). The mean coefficients of variability for resting values in the patients were 7.8% for cardiac output, 7.5% for calf blood flow, 10.1% for blood flow in the superior mesenteric artery and 10.8% for blood flow in the right renal artery. Corresponding values for the controls were between 6.5 and 9.5%.

#### Statistical analysis

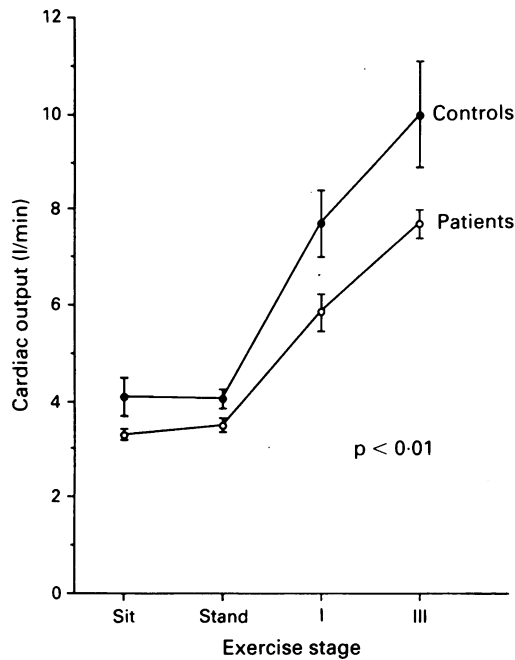
Differences in cardiac output and blood flow in the superior mesenteric and renal arteries were analysed by the Wilcoxon signed rank test; changes in calf blood flow and exercise cardiac output by analysis of variance for repeated measures (ANOVA); and correlations between cardiac output and regional blood flow by Pearson's moment correlation coefficient.

## Results

#### CARDIAC OUTPUT

Figure 1 shows the mean (SEM) values of cardiac output for the patients and controls. Measurements were made in all the patients while they were sitting and standing, in 17 patients at the end of stage I of the exercise protocol, but in only eight patients at the end of stage III because the remainder were incapable of performing this amount of exercise. Sitting measurements were lower in the patients (3.3 (0.1) l/min) than the controls (4.1 (0.4) l/min) ( $p < 0.01$ ). This difference became greater during exercise and the mean value at the end of stage I for the patients was 5.9 (0.4) l/min compared with 7.7 (0.7) l/min in the controls, while at the end of stage III it was 7.6 (0.4)

Figure 1 Mean (SEM) values of resting and exercise cardiac output in the patients with heart failure and controls. Measurements were made in all patients and controls in the sitting and standing positions and in 17 patients at stage I and eight patients at stage III.



l/min for the patients and 10.0 (1.1) l/min for the controls ( $p < 0.01$ ).

#### BLOOD FLOW IN THE SUPERIOR MESENTERIC ARTERY

Mean (SEM) resting values of blood flow in the superior mesenteric artery were 332 (12) ml/min in the patients compared with 446 (40) ml/min in the controls ( $p < 0.02$ ). In the patients this was 9.8% of cardiac output whereas in the controls it was 10.8% of cardiac output. Figure 2 shows the relation between resting blood flow in the superior mesenteric artery and resting cardiac output in the patients. The relation between the two variables failed to reach significance ( $r = 0.27$ ,  $p = 0.15$ ).

#### BLOOD FLOW IN THE RENAL ARTERY

Satisfactory renal artery Doppler waveforms were obtained in only 15 of the patients. The mean (SEM) value of blood flow in the renal artery in the patients was 317 (26) ml/min compared with 452 (50) ml/min in the controls ( $p < 0.01$ ). On the assumption that blood flow to both kidneys was the same, total renal blood flow represented 21.8% of cardiac output in the

Figure 2 Relation between resting cardiac output and blood flow in the superior mesenteric artery in the patients with heart failure.

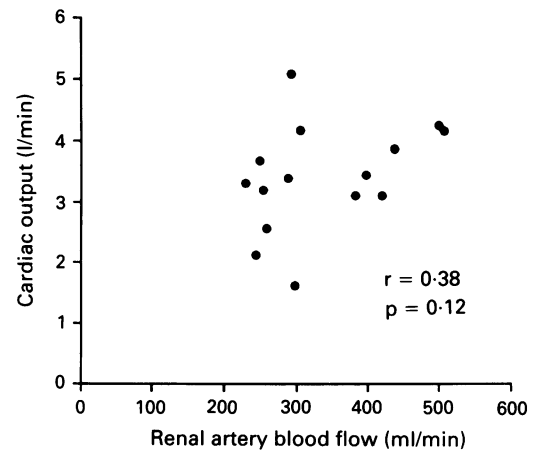
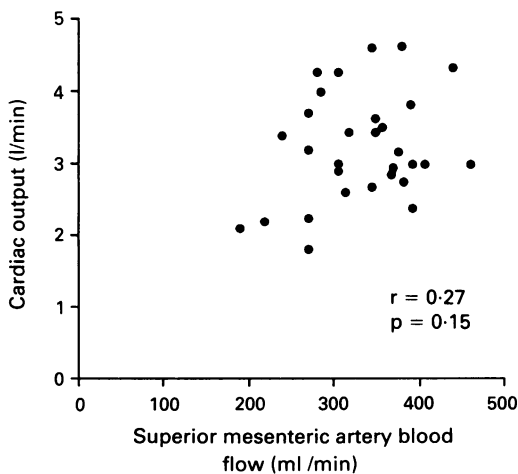


Figure 3 Relation between resting cardiac output and blood flow in the right renal artery in the 15 patients with heart failure in whom a satisfactory Doppler signal was obtained.

controls whereas it was 18.6% in the patients. Figure 3 shows the lack of relation between renal artery blood flow and cardiac output in the patients ( $r = 0.38$ ,  $p = 0.12$ ).

#### CALF BLOOD FLOW

The mean (SEM) values of resting calf blood flow in the patients was 1.9 (0.1) ml/100 ml/min whereas in the controls it was 2.7 (0.3) ml/100 ml/min,  $p < 0.05$ . Figure 4 shows the mean (SEM) values of calf blood flow at rest and from three to 13 minutes after a submaximal treadmill exercise test to a similar workload in the patients and the controls. Both groups showed the expected increase in calf blood flow after exercise but this was less in the patients than in the controls ( $p < 0.02$ ).

Figure 5 shows the relation between resting values of cardiac output and calf blood flow in the patients. Again there was no obvious relation between these two variables ( $r = 0.32$ ,  $p = 0.09$ ).

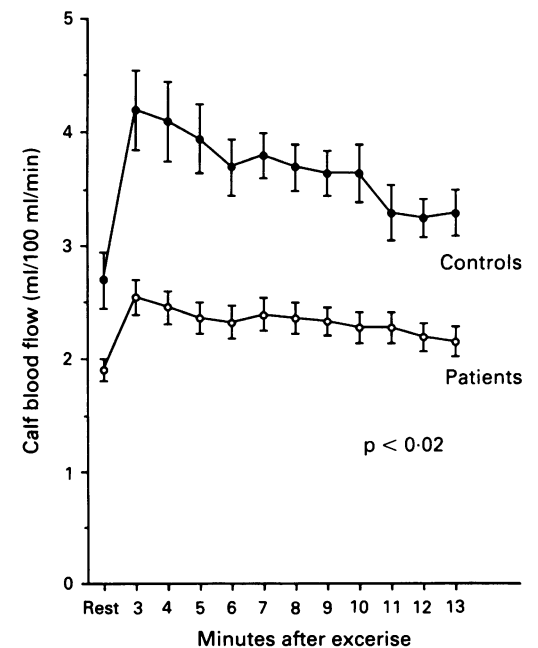
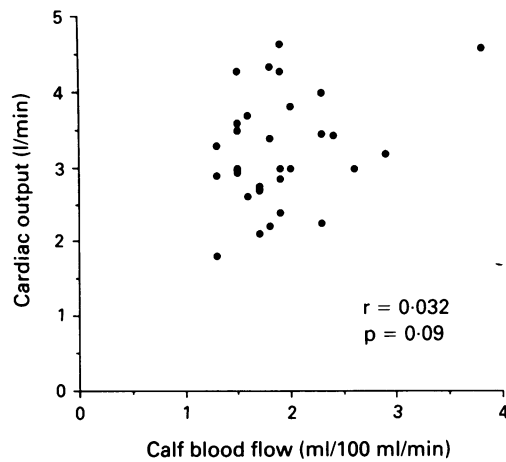


Figure 4 Mean (SEM) values of calf blood flow at rest and from 3 to 13 minutes after a fixed submaximal exercise workload in 30 patients with heart failure and controls.

Figure 5 Relation between resting cardiac output and calf blood flow in patients.



### Discussion

In this study we simultaneously measured cardiac output and regional blood flow in a group of patients with severe heart failure and compared the results with those in healthy controls. All the measurements were performed non-invasively. We showed, not surprisingly, that the patients with heart failure had lower values of cardiac output at rest and that the increase in cardiac output in response to low levels of treadmill exercise was considerably less than the controls. We also showed that blood flow to the gut, kidneys, and limbs was reduced in the patients.

It might be expected that the reduced cardiac output of patients with heart failure would lead to the same reduction in blood flow to all organs. This does not seem to be the case and there is differential redirection of the cardiac output in heart failure. Not only were the absolute values of blood flow to the tissues reduced, but the proportion of cardiac output to the gut and kidneys was also reduced in the patients compared with the controls. This presumably occurs to maintain blood flow to the cerebral and coronary beds. Similarly blood flow to the calf, which consists predominantly of skeletal muscle, was also reduced at rest and after exercise. We did not assess the other regional blood flow responses to exercise, but others have shown an expected reduction in blood flow to the superior mesenteric artery after exercise.<sup>14</sup>

There was no significant correlation between cardiac output and any of the measurements of regional blood flow. This indicates the importance of local factors in controlling regional blood flow. It also indicates why cardiac output does not correlate with patients' symptomatic impairment. Because blood flow to skeletal muscle is important in determining patients' symptoms the lack of correlation between limb blood flow and cardiac output helps to explain the lack of correlation between cardiac output and symptomatic impairment. The other major cause of symptoms is likely to be fluid retention and this is in part governed by renal blood flow. Again a lack of correlation between renal blood flow and cardiac output may also help to explain the apparent lack of importance of cardiac

output in determining patients' symptoms. Our results confirm the considerable reduction in regional blood flow reported elsewhere,<sup>5</sup> although we did not show any relation between cardiac output and regional blood flow. However, the correlations previously described<sup>5</sup> may have been spurious because they relied upon an analysis across two distinct groups, healthy controls and patients, and were not confined to the patients. Furthermore, those results were obtained with invasive techniques which in themselves are known to alter haemodynamic variables.

Although the absolute values of cardiac output may not be important in determining symptoms it is likely that any treatment that has a beneficial effect will need to increase cardiac output. If symptomatic improvement is dependent upon increasing renal and skeletal muscle blood flow then this will be most likely to occur only by an increase in cardiac output and not by further redistribution of cardiac output. The measurement of regional blood flow and cardiac output is likely therefore to be useful in evaluating new treatments for heart failure. Heart failure is characterised by important abnormalities of cardiac output and regional blood flow. Further investigation of these abnormalities will give us a better understanding of the pathophysiology of the disease. The use of non-invasive techniques similar to those we have described will permit measurements to be made in more patients with mild heart failure in whom invasive measurements may not be clinically justified and it will also permit frequent serial measurements to be made of the response to treatment.

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