Endogenous insulin and insulin sensitivity

An important determinant of skeletal muscle blood flow in chronic heart failure?


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Aim
Patients with heart failure have a reduced sensitivity to insulin’s actions on glucose metabolism and a compensatory increase in endogenous plasma insulin levels. As insulin has a selective vasodilatory action in skeletal muscle, we have studied the association between insulin sensitivity and central and regional haemodynamics in patients with heart failure.

Methods
Ten patients with stable symptomatic heart failure were studied. We used non-invasive techniques to measure cardiac output, forearm blood flow, superior mesenteric artery blood flow and right renal artery blood flow. Blood samples were assayed for noradrenaline, renin and atrial natriuretic peptide levels. Insulin sensitivity was assessed using the low dose short insulin tolerance test.

Results
There was a significant inverse correlation between forearm blood flow and insulin sensitivity ($r = -0.67, P = 0.03$), patients with lesser degrees of insulin sensitivity having the greater forearm blood flows. There was no correlation with the other haemodynamic or neurohumoral parameters. Patients with greater insulin resistance tended to have higher circulating endogenous insulin levels, although this relationship did not reach statistical significance ($r = -0.53, P = 0.12$).

Conclusions
Insulin sensitivity appears to be an important determinant of skeletal muscle blood flow in heart failure. We speculate that this is secondary to the increased circulating endogenous insulin levels, and suggest that the therapeutic potential of exogenous insulin merits further investigation.

Key Words: Insulin resistance, heart failure, forearm blood flow, Haemodynamics.

Introduction
Insulin resistance has been found to be a feature of a diverse range of disorders, including non-insulin dependent diabetes mellitus, obesity and hypertension[1,2]. Reduced sensitivity to insulin’s effects on glucose homeostasis has also been demonstrated in patients with chronic heart failure, regardless of whether the aetiology of the heart failure was valvular disease, ischaemic heart disease or idiopathic dilated cardiomyopathy[3,4]. Reduced insulin sensitivity in heart failure may have important effects on central haemodynamics by reducing the supply of glucose to the myocardium, thereby impairing myocardial contractility[4]. Evidence that this may be the case comes from the finding that the degree of hyperinsulinaemia in patients with insulin resistance secondary to chronic heart failure correlates with the severity of the heart failure[5].

However, insulin also exhibits a diverse range of physiological effects beyond its well-known metabolic actions. One effect that has attracted particular interest in recent years is its vasodilatory action, at physiological concentrations, in human skeletal muscle[6]. The administration of exogenous insulin in normal subjects causes vasodilatation in skeletal muscle, which is reflected by increase in forearm blood flow. We therefore decided to investigate the relationship between insulin sensitivity, levels of circulating endogenous insulin and regional blood flow in patients with chronic heart failure.

Methods

Patients

Eleven patients with chronic heart failure were entered into the study, one of whom was subsequently excluded because of repeated difficulties with haemodynamic
All the patients were required to have stable symptomatic heart failure with an ejection fraction \( \leq 40\% \) on echocardiography. All patients were taking a minimum dose of 40 mg of frusemide or equivalent daily. As angiotensin converting enzyme inhibitors have been shown to affect insulin sensitivity in both animals\(^7\) and humans\(^8\), patients who had taken angiotensin converting enzyme inhibitors at any time prior to this study were excluded. Patients with diabetes mellitus were also excluded. All the patients gave their informed consent and the study was approved by the local ethics committee.

**Protocol**

Patients attended a temperature controlled laboratory (23–24 °C) in the morning following an overnight fast. Medication was also omitted the morning of the study. An 18 gauge intravenous cannula was inserted into a dorsal vein of the left hand which was positioned in a warming box at 50 °C to arterialize the venous blood\(^9\). The patients were then rested supine for at least 30 min before any measurements were obtained.

**Cardiac output**

Cardiac output was measured using the indirect Fick principle, monitoring respiratory gases with a mass spectrometer (Marquette, Jupiter, Florida, U.S.A.) and using carbon dioxide as the indicator. The method has been demonstrated to correlate closely with cardiac output measurement by thermodilution\(^10\). 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 following a rebreathing manoeuvre. These three variables can then be used to solve the Fick equation.

**Regional haemodynamics**

Blood flow was measured in the right forearm by venous occlusion plethysmography\(^11\) with mercury in silastic strain gauges. Blood flows in the superior mesenteric artery\(^12,13\) and the right renal artery\(^14\) were measured by transcutaneous Doppler ultrasound using a 3·5 kHz curvilinear ultrasound probe (Sonotron, Santa Clara, California, U.S.A.). 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 with the subjects’ breath held in mid-inspiration. Vessel diameter was calculated from the mean of three values, with measurements and Doppler signals taken from the proximal portion of each vessel.

**CV% for non-invasive measurements**

With non-invasive haemodynamic measurements, close attention must be paid to potential errors resulting from measurement variability. The non-invasive methods used for this study have all been well-validated and the coefficient of variation (CV%) has previously been reported for patients studied in our laboratory as follows: cardiac output 7–8%, superior mesenteric artery blood flow 10–1%, and right renal artery blood flow 10–8%. The CV% for forearm blood flow was 10.5%\(^16\).

**Insulin sensitivity**

After all haemodynamic measurements had been completed, we measured insulin sensitivity using the low-dose short insulin tolerance test\(^17\). Before administering an insulin bolus, baseline blood specimens were taken for fasting glucose and insulin levels together with neurohormonal analysis. A bolus of human insulin (Human Actrapid, Novo Nordisk A/S, Bagsvaerd, Denmark) was administered at a dose of 0·05 units kg\(^{-1}\) body weight. Blood samples for measurement of glucose were taken at 1 min intervals from 3 to 15 min after the bolus of insulin. At the end of this period, all subjects were given a Lucozade glucose drink (Beecham, Greenford, U.K.) to correct any hypoglycaemia.

Values for insulin sensitivity were calculated for each patient, derived from the linear slope of the blood glucose concentration from 3 to 15 min after the insulin bolus. This gave a value for insulin sensitivity measured in \(\mu\text{mol} \cdot \text{l}^{-1} \cdot \text{min}^{-1}\); the greater the sensitivity to insulin, the more rapid was the observed fall in blood glucose and hence the larger the derived numerical value.

**Analytical methods**

Apart from the blood glucose assays, which were dispatched immediately to Corning Hazleton (Harrogate, U.K.) for analysis using the hexokinase method, all other blood samples were centrifuged and the plasma stored at \(-20\) °C until assayed by Corning Hazleton at a later date. Plasma insulin was determined by microparticle enzyme immunoassay (Abbott IMX), and plasma noradrenaline by radioimmunoassay (IBL Amicyl K atcombi). Plasma renin activity was measured by a two-step radioimmunassay (angiotensin I generation followed by solid phase radioimmunoassay). Atrial natriuretic peptide was measured by direct radioimmunoassay (Nichols Institute).
Statistical analysis

All baseline data are expressed as means and standard errors. Correlations of cardiac index or insulin sensitivity with haemodynamic or neurohumoral parameters were calculated by linear regression analysis using Pearson’s correlation coefficient.

Results

Demographic data for the ten patients studied are recorded in Table 1. Symptomatically, all were graded as belonging to New York Heart Association class II. The aetiology of left ventricular dysfunction was ischaemic heart disease in six, valvular heart disease in two, idiopathic dilated cardiomyopathy in one, and hypertensive cardiomyopathy in one. All the patients were receiving loop diuretics but none had ever received an angiotensin converting enzyme inhibitor.

Cardiac output and regional blood flow

The mean resting cardiac index of the patients studied was $2.1 \pm 0.1 \text{l.min}^{-1}.\text{m}^{-2}$. Reliable measurements of superior mesenteric artery blood flow were obtained in eight patients, with a mean blood flow of $157 \pm 11 \text{ml.min}^{-1}$. Right renal artery blood flow was measured in all ten patients, with a mean blood flow of $269 \pm 28 \text{ml.min}^{-1}$. The mean forearm blood flow was $1.8 \pm 0.3 \text{ml.100 ml}^{-1}.\text{min}^{-1}$. There was no correlation between cardiac index and any of the measures of regional blood flow or any of the neurohormonal measurements.

Insulin levels and insulin sensitivity

The mean fasting insulin level was $7.0 \pm 0.9 \mu\text{U.ml}^{-1}$. The mean calculated insulin sensitivity was $110.0 \pm 5.3 \mu\text{mol.l}^{-1}.\text{min}^{-1}$. There was a tendency for an inverse correlation between insulin sensitivity and fasting insulin levels, although this did not reach statistical significance ($r = -0.53$, $P = 0.12$); those patients with the lower insulin sensitivities tended to have higher fasting plasma insulin concentrations.

Insulin sensitivity did not correlate with cardiac index, superior mesenteric or right renal artery blood flow, nor any of the neurohormone levels (Table 2). In particular, there was no correlation with circulating noradrenaline levels. However, we did observe a significant inverse correlation between insulin sensitivity and forearm blood flow ($r = -0.67$, $P = 0.03$) (Fig. 1).

Discussion

Reduced sensitivity to insulin’s actions on glucose metabolism, or insulin resistance, is now recognized in a diverse range of disorders. These include diabetes mellitus, obesity and polycystic ovary syndrome[2]. It has also been linked with a number of cardiovascular disorders including hypertension[1] and, more recently, heart failure[3,4,5].

Insulin-resistant subjects compensate for their reduced insulin sensitivity with an increase in the level of circulating endogenous insulin, as long as pancreatic beta cell function remains intact. We believe that the resultant increase in endogenous plasma insulin levels underlies the haemodynamic differences between subjects observed in our study, as there was a trend towards higher circulating insulin levels in the less insulin-sensitive subjects, although the relationship did not reach statistical significance. Other studies have found a

Table 1  Summary of baseline patient data

<table>
<thead>
<tr>
<th>Study group</th>
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<tr>
<td>Gender (M/F)</td>
<td>8/2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>74 ± 1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.0 ± 2.4</td>
</tr>
<tr>
<td>Body mass index (kg.m$^{-2}$)</td>
<td>23.5 ± 0.8</td>
</tr>
<tr>
<td>Duration of heart failure (months)</td>
<td>23 ± 7</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>21 ± 3</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol.l$^{-1}$)</td>
<td>4.7 ± 0.1</td>
</tr>
<tr>
<td>Fasting plasma insulin (µU.ml$^{-1}$)</td>
<td>7.0 ± 0.9</td>
</tr>
<tr>
<td>Fasting plasma noradrenaline (nmol.l$^{-1}$)</td>
<td>2.2 ± 0.2</td>
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</tbody>
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Table 2  Correlation of insulin sensitivity with haemodynamic and neurohormonal parameters

<table>
<thead>
<tr>
<th>Correlation</th>
<th>r</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Cardiac index</td>
<td>0.08</td>
<td>0.83</td>
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<tr>
<td>Forearm blood flow</td>
<td>-0.67</td>
<td>0.03</td>
</tr>
<tr>
<td>Superior mesenteric artery blood flow</td>
<td>-0.19</td>
<td>0.65</td>
</tr>
<tr>
<td>Right renal artery blood flow</td>
<td>0.29</td>
<td>0.42</td>
</tr>
<tr>
<td>Plasma noradrenaline</td>
<td>0.38</td>
<td>0.28</td>
</tr>
<tr>
<td>Plasma atrial natriuretic peptide</td>
<td>-0.004</td>
<td>0.99</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>0.10</td>
<td>0.78</td>
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</table>

Figure 1  Correlation between forearm blood flow and insulin sensitivity

close correlation between insulin sensitivity and the degree of hyperinsulinaemia[20].

The recognition that insulin has a vasodilatory action at physiological levels suggested the possibility that reduced insulin sensitivity and the consequent elevation of circulating insulin levels may have important cardiovascular effects in patients with heart failure. The controversies over insulin’s haemodynamic actions are discussed in a comprehensive review by Baron[61]. Although much of the early work failed to suggest a physiological haemodynamic role for insulin, a substantial body of more recent evidence has reversed this view. A number of workers have now demonstrated that exogenous insulin increases limb blood flow over a range of physiological concentrations in humans[19–21]. Moreover, insulin’s vasodilatory action appears to be selective, with preferential vasodilatation of the skeletal muscle vascular bed[22].

These observations are in accordance with our own data, which indicate that there is an inverse relationship between insulin sensitivity and forearm blood flow in patients with heart failure. In other words, patients with the lower insulin sensitivities have the higher forearm blood flows. This is consistent with insulin’s known action as a physiological vasodilator in skeletal muscle: one would expect the raised endogenous insulin levels in the less insulin-sensitive patients to enhance forearm blood flow in these individuals. Moreover, we did not observe any relationship between insulin sensitivity and blood flow in the renal or superior mesenteric vascular beds. This too is in accordance with insulin’s selectivity as a vasodilator in skeletal muscle.

It might appear paradoxical that patients who most lack sensitivity to insulin also show the greatest forearm vasodilatation. The apparent contradiction can be explained by considering that insulin sensitivity is defined in terms of the action of exogenous insulin upon a subject’s glucose metabolism. Resistance to insulin’s metabolic effects does not necessarily equate with an equal degree of resistance (or, indeed, any resistance at all) to its cardiovascular effects.

We do not know whether heart failure patients show a reduced vasodilatory response to a fixed dose of insulin when compared with normal controls. In other conditions, there has been disagreement about whether the cardiovascular actions of insulin are decreased in the presence of reduced insulin sensitivity. In obesity, for example, some workers have found that insulin-mediated skeletal muscle vasodilatation is impaired[23], while others have found that the cardiovascular responses to insulin are preserved despite reduced insulin sensitivity[24,25]. This question has not yet been directly addressed in heart failure, but our data indicate that the increase in endogenous insulin levels resulting from resistance to insulin’s metabolic effects is sufficient to overcome any resistance to its vasodilatory actions, suggesting that insulin’s actions on glucose metabolism and vasodilatation occur via separate mechanisms.

Indeed, the mechanisms of both insulin resistance and insulin’s vasodilatory effects remain uncertain. A number of mechanisms for insulin resistance in various conditions have been suggested, including abnormalities of the interaction between insulin and its receptor[26], increased sympathetic nervous system activity[27], and, in hypertension, pressure-induced restriction of the microcirculation[28]. In heart failure it has been suggested in one small study that insulin resistance may be related to increases in free fatty acid levels secondary to increases in plasma noradrenaline levels[29], although we observed no relationship between insulin sensitivity and plasma noradrenaline in our data.

There has been much speculation as to what mechanism may underlie insulin’s vasodilatory actions. It has been suggested that insulin might cause the local release of endothelium-derived nitric oxide, because the vasodilatation can be blocked by the nitric oxide synthase inhibitor N^G^-monomethyl-L-arginine[29]. Other work has suggested the involvement of beta adrenergic mechanisms[30], or a more direct action on vascular smooth muscle cells[31], perhaps via insulin’s known effect on Na^+K^+ ATPase activity[32].

Whatever the mechanisms involved, the suggestion that insulin has an important role as a determinant of skeletal muscle vasodilatation is of considerable interest in heart failure. Although regional blood flow in heart failure is reduced in response to the reduced cardiac output, this is selective and the degree of the reduction in blood flow between the different vascular beds varies. Blood flow in the cerebral and coronary circulations is generally well-preserved, whereas blood flow to skeletal muscle in the limbs in substantially reduced. As limb blood flow may be more important than cardiac output as a determinant of exercise capacity in heart failure[33], there is interest in therapeutic interventions that can selectively increase blood flow to this region.

Previous workers have suggested that, by reducing the supply of glucose to the myocardium and thereby impairing myocardial contractility, insulin resistance is detrimental in heart failure[41]. However, we have found evidence that, by causing selective vasodilatation in skeletal muscle, insulin resistance and elevated endogenous insulin levels may actually be of benefit in heart failure. If this proves to be the case, exogenous insulin could be of therapeutic interest in this condition. This compelling question remains to be answered by future studies.

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References

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