

## Cardiac cachexia //

### *We know about the mechanisms but not how to reverse it*

Longstanding severe congestive heart failure is often accompanied by a loss of total body fat and lean body mass, principally skeletal muscle, known in its most severe form as "cardiac cachexia."<sup>1</sup> It has been recognised since Withering's description in 1785,<sup>2</sup> is common in patients referred for transplantation, and has a poor prognosis.<sup>3</sup> Right sided cardiac dysfunction with tricuspid regurgitation is generally the rule.<sup>4</sup> Cachexia itself may lead to cardiac atrophy with further deterioration in cardiac function.<sup>5,6</sup> Conventional treatment of cardiac failure with diuretics, cardiac glycosides, angiotensin converting enzyme inhibitors, and vasodilators may improve cardiac function somewhat, but patients often remain wasted. Recent work has increased our understanding of the mechanism of the skeletal muscle wasting in this condition, though it has not yet contributed much to reversing it.

The muscle wasting may theoretically result from reduced muscle protein synthesis, increased muscle protein breakdown, or both. In cardiac cachexia whole body protein synthesis seems to be depressed and breakdown of myofibrillar protein from leg tissue (principally composed of skeletal muscle) is increased.<sup>7</sup> This pattern of wasting differs from that seen with other causes of cachexia, in which the predominant mechanism seems to be a fall in protein synthesis, with either normal or depressed protein breakdown.<sup>8-11</sup>

Various mechanisms have been postulated to explain the pathogenesis of cardiac cachexia. Reduced blood flow to the limbs<sup>12</sup> may deprive tissues of the necessary substrates for normal protein turnover and growth. The immobility of patients who are breathless and have effort intolerance may result in disuse atrophy and deconditioning, which contribute to muscle wasting through reduced skeletal muscle protein synthesis.<sup>13</sup> Anorexia as a result of hepatic congestion, hypoxia, or drug toxicity together with delayed emptying and hypomotility of the gut may cause malassimilation of nutrients,<sup>14</sup> resulting in an energy supply too small to maintain tissue growth. Protein losing enteropathy and steatorrhoea may also be present.<sup>15,16</sup> Furthermore, energy requirements are increased owing to increased general and myocardial oxygen consumption<sup>5</sup> and the increased metabolic cost of breathing; if these requirements are not met tissue wasting will occur. Neurohumoral mechanisms in heart failure include increased secretion of catecholamines and corticosteroids, both of which accelerate muscle protein breakdown in animal studies.<sup>17,18</sup> Heart failure has been shown to produce cellular hypoxia, resulting in poor oxidative

metabolism in muscle with subsequent reduced ATP production and reduced sodium pump activity. Because protein synthesis depends on ATP this depresses protein synthesis.<sup>7</sup> The role of cell mediators such as cachectin (tumour necrosis factor)<sup>19</sup> and interleukin in tissue wasting is under investigation, but preliminary studies on cardiac cachexia have shown raised concentrations in some patients.<sup>20</sup>

Magnetic resonance spectroscopy has given useful information on metabolic abnormalities in skeletal muscle in patients with congestive heart failure,<sup>21</sup> though not all the patients were cachectic: repetitive submaximal finger flexion exercise under both aerobic and ischaemic conditions resulted in raised intracellular acidosis, reduced pH values, and increased phosphocreatine depletion. Lactate production and ATP consumption rates were also significantly higher in the patients with congestive heart failure, suggesting that anaerobic glycolytic metabolism was increased and oxidative phosphorylation reduced, and that the muscle was less "efficient" (in terms of work output in relation to energy consumption).<sup>21</sup> These findings suggest intrinsic changes in skeletal muscle energetics that might reflect changes in fibre composition, recruitment patterns, contractile efficiency, and metabolism. Muscle biopsy studies show non-specific changes common to many muscle disorders: variation in fibre area, increased intracellular acid phosphatase activity (a marker for lysosomal activity), accumulation of intracellular lipid, and normal mitochondrial enzyme activity.<sup>22</sup>

Can the wasting in cardiac cachexia be reversed? Infusion of branched chain amino acid solutions, suggested by experimental work to stimulate skeletal muscle synthesis and inhibit protein breakdown,<sup>23</sup> has shown no benefit in patients with cardiac cachexia.<sup>7</sup> Similarly, parenteral nutrition with Fre-Amine III 8.5% (nitrogen 13 g/l) plus 70% dextrose had no effect on morbidity or mortality after cardiac surgery in cachectic patients,<sup>24</sup> but it was given for only five days postoperatively, which is not long enough to achieve positive nitrogen balance. At least three weeks of optimal nutritional support (preferably before surgery) are needed to produce clinically important changes in body consumption and facilitate metabolic responses. Electrical muscle stimulation reduces muscle wasting in patients with immobilised legs by preventing the fall in protein synthesis and type I atrophy<sup>25</sup> and may prove beneficial in patients with heart failure. Exercise training to 75% peak oxygen consumption for four hours a week over four to six months by patients with severe left ventricle dysfunction improved peripheral adaptation in

heart failure.<sup>26</sup> Although the central haemodynamics remained unchanged, the training improved exercise performance, systemic arteriovenous oxygen difference, and leg blood flow on exercise, and resulted in reduced arterial and femoral venous lactate concentrations. Thus exercise training may delay the onset of anaerobic metabolism and facilitate more efficient peripheral oxygen extraction.

Nevertheless, the only longer term solution for most patients with cardiac cachexia remains transplantation, after which the tissue wasting and abnormal protein turnover can be reversed.<sup>27</sup> Reversal occurs through correcting peripheral oxygenation as a result of correcting systemic hypoxaemia, increased activity and exercise, and improved substrate availability with an improved diet and assimilation of nutrients. The results of further research, however, into the mechanisms of cardiac cachexia and their reversal with treatment are awaited.

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## Good surveys guide

### Go for small random samples with high response rates

Most surveys are cross sectional studies that set out to ascertain the prevalence of a condition or look for associations. Their design and analysis may be complex, requiring professional help, but there are some general principles that should be understood by everyone using surveys, whether as originator or consumer of results.

In any research the two enemies of sound conclusions are imprecision and bias. In surveys imprecision may result from not asking precise enough questions but usually results from taking too small a sample from the population of interest. The uncertainty in estimates of prevalence depends on the number studied rather than the proportion of the population from which the sample comes. For example, if a prevalence of 20% is found with a sample of 50 then the uncertainty (95% confidence interval) for the prevalence is about 10% to 34%. With a sample of 100 the interval is 13% to 29%, and with a sample of 1000 it is 17.5% to 22.5%. Obtaining as large a sample as possible is therefore desirable, though the cost and benefit of this will need to be examined carefully.

The two main sources of bias in surveys arise from selection of the sample and non-response. The only way to eliminate bias from selection of samples is to take a random sample in which every individual in the survey has the same chance of inclusion as every other. This is the technical meaning of "random," which is not the same as "haphazard." The only way to ensure that a response is unbiased is to obtain a 100% response rate, but this is impossible in practice.

Non-response can destroy the advantages of a random

sample. Suppose that 50% of the total "population" of 2000 surgeons like the new format of a journal. A survey that attempts to obtain answers from all of them has a 30% response rate from the half in favour and a 40% response rate from those who dislike it. (Such a disparity is less than might occur in practice.) The apparent result is that 300 of the 700 (43%) approve (95% confidence interval 39.0% to 46.6%). The true prevalence of approval is not only underestimated but also lies outside the apparent confidence interval. Had a random sample of 400 of the surgeons been studied intensively to improve the total response rate to 95%, the approval rate would then be estimated as say 180 out of 380 (47%; with 95% confidence interval 42% to 52%). Even if the 5% who did not reply were all of one opinion, this approach would lead to a more nearly "correct" answer. The confidence interval is wider but more reliable.

A special problem of association may occur in a survey of a selected subgroup that is unrepresentative of the population, such as patients in hospital. This may result in a spurious association known as "Berkson's fallacy."<sup>1</sup> For example, based on necropsy findings a negative relation was reported between tuberculosis and cancer, which led to patients with cancer being treated with active tuberculosis. This came about because hospital patients on whom necropsies had been performed were unrepresentative of the population. Statistical significance in such circumstances will be nonsense; sample size cannot compensate for bias.

One way of assessing the sensitivity of a study to possible