PostScript

LETTERS

Looking beyond haemodynamics in chronic heart failure

We read with great interest the excellent review article on drug therapy in chronic heart failure (CHF) by McKenzie and Cowley.[1] The authors discuss the haemodynamic, neurohormonal, and sympathetic nervous system mechanisms contributing to heart failure, but maintain a cardiocentric view in explaining how these three mechanisms together lead to the deterioration of the failing heart and its haemodynamics. The cardiocentric view holds that the exercise intolerance and dyspnoea are direct consequences of insufficient adaptation of the cardiac output to the increased demands during physical exertion. In the early 1980s, this view was challenged by Franciosa and others, who documented a complete lack of correlation between the left ventricular ejection fraction and exercise capacity as determined by ergometry.[2]

Initially neurohormonal and sympathetic influences were recognised to adversely influence cardiac function and even increase mortality, as discussed in the article.

After years of extensive research, we now know that CHF causes a peripheral hypoperfusion due to impaired endothelium-dependent vasodilation and leads to profound morphological, metabolic, and functional alterations in the skeletal muscles. These changes represent intrinsic alterations induced by the systemic neurohumoral and inflammatory response in CHF and not just a consequence of ''deconditioning''.

Coats *et al* first proposed the ''muscle hypothesis'' which emphasised the key role of the skeletal muscle in the pathophysiology of exercise intolerance in CHF.[3] In this model, left ventricular dysfunction initiates a systemic inflammatory process accompanied by an imbalance between anabolic and catabolic factors. Together, these processes induce muscle catabolism leading to a peripheral and respiratory myopathy contributing to early muscular fatigue and dyspnoea respectively. In recent years, the molecular mechanisms involved in the development of this ''CHF-induced myopathy'' have been extensively investigated. Hambrecht and others confirmed raised levels of proinflammatory cytokines (especially interleukin-1α and interferon-α) in skeletal muscle biopsies of CHF patients; these cytokines stimulate the expression of inducible nitric oxide synthase which produces intracellular levels of nitric oxide high enough to inhibit key enzymes of the mitochondrial oxidative phosphorylation.

Exercise training has been shown to interrupt the vicious circle described in the muscle hypothesis. Signs of local inflammation (local cytokine levels, iNOS expression, etc) are reduced and mitochondrial volume density raised. Together, these beneficial effects lead to delayed muscular fatigue and improved exercise capacity. Braith and colleagues recently confirmed that endurance training in patients with CHF reduces resting levels of neurohormones (angiotensin, −26%; aldosterone, −32%; vasopressin, −30%; atrial natriuretic peptide, −27%) in addition to the effects of optimal medical therapy.[4] Interestingly, peak exercise levels of neurohormones remained unchanged after training intervention. Exercise training in CHF can improve basal nitric oxide production and enhance endothelium-dependent peripheral vasodilation.[5]

In conclusion it is important to understand that fatigue and dyspnoea in CHF are related to the activity and strength of the peripheral and respiratory muscles and not just on reduced peripheral blood flow, pulmonary vascular congestion as suggested in the article.

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Drug therapy in chronic heart failure

In their recent paper on drug therapy in chronic heart failure the authors addressed all the important issues.[1] Blood volume depletion (mediated by drug related augmentation of diuresis) complicates ''triple therapy'' when spironolactone is co-prescribed with loop diuretics and angiotensin converting enzyme inhibitors.[2–4] Therefore, over and above the recommendation to check renal function and potassium levels, I would add that patients on triple therapy should have strict monitoring of their daily weight so as to pre-empt prerenal uraemia by appropriate titration of diuretic dosage.

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Drug therapy in chronic heart failure

We welcome McKenzie and Cowley's update on drug therapy in chronic heart failure.[1] Interestingly, they fail to mention hawthorn (*Crataegus*) extract as a possible additional treatment option for this condition. We would like to draw readers' attention to our recent meta-analysis, which suggests a significant increase in maximal workload and an improvement of heart failure related symptoms compared with placebo in New York Heart Association stage II patients.[2] Hawthorn extract seems to be safer than many other drugs for this indication. Trial patients reported only mild and infrequent adverse events even on very high doses of hawthorn extract. This implies that its therapeutic window is relatively wide.

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Herbal medicines: public should be informed about the factual evidence of their effects

The editorial on herbal medicines warning about the possibility of serious side effects from some herbal medicines is welcome.[1] The message was quite clear: ''always ask your patient about herbal medicines''. It was prompted by the case report in the same issue by Fong and Kinnear on a patient with retrobulbar haemorrhage associated with chronic *Ginkgo biloba* ingestion.[2] The editorial brought to the attention of readers the risks of improperly tested ''herbal medicines'' to the general population, and in particular, their interactions with orthodox medications. Important drugs included in the modern pharmacopoeia have originated from plants but only after adequate scientific research. They have also been marketed following ethically approved policies. Unfortunately the latter has not been the case for some ''herbal medicines'' sold as complementary and alternative medicine. A very good example is the marketing of mastic gum as a killer of *Helicobacter pylori*. A letter published in the *New England Journal of Medicine* showed that mastic gum kills *H pylori* in vitro.[3] The in vitro antibacterial effects of mastic gum has also been corroborated by another study in Italy.[4]

However, the initial report led to a frenzy of marketing mastic gum as a definitive killer of *H pylori*. Unfortunately, the information passed to the public appeared to show that crude mastic gum has an anti-*H pylori* effect but it did not state that the results were not from human studies. Indeed, more recently a report from Nottingham has shown that mastic gum does not kill *H pylori* in mice.[5] Any anti-*H pylori* effect of mastic gum in humans remains to be seen. Until then, the public should be aware of the facts.

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DIARY

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18–23 July 2004, Montreal, Quebec, Canada. This conference brings together leading researchers from within the immunology field to discuss their latest findings. For further information contact: Immunology/FOCIS 2004 Secretariat, National Research Council Canada, Building M-19, 1200 Montreal Road, Ottawa, Ontario K1A 0R6, Canada (tel: +1 613 993 7271, fax: +1 613 993 7250, email: immuno2004@nrc.ca, website: www.immuno2004.org).

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23–26 September 2004, Mumbai, India. The *Journal of Postgraduate Medicine* celebrates 50 years of publication in 2004. An international conference on journal writing and publishing has been organised to commemorate this event and will discuss many aspects of writing, editing, electronic publishing, and open access. For further information contact: Professor Atul Goel, Editor, Department of Neurosurgery, Seth G S Medical College, Parel, Mumbai, 400 012, India (tel: +91 22 24129884, fax: +91 22 25032398, email: goldcon@jpgmonline.com, website: www.jpgmonline.com).

ECHO

Public understanding and acceptance of randomisation

Please visit the *Postgraduate Medical Journal* website [www.postgradmedj.com] for a link to the full text of this article.

Although most health professionals accept that randomisation in clinical trials is important there is evidence that patients may not understand randomisation (either the word or the concept) and may not accept its validity. A study in North Staffordshire UK has shown that, while most people understand randomisation, many do not accept it.

The participants were 130 students at five further education and leisure courses. They varied in age from 18 to 70 years (mean 32 years) and in occupation from unskilled to professional. Two thirds were women. Participants were given two scenarios, one medical (referral to a consultant nearby or far away) and one non-medical (a free trip locally or to Spain) and asked to say which of five methods of allocation were random. The methods were selection by computer with no information about individuals, toss of a coin, drawing paper slips out of a hat, individual choice, and alternate allocation in turn. They were then asked to imagine they had been asked to take part in a clinical trial comparing two drugs, each of them known to be of value, to try to find out which drug was the better. The five methods of allocation were stated again and participants were asked to decide whether each method was acceptable. (It was left open whether that meant acceptable to the participant as a patient or acceptable as a feature of the trial.) Half of the participants were given a written justification for randomisation in clinical trials and half were not.

Most participants (73–92%) considered computer allocation, coin tossing, and drawing from a hat to be random methods. Most (77–92%) considered patient choice to be non-random. Participants were divided about allocation in turn. The answers were similar for the medical and the non-medical scenario. On the whole most people did not find any method of randomisation acceptable in a clinical trial. Among those who judged the randomness of each of the five methods correctly a minority (around one third) considered randomisation acceptable. Three quarters of the group considered that asking the patients to choose their own allocation was acceptable. When written justification of randomisation was given, the proportion of participants considering computer allocation to be acceptable rose to 58% but a majority still considered tossing a coin or drawing from a hat unacceptable.

Members of the general public mostly understand randomisation but balk at its use in clinical trials. Methods such as tossing a coin or drawing from a hat are considered too frivolous for medical use but computer allocation, after explanation, is more acceptable.

This Echo has also been published in the *Annals of the Rheumatic Diseases* 2004;**63**:548.

▲ *Journal of Medical Ethics* 2004;**30**:80–84.

Public understanding and acceptance of randomisation

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Notes