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CURRENT TREATMENT OF HEART FAILURE

Sir,

A recent paper published in the *Journal* dealt expertly with the management of systolic failure,[1] perhaps to the neglect of treatment options in heart failure (HF) patients with intact systolic function, who now constitute 30–50% of the HF population.[2] The latter have so-called diastolic failure in which the treatment options include blockade of the renin-angiotensin-aldosterone system (RAAS),[3–6] re-evaluation of the role of diuretic therapy,[7–15] and rate control in the event of supervention of atrial fibrillation (AF).[16] It was the prospective study entitled CHARM-Preserved which gave the most promising results for RAAS blockade in diastolic failure by documenting a significant (p=0·017) reduction in hospital re-admission rates in HF patients (New York Heart Association functional class II-IV) treated with the angiotensin receptor blocker (ARB) candesartan in the presence of a left ventricular ejection fraction (LVEF ≥40%.[3] In the same year, a retrospective chart audit showed a significant (p=0·006) reduction in 1-year mortality in HF patients with LVEF >50% discharged on either ARB's or angiotensin converting enzyme (ACE) inhibitors vs counterparts discharged on neither of these drugs.[4] Already, in the context of recent myocardial infarction, the ACE-inhibitor ramipril had been shown to confer a reduction in mortality risk in a cohort of HF patients which included a substantial minority with LVEF >50%.[5] Ramipril was subsequently shown to confer a significant reduction (p <0·001) in the rate of death from cardiovascular causes, and also a reduction (p <0·001) in the rate of occurrence of myocardial infarction in high risk subjects with vascular disease or diabetes irrespective of LVEF.[6] The rationale for the re-evaluation of diuretic therapy in systolic as well as in diastolic failure comes from a recent observational study (using propensity score methods) suggesting that diuretic-related activation of the RAAS might increase mortality and morbidity in HF.[7] On the basis of the documentation of increased risk of all-cause mortality in diuretic vs non-diuretic treated HF patients (29% vs 21%: p=0·002), and a significant increase in hospitalisation (p=0·001) in the former group, the authors recommended that diuretics should be used minimally or not at all in HF patients who are only mildly symptomatic without fluid retention, and are on complete neurohormonal blockade.[7] Blockade of the hormonal component (i.e. the RAAS) might itself be more easily achieved by co-prescribing either spironolactone or eplerenone with ACE-inhibitors when patients are being treated with loop diuretics.[8, 9] Such a drug combination could, in theory[10] as well as in practice[11] prove to be diuretic-sparing, perhaps even giving rise to life-enhancing de-activation of the RAAS. A further refinement would be the preferential use of torasemide as a loop diuretic, given the fact that it possesses anti-aldosterone,[12, 13] as well as antifibrotic properties.[14] Antifibrotic properties might, in turn favourably modify the natural history of diastolic failure, given the role of myocardial fibrosis in the aetiopathogenesis of this disorder.[15] In the event of HF being complicated by AF, rate control is preferable to pharmacological rhythm control because, with current drugs, although the two modalities have comparable mortality risk, the risk of drug-related side effects is lower with rate control.[16] Finally, for prophylaxis against AF itself, even in the context of risk factors for diastolic heart failure such as hypertension-related left ventricular hypertrophy, RAAS blockade does have a role, exemplified by the superiority of losartan to atenolol in preventing the onset of hypertension-related AF (p <0·001) despite similar blood pressure reduction.[17] Even in the presence of proven diastolic dysfunction, the additional benefits that hypertensive patients derive from blockade of the RAAS include an improvement in exercise tolerance, exemplified by an increase in treadmill exercise time relative to that attributable to hydrochlorothiazide (p <0·011) despite equivalent lowering of exercise systolic blood pressure.[18]

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AUTHORS' RESPONSE

Sir,

We are aware of the data referred to by Dr Jolobe, but must point out that very few of these are from prospective randomised controlled trials. The notable exception is CHARM-Preserved,[1] but even in that trial, the active treatment did not reduce the risk of the pre-defined primary outcome. Non-randomised and retrospective analyses are unreliable and should not be used as a basis for the recommendation of a treatment. That is why there is no treatment specifically for heart failure with preserved ejection fraction recommended in any evidence-based guideline. Of course, atrial fibrillation, hypertension and coronary heart disease should be treated as appropriate in these patients.

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TREATMENT OF CHOLERA BY INTRAVENOUS SALINE

The early use of such a rational treatment as Dr Latta's intravenous saline in cholera[1] is quite fascinating as are the reasons for its abandonment. The influential French physician Magendie, in his *Lecture Notes* on the blood published in the *Lancet,*[2] also poured cold water (or should it be cold saline?) on intravenous saline in cholera ,claiming that he had no success with a 'serum' and that this was a good example of a treatment based on theory only. This was of course incorrect, which was pointed out in a footnote by the editor of the *Lancet*, stating that the deficiency of salts had been found by analysis of the blood.

To Magendie's credit, however, he was among the first to sound the alarm regarding the rival treatment of bloodletting, itself based entirely on theories. In his *Lecture Notes*,[3] he quotes the case of a patient with pneumonia who was bled 'abundantly' on three occasions. The custom was to take daily blood specimens and examine them after 24 hours for the 'buff' (presumably the buffy coat), for signs of inflammation. He observed that on the first occasion there was a ratio of 11g of serosity to 50 g of clot, on the second the ratio was 24:50, and the third 34:35. Bearing in mind that he was unaware of the true nature or function of red blood cells, his comments are none the less telling. 'These augmentations of the serum induced by bleeding ought surely to have struck practitioners. I have full room for astonishment at their having excited so little attention.' He complained that physicians found this of little account even when pointed out to them, 'the majority of medical men persist in blindly following a regular routine that brings discredit on their art'.

Magendie has been regarded by some as the pioneer of experimental physiology and perhaps if he had endorsed it, once the perils of sepsis were recognised, intravenous saline might have been life-saving in cholera and related diseases. It should be noted however that Manson in his 1898 *Tropical Diseases*[4] mentions intravenous replacement therapy in desperate cases but mentions like others its transient effect although a 'Dr Cox of Shanghai' had better results with prolonged administration. On the other hand in 1892 Osler[5] was already recommending subcutaneous infusion of saline in cholera as being 'a really valuable method, thoroughly physiological, and should be tried in all severe cases'.

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APOLOGIES

Please note that the letter published in Issue 2 of *The Journal*, entitled *CD4$^+$CD28null T cells and toll like receptor interaction: a new link to rheumatoid arthritis and atherosclerosis?* was co-authored by S Khan,[1] PC Dore[2] and WAC Sewell[3].

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