Augmenting outcomes in patients with advanced heart failure

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This editorial refers to ‘A prospective comparison of alginate-hydrogel with standard medical therapy to determine impact on functional capacity and clinical outcomes in patients with advanced heart failure (AUGMENT-HF trial)†, by S.D. Anker et al., on page 2297.

There are two ways of being happy—we must either diminish our wants or augment our means—either may do.

Benjamin Franklin

Designing and conducting early phase studies of novel interventions is a challenging aspect of heart failure research. Such studies are typically underpowered to demonstrate conclusively improvement in ‘hard’ clinical outcomes such as mortality or hospitalization, and must therefore rely on either other clinically relevant endpoints (such as functional capacity or quality of life) or ‘surrogate endpoints’, typically physiological endpoints intended to predict outcome benefit in larger studies. Unfortunately, the history of heart failure research suggests that surrogate endpoints in smaller trials have frequently failed to predict benefit in larger studies.1

Remodelling is a fundamental mechanism by which the heart responds at the structural and cellular level to the chronic haemodynamic load and altered neurohormonal milieu of heart failure.2 Among available surrogates, favourable changes in remodelling have been the most consistently predictive of improved clinical outcomes in larger studies.3 Given the known association of pathological remodelling with poor outcomes in heart failure, the concept of intervening directly to reshape the failing ventricle is inherently attractive. Despite its theoretical appeal, previous studies of interventions designed to remodel or restrain ventricular dilation mechanically have either failed to show substantial clinical benefits or have not been accepted into routine clinical use.4,5

In this context, Anker and colleagues present the intriguing results of the AUGMENT-HF trial in this issue of the journal.6 In this multicentre randomized clinical trial, patients with advanced heart failure and reduced ejection fraction were randomized to receive either usual care or injections of alginate hydrogel into the mid-ventricular free wall of the left ventricle via a lateral thoracotomy approach. Previous animal data support the concept that alginate hydrogel injections may improve ventricular structure and function, presumably by reducing ventricular wall stress and potentially down-regulating stretch-activated pathways that may lead to heart failure progression.7

The AUGMENT-HF study met its primary efficacy endpoint of improvement in maximal exercise capacity (peak VO₂) over 6 months, and this was accompanied by potentially clinically important improvements in 6-min walk distance, patient-reported symptoms, and NYHA class. Despite these favourable effects, neither ventricular structure and function (as determined by echocardiography) nor more formally assessed quality of life [using the Kansas City Cardiomyopathy Questionnaire (KCCQ)] was improved with the intervention. Thirty-day mortality was 8.6% in the intervention arm (three deaths), with no deaths occurring in this time frame in the usual care group.

In assessing any clinical trial of a new intervention, we must consider several critical issues. Are the results biologically plausible, internally consistent, and suggestive of a meaningful clinical benefit? Are there substantive methodological concerns in study design, conduct, or analysis? Is there sufficient evidence of safety to proceed with larger studies?

Are the results biologically plausible, internally consistent, and suggestive of a meaningful clinical benefit?

One notable feature of the AUGMENT-HF results is that an intervention designed to improve ventricular structure and function did not demonstrably affect these variables (as measured by echocardiography), but still improved functional capacity and symptoms. Is such an effect biologically plausible? Exercise capacity in patients with heart failure is determined by a complex interplay of multiple...
factors including central haemodynamics, alternations in peripheral skeletal muscle, co-morbidities, and patient motivation. Some previous studies have suggested discordance between changes in outcomes and changes in exercise capacity with specific therapies. For example, in the V-HeFT-II study, enalapril significantly improved outcomes compared with a combination of nitrates and hydralazine, but only the latter had a favourable effect on peak VO₂. Some therapies that clearly improve ventricular remodelling and clinical outcomes (such as beta-blockers) have little effect on exercise capacity. Is 6 months a long enough follow-up to see a change in ventricular remodelling? Animal studies of this approach certainly suggest a more rapid course of favourable remodelling, and other therapies with effects on ventricular remodelling such as cardiac resynchronization therapy lead to improvements in ventricular geometry and function within 3 months. As the authors point out, the sample size for echocardiographic endpoints limited statistical power, but point estimates for changes in ventricular dimensions were modest and similar for both the intervention and placebo groups. The authors do not provide any data on changes in natriuretic peptides, which would have been of substantial interest for an intervention targeting ventricular wall stress, which is the primary determinant of natriuretic peptide release from the myocardium. Is the magnitude of benefit observed clinically important? An improvement in peak VO₂ of 1.24 mg/kg/min is clearly a clinically significant benefit in this advanced heart failure population, a larger benefit than that seen with exercise training in the HF-ACTION study. The reported improvements in 6-min walk distance, NYHA class, and patient global symptom assessment were large, although strangely not associated with demonstrable improvements in any domain of the KCCQ score.

Are there substantive methodological concerns in study design, conduct, or analysis?

Strengths of the AUGMENT-HF study include randomization, the use of blinded core laboratories for exercise and echo endpoints, blinded endpoint adjudication, and the use of a relatively objective primary endpoint. The majority of patients were enrolled in a single country (Romania), although there was no evidence for heterogeneity of results based on geography. The study was not blinded, but the authors point out that use of a sham surgical procedure at this early stage of development may not be considered ethical, though this is a matter of controversy. Although the potential bias of an unblinded study was mitigated in part by the study design, it is important to recognize the power of the placebo effect on both patients and physicians, especially on more subjective endpoints such as NYHA class and patient global assessment. Given the known placebo effect in unblinded trials, especially those with a dramatic intervention such as cardiac surgery, the results of these more subjective endpoints must be interpreted with great caution.

A major challenge in the interpretation of these results relates to data missingness. Missing data are a frequent issue for studies using serial cardiopulmonary exercise testing as the primary endpoint, as a significant portion of study subjects may become unable to perform repeat exercise testing due to hospitalization, progressive illness, loss to follow-up, or death. In the current study, of the 78 patients initially randomized, only 56 (72%) had 6-month peak VO₂ data available. Missingness was somewhat higher in the intervention group, as five patients did not proceed with the randomized intervention and six patients died (compared with three in the control group) prior to the 6-month endpoint. While it is impossible to determine the extent to which this imbalance may have influenced the results, this degree of missing data for the primary endpoint does suggest the need for caution in the interpretation of these results.

Is there sufficient evidence of safety to proceed with larger studies?

An important role for early phase studies is the evaluation of safety, especially for interventions that require an invasive surgical procedure. By their nature, surgical interventions assume some amount of upfront procedural risk in the hope that this will be counterbalanced by improvements in the long-term clinical course. Based on data from surgical procedures in similar patient populations, the investigators set as the primary safety target a 30-day mortality of 5%. It could be argued that given differences in the surgical procedures (lateral thoracotomy vs. median sternotomy), it could be expected that alginate hydrogel injection should be associated with a lower surgical mortality than seen in these previous studies. The observed 30-day mortality was 8.6% in the intervention arm (3 deaths out of 35 patients who underwent the implant procedure). There were no deaths in the control arm within 30 days. Rates of major adverse cardiac events (MACE) were similar between the groups. Despite the theoretical concern, there was no evidence that the intervention was proarrhythmic.

Given these considerations, how should we interpret the results of the AUGMENT-HF study? If the purpose of such studies is to look for signals of clinical efficacy that justify pursuing larger clinical studies, then the favourable changes in exercise performance seen in AUGMENT-HF would seem to suffice. However, the possible favourable effects on exercise capacity and functional status must be carefully weighed against the early risks of the intervention, in particular the early surgical mortality. Whether this procedural risk could be mitigated with greater clinical experience, by performing the intervention in patients already undergoing cardiac surgery for other purposes, or through less invasive (e.g., percutaneous) approaches, is unknown. All this must be weighed against the inherent risks of the condition itself—advanced heart failure is a highly symptomatic condition with a worse prognosis than most forms of cancer. Affected patients are frequently forced to ‘diminish their wants’ in terms of both quality and quantity of life. The search for new interventions that may help them to ‘augment their means’ continues.

Conflict of interest: none declared.

References


