The challenges of generating evidence to guide mechanical circulatory support-based management of advanced heart failure

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This editorial refers to 'Advanced heart failure: feasibility study of long-term continuous axial flow pump support'† by M.P. Siegenthaler et al., on page 1031

The heart failure epidemic is increasing globally. The epidemiological transition will, because of (i) a reduction of mortality from infectious diseases and (ii) increased life expectancy, go with an increased mortality risk secondary to cardiovascular diseases including heart failure. Within this background scenario, in the USA and Europe alone, with more than 600 million inhabitants and more than 6 million patients with heart failure, the prevalence of advanced heart failure, constituting 1–10% of the heart failure population, is estimated to total between 60 000 and 600 000 patients.

Correspondingly, the evolution of treatment options for advanced heart failure patients over the last decades has been impressive. It includes medical treatment (angiotensin-converting enzyme inhibitors, beta-blockade), defibrillator therapy, heart transplantation, and most recently mechanical circulatory support devices (MCSDs). The comparison of outcomes between different therapies for advanced heart failure has been challenging. For example, heart transplantation has never been tested in a randomized clinical trial because of the obvious survival advantage in the 1970s when compared with medical therapy1 which has been questioned during the last decade. 2 Therefore, the clinical decision making algorithm is subject to continuing debate3 and consensus processes, as exemplified by the recent guideline development initiative of the International Society for Heart and Lung Transplantation.

In 2001, in the first randomized clinical trial testing the survival benefit of MCSDs in a patient population ineligible for heart transplantation secondary to noncardiac reasons including age and comorbidities, the HeartMate I pulsatile MCSD has been shown to improve survival as well as quality of life.4 Within the evolving family of first, second, and third generation MCSD, comparison has been difficult. The first trials comparing, in patients ineligible for heart transplantation, other MCSDs against the goldstandard MCSD HeartMate I, are ongoing in the USA, testing the pulsatile Novacor MCSD and DeBakey continuous flow MCSD.

Siegenthaler et al.5 reports on an observational study using the Jarvik 2000 continuous flow pump in 17 patients with advanced heart failure who were deemed ineligible for heart transplantation. Heart failure etiology was secondary to idiopathic dilated cardiomyopathy, ischaemic cardiomyopathy, or amyloid cardiomyopathy. All patients were deemed ineligible for heart transplantation for various reasons. Implantation of the device was by left thoracotomy or median sternotomy. Power delivery was by a skull-mounted titanium pedestal. All patients survived surgery without needing right ventricular support. There were three hospital deaths, two early from subdural haematoma and aortic thrombosis, one late after switching to transplantation. Fourteen patients left the hospital with accumulated support time of 15.9 years. One-, two-, and three-year survival was 56, 47, and 24%, respectively. There was no pump failure, and quality of lives was improved. Two superficial pedestal infections were successfully treated. Four patients had cerebral thrombo-embolism: two early events attributable to inadequate anticoagulation and two late events with near complete resolution. An improved anticoagulant regimen addressed this problem during the course of this observational study. Late death occurred in 5 patients from battery disconnection, subdural haematoma, bowel ischaemia, respiratory failure, and post-cardiac transplantation. The authors concluded that continuous flow MCSD type Jarvik 2000 provide
symptomatic relief in severe heart failure with an improved quality of life, with survival eventually reaching 4 years. The authors further conclude that with the observation reported, in order to test the Jarvik 2000 assist device against the gold standard HeartMate I in the patient population discussed, a randomized clinical trial be warranted. The group in Oxford and Freiburg University, along with the Texas Heart Institute group in Houston, and the producer of the Jarvik Heart in New York City, have to be congratulated on this largest observational series of Jarvik 2000 MCSD implantation in transplant- ineligible recipients.

Several issues are of interest in this context. The first area is the patient population considered for this type of second-generation partial unloading low-pulsatility left ventricular assist device. Although the patient population was formally considered ineligible for heart transplantation, out of the series of 17 patients, 3 transitioned to heart transplantation later on. This indicates the relativity of criteria considering advanced heart failure patients either eligible or ineligible for heart transplantation, as discussed earlier. Consecutively, it should be discussed whether or not centre practice and research study inclusion criteria should change towards a study population which is not prespecified either as transplantation eligible or ineligible. The intensity would be long-term support, conditionally followed by heart transplantation.

As a second issue, the conceptual discussion about axial flow MCSD and their impact on recipient physiology is actively ongoing. For example, as these MCSD are preload- and afterload-sensitive, native left ventricular contribution and arterial blood pressure contribute to some degree of ‘low’ pulsatility, suggesting that the term ‘pulseless’ MCSD support might be considered a misnomer. In addition, the important question of whether partial unloading devices such as the Jarvik 2000, DeBakey, and Heartmate II MCSD unload the left ventricle sufficiently enough to allow for recovery of left ventricular and biventricular failure to a similar extend as more completely unloading first-generation pulsatile MCSD such as Heartmate I and Novacor is unresolved. The scarce comparative literature suggests that this may well be the case.

The third issue relates to the management of patients with the Jarvik 2000 MCSD and the associated spectrum of mortality and morbidity in this series, which compares favourably with the REMATCH study report with the HeartMate I assist device. However, all the complications mentioned including infection, bleeding, and stroke have been qualitatively similar to the ones experienced with the HeartMate I MCSD. The overall quantitative comparison to the REMATCH trial is not possible secondary to the small number of patients included in this series. The only mechanism of generating scientific evidence, in the absence of a randomized comparison, would be mandatory participation in an MCSD observational database which has been inaugurated as a voluntary mechanism by the International Society for Heart and Lung Transplantation during the last 3 years following consensus recommendations of international experts.

In the USA, the National Institutes of Health are organizing a mandatory MCSD-registry for centres participating in lifetime or destination MCSD therapy. This mechanism, hopefully staged as international registry, will over time provide uniform standards and definitions of morbidity and mortality events, allowing for a comparison of outcomes between different MCSDs.

Next, the similar profile of complications in Jarvik 2000 MCSD recipients in comparison to Heartmate I MCSD recipients, such as infections and coagulopathies, warrant a fully developed translational research program addressing these problems and transitioning them from ‘halfway technology’ to mainstream cardiovascular medicine accepted by referring cardiologists, internists, and cardiac surgeons, in addition to the general public. Such research funding, e.g. with the Specialized Centre for Clinically Oriented Research at Columbia University in New York on ‘Biology of Human Longterm Mechanical Circulatory Support’ are essential to foster the translation of this new technology into clinical practice.

The final comment relates to the question of which centres should be embarking on long-term MCSD therapy. It is impressive that the patient selection criteria in this two-centre trial differed between Oxford and Freiburg. Also, the morbidity rates, e.g. with infection, differed between the two centres, which should both be considered centres of excellence related to their experience in MCSD implantation. The overall spectrum of centres embarking on this type of therapy should be on the basis of an international and national consensus of the type of expertise that needs to be in the centre in order to provide the program with a low morbidity and mortality profile. This approach is in line with a consensus recommendation by the International Society for Heart and Lung Transplantation, which was endorsed by the American Heart Association, the American College of Cardiology, and the Heart Failure Society of America.

The entire community of advanced heart failure cardiologists and cardiac surgeons as well as nurses, social workers, psychologists, physiotherapists, and financial experts participating in this mode of therapy will have to face the challenge of developing safe and efficacious MCSD therapy. We have the responsibility to counsel our patients regarding their best options and to allow them to come to an informed decision according to their personal preferences. The type of evidence that has to be generated for this approach includes the observations reported by Siegenthaler et al., and also the comparison of different MCSDs using a mandatory international registry mechanism in addition to, in a complementary way, the framework of randomized clinical trials.

References


