THE ROLE OF CARDIAC SUPPORT DEVICES IN THE TREATMENT OF PATIENTS WITH HEART FAILURE

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INTRODUCTION

Natural history studies have shown that progressive left ventricular (LV) remodeling is directly related to future deterioration in LV performance and a less favorable clinical course in patients with heart failure.[1,2] These studies have led to the hypothesis that the mechanical burdens engendered by left ventricular remodeling - increased wall stress, decreased cardiac output, increased mitral regurgitation with increased hemodynamic overloading - may contribute to disease progression independently of the patient's neurohormonal status (reviewed in [3]). Accordingly, several innovative approaches have been evaluated to address LV remodeling, including cardiomyoplasty, partial left ventriculectomy ("Batista procedure") and the endoventricular circular patch plasty (the "Dor procedure").[4-7] The suggestion that passive containment of the ventricle might prevent and/or reverse LV remodeling arose from studies in patients who underwent the cardiomyoplasty procedure and found the external girdling provided by the skeletal muscle wrap more beneficial than the systolic assistance provided by the skeletal muscle contraction.[4] This review examines the role of cardiac support devices (CSD), specifically the CorCap™ CSD (Acorn Cardiovascular, Inc.™, St. Paul, MN) currently being evaluated in clinical trials.

CARDIAC SUPPORT DEVICES

CorCap™ CSD: Design and Implant Procedure. The CorCap™ CSD: (Figure 1) is made from a mesh-like polyester fabric constructed from a multi-filamentous yarn with high-strength, fatigue-resistant properties. The device is designed with bi-directional compliance to minimize the potential constriction while providing a degree of cardiac support - stretching more in the base-to-apex direction than the circumference to effectively maintain the heart's normal ellipsoidal shape. The CSD's knit construction allows a smooth fit around the heart with minimal abrasion of the epicardium and coronary vessels, and its base material has been used in other implantable devices with long-term biocompatibility. Currently, the CorCap™ CSD is implanted by a sternocomy, after which the baseline internal diameter of the left ventricle is measured at the mid-papillary muscle level using transesophageal echocardiography.[8] The CSD is secured to the heart with a series of 4-0 polypropylene sutures placed around the base. Excess fabric is accumulated anteriorly and a new anterior seam is formed. Transesophageal echocardiography measurements are then repeated to ensure that the LV end-diastolic diameter has not reduced by more rhan 10% compared to baseline.

Pre-Clinical Experience with the CorCap™ CSD: In three different animal models of heart failure, CSD implantation resulted in decreased LV wall stress, decreased LV pressure and volume (i.e. reverse remodeling), and improved adrenergic sensitivity.[9-11] Moreover, in experimental studies, CSD implantation resulted in decreased cardiac myocyte hypenrophy, improvements in cardiac myocyte shortening, favorable changes in LV geometry and decreased myocardial fibrosis.[12-14]

Thus, CSD implantation appears to reverse many aspects of the "heart failure phenotype."

Early Clinical Experience with the CorCap™ CSD: Phase I safety studies in patients with moderate to advanced heart failure - either alone or in conjunction with micral valve repair, mitral valve replacement, or coronary artery bypass grafting - have shown CSD implantation to be safe and associated with improvements in ventricular structure and function similar to those observed in pre-clinical models.[15,16] Initial safety studies were undertaken in 48 patients with NYHA functional class III or early IV heart failure, of either ischemic or idiopathic etiologies.[17] In a second safety study, 29 patients were enrolled at Charit<! Universitatsklinikum, Humboldt-Universitat in Berlin, Germany.[18] Twelve patients had the CorCap™ CSD-only implant while 17 patients had a concomitant cardiac surgery such as mitral valve repair or replacement, and all 29 patients were followed for up to 48 months. The LV end-diastolic dimension significantly decreased as early as three months post implant with an even greater reduction at six months,

and this benefit was sustained at one, two and three years of follow-up. LV function also improved as manifested by an improvement in LV ejection fraction at three months that appeared to peak by six months and was maintained at one, two and three years post surgery.19

Safety Issues: One objective of these early studies was to assess the risk of excessive fibrosis around the device and the subsequent development of constrictive physiology. Kleber et al performed pressure-volume loop analyses in 11 patients from Charite using biplane contrast left ventriculography and measured LV pressures using a Millar catheter at baseline and at 3, 6 and/or 12 months following CSD implantation.[20] These hemodynamic studies showed no evidence of constrictive physiology. Furthermore, pressure-volume loops were shifted to the left, consistent with an improvement in LV size and function, and with no change in diastolic filling parameters. To exclude any adverse effect on coronary vasculature and vasomotor tone, the same patients also underwent selective coronary angiography and flow velocity studies using a Doppler wire and intracoronary injections of adenosine. Coronary angiograms were normal in all patients, with no signs of vascular constriction, and coronary flow reserve was maintained at 3, 6 and 12 months.

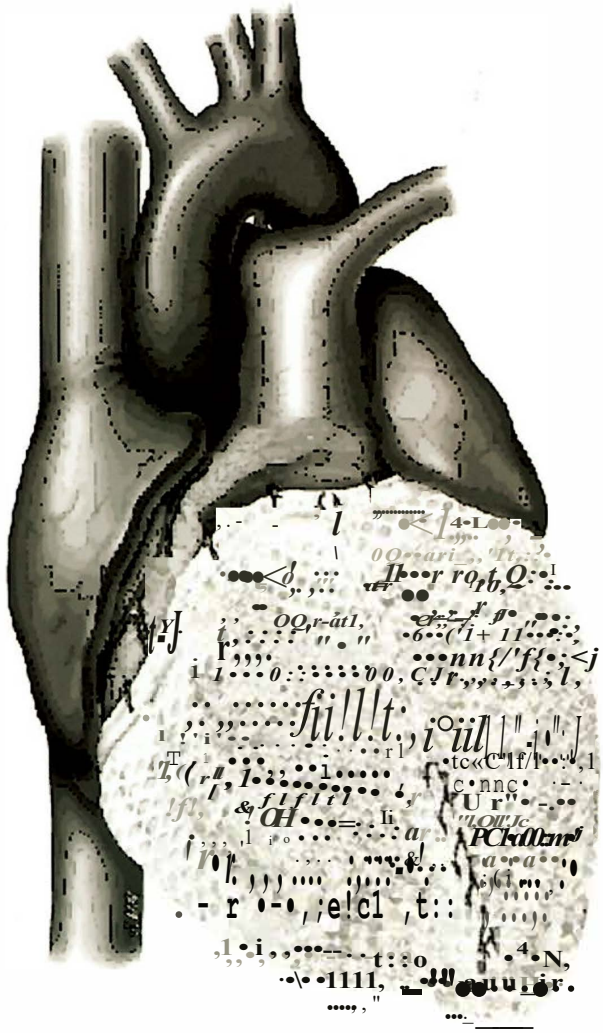

Figure 1.
CorCap™ Cardiac Support Device, (Adapted with permission from Journal of the American College of Cardiology 9).

Acorn Randomized Clinical Trial: Based on the preliminary safety studies showing that the CorCap™ CSD could be implanted safely and without excess operative morbidity or mortality, a much larger trial was initiated in June 2000. The Acorn trial is one of the largest studies of its kind - a prospective, randomized, controlled evaluation of 300 patients with NYHA III-IV heart failure, of ischemic or non-ischemic etiology, who are symptomatic on optimal medical therapy (reviewed in 21). Inclusion criteria included patients with evidence of LV dilation (LVEDD > 60 mm or LVEDD index> 30 mm/m2), and decreased LV function (LVEF < 35%). Patienrs needed a six-minute walk test < 450 meters and laboratory and pulmonary function tests within a relatively normal range. Patients were enrolled in one of two strata, depending on whether or not there was a clinical indication for mitral valve repair or replacement (MVR) (Figure 2). Patients about to undergo a MVR were enrolled in the "MVR Stratum" and randomized to either treatment (MVR plus CSD implant) or control (MVR alone) groups. Patients without an assessed need for MVR surgery were enrolled in the "no MVR" stratum (or CSD-only stratum), and also were randomized to either treatment (CSD implant plus optimal medical therapy) or control (optimal medical therapy alone) groups. All patients were maintained on optimal medical therapy conforming with established guidelines that included beta blockers and ACE inhibitors where tolerated.

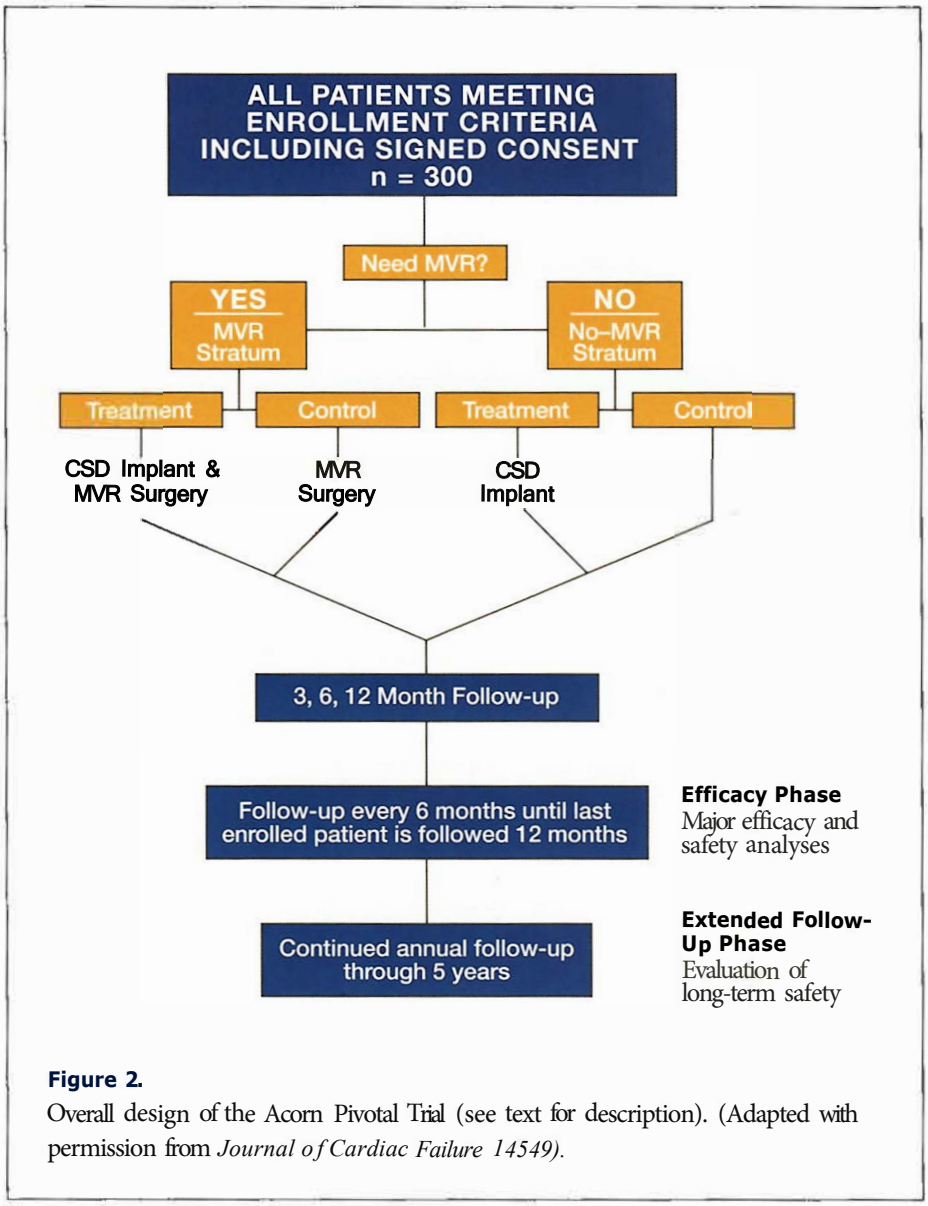

Figure 2.
Overall design of the Acorn Pivotal Trial (see text for description). (Adapted with permission from *Journal of Cardiac Failure 14549).*

Trial enrollment commenced in June 2000 and was completed in June 2003 after 300 patients were enrolled. Twcnty-nine centers in the United States and Canada participated. Follow-up in the trial is divided into two phases. The "primary efficacy phase" starred at the time of enrollment and ended when the last enrolled patient was followed for a minimum of one year (July 2004). The median follow-up will be approximately two years. During the efficacy phase, patients are followed at 3, 6, 12 months, and every 6 months there after. After the efficacy phase, patients enter into the "extended follow-up phase." Long-term safety monitoring is continued for each patient up to five years after enrollment. The primary endpoint of the trial is a change in clinical status from baseline to the end of the efficacy phase, as determined by a clinical composite score. Patients are classified into one of three mutually exclusive categories - "improved," "unchanged" or "worsened" - based on three criteria: vital status, the occurrence of a major cardiac procedure consistent with the progression of heart failure (e.g. heart transplant, LVAD), and change in NYHA functional class. Patients are considered "improved" if they are alive, did not have a major cardiac procedure and improved by at least one NYHA class compared to baseline. Patients are considered "worsened" if they died, experienced a major cardiac procedure, or if NYHA class worsened by one class. Patients were "unchanged" if th$_{ey}$ are alive, did not have a major cardiac procedure and NYHA was unchanged compared co baseline. Secondary endpoints included measures of LV structure and function, exercise capacity, quality of life and levels of BNP. The results of this study, which were presented at the 2004 Scientific Sessions of the American Heart Association, showed that CorCapTM CSD implantation was safe and resulted in significant improvements in patient functional status, LV structure and patient quality of life.

CONCLUSION

The current interest in devices such as the CorCap™ CSD stems from the hypothesis that relief of wall stress and myocyte stretch could have important benefits in heart failure b$_{ey}$ond chose provided by pharmacotherapy. The Acorn Trial is the first human study to directly test and confirm this hypothesis by examining the effects of the CorCap™ CSD on the functional status of patients with NYHA class III-IV heart failure, on LV structure and function, and on patient morbidity and mortality.

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