Non-pharmacological heart failure therapies : evaluation by ventricular pressure-volume loops

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CHAPTER 1

General introduction and outline of the thesis

END-STAGE HEART FAILURE

Chronic heart failure is one of the major healthcare problems in the world both in terms of patient numbers, hospitalizations, and economic costs. In the United States, 4 to 5 million people have chronic heart failure, which leads to more than 2 million hospitalizations each year.[1,2] Recently, the Rotterdam study showed an overall incidence of chronic heart failure of 1.4% in the Netherlands with an overall prevalence of 7.0%.[3]

Despite optimal medical therapy (β-blockers, angiotensin-converting enzyme inhibitors, spironolactone), many patients develop end-stage heart failure and remain severely symptomatic.

In these patients, cardiac transplantation remains the most effective surgical therapy with 1-, 5- and 10-year survival rates of 94, 78, and 46 percent, respectively.[4,5] Although effective, heart transplantation is hindered by donor shortage and its limited applicability. The International Society of Heart and Lung Transplantation has reported a progressive worldwide decline of cardiac transplantation.[6]

Given the limitations of medical therapy and cardiac transplantation, several alternative therapies for end-stage heart failure have been adopted in the last decade. Most prominent is cardiac resynchronization therapy (CRT), after the first implant in 1995, large multi-center trials have been performed indicating improved symptoms, exercise tolerance and quality of life.[7] A recent study shows an additional survival benefit in patients treated by CRT and pharmacological therapy above patients treated with only pharmacological therapy.[8] In addition, new surgical therapies such as restrictive mitral annuloplasty and surgical ventricular restoration have evolved and are currently widely performed in patients with end-stage heart failure.[9,10] These therapies aim to correct frequently observed end-stage complications as mitral regurgitation and left ventricular (LV) aneurysm. If not treated, these complications have important adverse effects on long-term survival.[11-13]

The long-term survival rates of patients with end-stage heart failure treated with several therapies are summarized in table 1. Obviously, comparison is hampered by the fact that the etiology of heart failure is different in the various subgroups.

Other alternative therapies in patients with end-stage heart failure involve the use of LV devices. Heerdt et al. showed that chronic unloading by LV assist devices reverses contractile dysfunction and alters gene expression in patients with end-stage heart failure.[14] Recently, the cardiac support device (Acorn device) was introduced, which seems to reverse LV dilatation and improves functional capacity of heart failure

patients.[15] However, long-term studies with these devices implanted in more patients should be awaited. Finally, preliminary data suggest that cell transplantation or stem cell therapy may be applied for repairing damaged myocardium.[16-18] These therapies are currently under clinical investigation and future data should define their clinical efficacy.

Table 1. Survival in patients with NYHA III/IV heart failure after different treatments

	Follow-up (years)		
Therapy (ref)	1-year	5-year	10-year
Medical [3,19]	63%	35%	9%
HTX [4,5,20]	94%	78%	46%
CRT [8,21]	86%	75%	-
RMA [22-25]	84%	50%	-
SVR [26]	88%	69%	-

Ref: references; HTX: cardiac transplantation; CRT: cardiac resynchronization therapy; RMA: restrictive mitral annuloplasty; SVR: surgical ventricular restoration

PHARMACOLOGICAL THERAPIES

Currently, angiotensin-converting-enzym inhibitors and beta-blockers constitute the most important pharmacological therapies for heart failure and large trials have shown their capacity to improve survival and to lower morbidity.[27-32] Aldosterone antagonists and angiotensin receptor blockers may provide additional benefit.[33-35,36,37] However, the sustained benefit of medical treatment appears relatively short-lived.[38] Non-pharmacological therapies such as heart transplantation and implantable assist devices are only considered in the late stage of the disease and access to such therapies is limited.[39] Alternative non-pharmacological treatments for the failing heart such as CRT, mitral valve repair and surgical ventricular restoration are currently widely performed.

NON-PHARMACOLOGICAL THERAPIES

Cardiac resynchronization therapy

LV mechanical dyssynchrony in patients with end-stage heart failure is related to electrical, structural, and morphological features.[40,41] Mechanical dyssynchrony is

present in the normal heart, but becomes more apparent in pathological conditions such as heart failure. [42,43] In patients with heart failure, LV electrical dyssynchrony typically results from left bundle-branch block. Notably, left bundle-branch block changes LV contraction patterns, leading to early and late contraction.[44,45] This, in turn, impairs systolic function, reduces cardiac output, and increases end-systolic volume and LV wall stress.[40]

CRT is a novel treatment option in symptomatic patients with end-stage heart failure and LV mechanical dyssynchrony. Current indications for CRT in patients with drug-refractory end-stage heart failure are NYHA class III/IV symptoms, LV ejection fraction below 35 percent, QRS duration above 120 ms and left bundle branch block configuration. Large randomized placebo controlled studies have demonstrated the beneficial effects of CRT on symptoms, exercise capacity, and quality of life.[46,47] In addition, a recent prospective randomized study showed that CRT substantially reduced the risk of complications and death among patients with heart failure and cardiac dyssynchrony.[8] In this study, a total of 404 patients were assigned to receive medical therapy alone and 409 patients to receive medical therapy plus cardiac resynchronization therapy and all patients were evaluated in a mean follow-up period of 29 months. The mortality rate in the medical-therapy group was 13% at one year and 25% at two years, as compared with 10% and 18%, respectively, in the CRT group. This study therefore concluded that implantation of CRT should routinely be considered in patients with moderate to severe heart failure and cardiac dyssynchrony. Several studies have demonstrated that CRT has beneficial effects on LV hemodynamics including reverse LV remodeling.[48-50] Recently, Yu et al. demonstrated that LV reverse remodeling is a strong predictor of lower long-term mortality and heart failure events.[51] In addition, CRT is associated with reduced sympathetic nervous activity, suggesting potentially favourable neurohormonal effects.[40] These benefits are pacing dependent, because discontinuation of pacing resulted in a rapid loss of cardiac improvement. Penicka et al. have recently demonstrated that the degree of baseline LV dyssynchrony is the main predictive factor for LV functional recovery and reversed remodeling after CRT.[52] Therefore, LV dyssynchrony assessed by tissue Doppler imaging may be an important additional selection criterium for CRT.[53] Bax et al. have recently shown that patients with septal to lateral delay above 65 ms will respond to CRT and will have an excellent prognosis after CRT. Furthermore, CRT also has beneficial effects on mitral regurgitation.[54,55] Improved coordinated timing of mechanical activation of papillary muscle insertion sites appears to be a mechanistic contributor to immediate reduction of

mitral regurgitation by CRT in patients with heart failure. Despite the clear clinical benefit, accurate hemodynamic data, i.e. effects on systolic and diastolic LV function, remain largely limited to the acute effects of CRT. Long-term effects are reported mainly in terms of ejection fraction and reversed remodeling. More detailed hemodynamic studies would provide potentially important insight in the working mechanisms of long-term CRT.

Restrictive mitral annuloplasty

Patients with chronic heart failure due to LV systolic dysfunction frequently develop mitral regurgitation.[56] Several studies have shown that coaptation failure arises in these patients as a consequence of geometric alterations, which affects mitral annular size and the geometric position of the subvalvular apparatus.[57,58] Previously, surgical treatment of mitral regurgitation was avoided in patients with heart failure owing to concerns about operative risk and peri-operative complications.[59] However, patients with mitral regurgitation have a significantly decreased survival at 2 years follow-up versus patients without mitral regurgitation.[11] More recently, with improvements in surgical techniques, surgical mitral annuloplasty for mitral regurgitation in the setting of heart failure has become a more popular treatment option. Bolling et al. have demonstrated the feasibility of mitral valve repair in patients with heart failure by downsizing the annulus using a flexible ring.[23] Their initial results in 48 patients who underwent restrictive mitral annuloplasty showed an early mortality rate of approximately 5% with 1- and 2-year survival rates of 82% and 71% respectively. Several recent studies have confirmed that early mortality is low (between 5 and 7%), heart failure symptoms are ameliorated, LV size and ejection fraction improve, and intermediate outcome is favorable.[24,25] However, several studies in patients treated with mitral annuloplasty demonstrated a high recurrence rate (30%) of mitral regurgitation after six months follow-up.[60,61] In contrast to these results, Bax et al. reported no recurrences of mitral regurgitation in 51 patients with ischemic LV dysfunction at 2-years follow-up.[22] Similarly, Szalay et al. reported in 121 patients with end-stage heart failure a recurrent rate of 3% with a mean mitral regurgitation grade 0.6 at 1-year follow-up.[25] The low recurrence rates in these latter studies may be associated with a more truly restrictive annuloplasty performed in these patients.

The effects of restrictive mitral annuloplasty on systolic and diastolic LV performance are relatively unknown. Bolling and coworkers hypothesized that restrictive mitral annuloplasty leads to LV systolic improvement by acute remodeling of the base of the

heart and re-establishing the ellipsoid shape.[62,63] Recent data from Bax et al. reported that 50% of patients showed significant reduction in LV end-systolic diameter over time.[22] Of note, a substantial percentage (60%) of patients in this study especially those with a preoperative LV end-diastolic diameter and LV end-systolic diameter of 65 mm and 51 mm, respectively, showed reverse remodeling at late follow-up. These findings indicate that the process of reverse remodeling may need substantial time in some patients. These issues are clinically relevant, since a reduction of LV dimensions and an increase in LV ejection fraction are associated with a favorable prognosis.[64,65] However, until now there is no randomized clinical trial that demonstrates that surgical correction of mitral regurgitation by mitral annuloplasty improves survival or leads to reverse LV remodeling. Wu and colleagues have recently demonstrated that there is no clearly demonstrable survival benefit conferred by mitral annuloplasty for significant mitral regurgitation in patients with chronic heart failure.[66] In addition, Enomoto et al. demonstrated in an animal model that mitral regurgitation might not contribute significantly to adverse remodeling suggesting that it is likely a manifestation rather than an important impetus for post-infarction remodeling.[67]

In summary, current data demonstrates that restrictive mitral annuloplasty is safe in patients with heart failure. Still, data about long-term survival benefits, recurrent mitral regurgitation, and LV reverse remodeling is inconclusive. Future prospective randomized controlled trials should answer these questions. In addition, hemodynamic studies may provide insight in the effects of restrictive mitral annuloplasty on LV systolic and diastolic function.

Surgical ventricular restoration

In patients with ischemic heart failure, structural changes like LV aneurysm, may contribute to substantial mechanical LV dyssynchrony. At least 88% of dyskinetic LV aneurysms result from anterior-septal infarctions, while the remainder follow after inferior infarction.[68] The LV nonuniformity of contraction and relaxation reduces mechanical efficiency of LV filling and ejection and contributes to diastolic and systolic dysfunction.[42,69] Furthermore, scarring and LV dilatation associated with aneurysm formation may provide a substrate for LV arrhythmias. Surgical ventricular restoration is increasingly applied in patients with heart failure and LV aneurysm. Controversy still exists regarding the question whether similar techniques may also be useful in treating patients with dilated ventricles and scarred regions of the heart when the shape is not seriously distorted by an LV aneurysm. Dor et al. described the endoventricular circular

patch plasty for LV reconstruction and demonstrated that the results of this technique were just as good in patients with akinetic regions as in patients with dyskinetic regions.[70] Several studies further advocated the use of the endoventricular circular patch technique above the simple linear technique in patients with LV aneurysm.[71,72]

Although surgical ventricular restoration is increasingly performed, it has not yet found general acceptance. Possible reasons include a lack of evidence that demonstrates improvement in morbidity and mortality with this technique in patients with ischemic heart failure. A recent retrospective analysis has demonstrated that the outcome was significantly better in patients who received CABG plus surgical ventricular restoration compared to patients who received CABG alone.[73] In most studies, operative mortality ranges between 0 and 20% and the reported 1- and 5-year survival hovers around 85% and 70%, respectively.[74-76] Patients in these studies had a subjective clinical benefit, as indicated by a significant improvement of their NYHA classification (from III-IV to I-III) with significant improvement of LV ejection fraction and reduction in end-diastolic and end-systolic volumes. However, none of these studies has been conducted in a prospective, randomized manner with an acceptable number of patients.

Initial results with surgical ventricular restoration have recently been published in a 3-year observational study by the RESTORE group.[26] The surgeons in this international group performed the surgical ventricular restoration in 662 patients who mainly had akinetic defects of the anterior wall. The results have been promising, although any conclusions on the incremental efficacy of surgical ventricular restoration relative to CABG must be made with caution because of the absence of a control group in the RESTORE registry. LV ejection fraction was improved on an average of 10% and all patients had significant improvement of NYHA classification. Despite these promising data, Elefteriades et al. demonstrated a similar improvement in contractile function in a small and selected group of patients who underwent isolated CABG.[77] Therefore, controversy remains regarding the question whether surgical ventricular restoration or CABG alone provide additional benefit above medical therapy. These questions will not be answered unless they are investigated in a prospective randomized fashion. The STICH (Surgical Treatment for IschemiC Heart failure) trial is the first prospective randomized study in the history of coronary artery surgery to specifically assess the potential benefit of CABG in patients with ischemic heart failure. This trial is designed and powered to answer fundamental clinical questions regarding the ischemic heart failure population. The trial tests two hypotheses: (1) CABG combined with intensive medical therapy improves long-term survival compared with medical therapy alone and

(2) surgical ventricular restoration combined with CABG and medical therapy improves survival free of cardiac events compared to CABG and medical therapy without surgical ventricular restoration.

Several studies demonstrated beneficial hemodynamic effects of surgical ventricular restoration in patients with ischemic heart failure. These studies reported acute improvements in contractile state, energy efficiency, and relaxation, together with a decrease in LV mechanical dyssynchrony in patients with heart failure.[78,79] Buckberg et al. emphasized the importance of considering size, shape and LV fiber orientation in patients with heart failure.[80-82] It has been proposed that surgical ventricular restoration of the dilated LV will restore myofibers in the diseased ventricle to a normal, oblique orientation.[83] However, this issue remains still controversial and data supporting these claims are lacking.[84,85]

In conclusion, despite the promising results of these alternative therapies in patients with end-stage heart failure, the working mechanisms and effects on LV function are relatively poorly defined.

AIM AND OUTLINE OF THE THESIS

The aim of this thesis was to study the hemodynamic effects of CRT, surgical ventricular restoration and restrictive mitral annuloplasty in patients with end-stage heart failure by use of pressure-volume loops derived by the conductance catheter. An important rational for this approach is that pressure-volume derived indices reflect intrinsic systolic and diastolic LV function in a relative load-independent fashion, whereas conventional methods are importantly influenced by changes in loading conditions. This may be particular relevant during cardiac procedures such as valve surgery and surgical ventricular restoration where loading conditions may change substantially. Moreover, it is increasingly recognized that mechanical dyssynchrony, importantly influence LV function and that benefit of CRT and surgical therapies may be partly explained by reduced mechanical dyssynchrony. The ability of the conductance catheter to quantify mechanical dyssynchrony in an objective and on-line fashion may therefore add to the diagnostic power of this methodology.

The quantification of effects of these therapies on global and intrinsic LV systolic and diastolic function and mechanical dyssynchrony may provide further insight in the

working mechanisms of these therapies. This may help to explain improved survival, functional status and exercise tolerance in heart failure patients treated with these therapies. In this thesis, acute effects of surgical therapies on LV function were assessed by peri-operative measurements by the conductance catheter in the operating room, whereas chronic effects of CRT and surgical therapies were assessed in the catheterization laboratory at baseline and at 6 months follow-up.

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