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New and Emerging Drugs and Device Therapies for Chronic Heart Failure in Patients With Systolic Ventricular Dysfunction

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ABSTRACT

Chronic heart failure remains a common end product of cardiovascular diseases and, despite significant advances in therapy, continues to be accompanied by significant morbidity and mortality. Attenuation of neurohumoral overactivation with blockers of the renin-angiotensin-aldosterone system and β-blockers has improved outcome and helped reverse or halt disease progression in many patients; however, despite this, morbidity and mortality have remained elevated, and only marginal advances have occurred over the last few years. How best to combine these various agents continue to be tested but, apart from the addition of aldosterone receptor blockers and reduction of heart rate with ivabradine, advances have been few. Implantable defibrillators and cardiac resynchronization devices have proved to be very beneficial, and the limits of their use are presently still being tested. How best to handle atrial fibrillation in patients with heart failure remains unanswered, but for now, rate control appears to be appropriate in many patients. Surgical ventricular restoration of the left ventricle has not proved to generally be useful, and although the role of coronary artery bypass graft surgery (CABG) is well established in some patients, its use in others is being reevaluated. The use of biomarkers in patients with heart failure has stimulated great interest; however, much work remains before its full potential can be realized.

RÉSUMÉ

L'insuffisance cardiaque chronique demeure une conséquence fréquente des maladies cardiovasculaires et, malgré des progrès considérables dans le traitement, elle continue d'être associée à une morbidité et une mortalité importantes. L'atténuation de la suractivation neurohumorale à l'aide d'inhibiteurs du système rénine-angiotensine-aldostérone et de bêta-bloquants a amélioré l'état de santé, et a aidé à ralentir ou à stopper la progression de la maladie chez plusieurs patients; cependant, malgré cela, la morbidité et la mortalité sont demeurées élevées, et seuls des progrès mineurs sont apparus au cours des quelques dernières années. La meilleure façon de combiner ces différents agents est encore mise à l'épreuve, mais, à part l'ajout d'antagonistes des récepteurs de l'aldostérone et la réduction de la fréquence cardiaque avec l'ivabradine, les progrès ont été peu nombreux. Les défibrillateurs implantables et les dispositifs de resynchronisation cardiaque ont prouvé leurs très grands bénéfices, et les limites de leur utilisation sont encore examinées actuellement. La meilleure façon de prendre en main la fibrillation auriculaire chez les patients avec une insuffisance cardiaque demeure sans réponse, mais, pour le moment, le contrôle de la fréquence semble être approprié pour plusieurs patients. La restauration chirurgicale ventriculaire du ventricule gauche n'a pas prouvé en général son utilité, et même si

This review aims at presenting recent approaches, those successful and those not successful in advancing the therapy of patients with heart failure (HF). This review will concentrate on the reasoning driving these approaches, and thus the implications that successful and unsuccessful interventions have had on future approaches to developments in the therapy of HF, approaches that will be briefly outlined. New evidence regarding the use of cardiac surgery and the use of biomarkers in guiding the therapy of patients with HF are also briefly addressed.

HF is the fastest growing cardiac diagnosis in North America in individuals older than 65 years.[1] It is estimated that there are 50,000 new patients diagnosed with HF in the United States each year.[2] The average annual mortality rate for HF is 10%-35%.[3] Over the past decade, with HF patients getting older and having more comorbid conditions, HF therapy has become increasingly complex, including the concomitant use of multiple medications, devices, and other interventions.

For nearly 2 centuries after the 1785 account of Withering regarding the use of foxglove in patients with HF, apart from bed rest, few therapies existed for helping patients with HF. It is not until the middle of the twentieth century that the introduction of diuretics had a major beneficial impact in acute and chronic HF. The introduction of direct-acting vasodilators also had some beneficial impact in the treatment of acute HF, but it has had little beneficial impact on chronic HF.[4]

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As the complexity of the use of pharmacogenomics in clinical practice becomes clearer, research in the area is intensifying, but much work remains to be done before its use can be clearly outlined in patients with heart failure.

le rôle du pontage aortocoronarien (PAC) est bien démontré chez certains patients, son utilisation dans d'autres cas est actuellement réévaluée. L'utilisation de biomarqueurs chez les patients avec une insuffisance cardiaque a suscité un grand intérêt; cependant, beaucoup de travail demeure avant que son plein potentiel puisse être réalisé. Comme la complexité de l'utilisation de la pharmacogénomique dans la pratique clinique devient plus claire, la recherche dans ce domaine est intensifiée, mais beaucoup de travail reste à faire avant que son utilisation puisse être clairement indiquée chez les patients avec une insuffisance cardiaque.

Newer Approaches to Drugs in Heart Failure—Successful, Unsuccessful, and in Evaluation

Not until about 40-50 years ago did the major breakthrough in the therapy of HF come as a result of a better understanding of the role of neurohumoral overactivation in the pathophysiologic process of HF (Fig. 1), and the development of medications (35 years ago) that could successfully block this overactivation[5] (Table 1). In HF, neurohumoral activation is in response to myocardial damage and dysfunction, which sets in motion the neurohumoral cascade and which is manifest through abnormal function and myocardial remodelling. The first study to demonstrate that attenuation of neurohumoral activation could reduce morbidity and mortality was the Cooperative North Scandinavian Enalapril Survival Study (CONCENSUS-1) trial in 1987, in which attenuation of the renin-angiotensisn-aldosterone system (RAAS) was obtained with angiotensin-converting enzyme inhibitors (ACEIs).[6] This landmark study was followed by a long series of successful studies involving blockade of the RAAS, in patients with chronic HF, and post–large myocardial infarction (MI).[7] In addition, these medications were shown to reduce adverse left ventricular remodelling post–large MI and to preserve, and in some cases even improve, left ventricular function in chronic HF.[8] All of these successful trials led to the recommendation that all patients with HF and impaired left ventricular function should receive an ACEI or angiotensin II receptor blocker (ARB) in doses proved to be effective in large clinical trials.[9] The combination of these 2 classes of drugs can be used in selected patients; however, in clinical practice, clinicians favor adding an aldosterone receptor blocker. The addition of an aldosterone receptor blocker has been shown to more effectively improve outcome when added to optimal medical therapy in patients with severe HF or post–large MI than does combining an ACEi and an ARB.[10-12] More recently, the Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms (EMPHASIS-HF) trial has shown that aldosterone receptor blockers can also improve morbidity and mortality when added to optimal medical therapy in patients with only mild to moderate HF due to left ventricular dysfunction.[13]

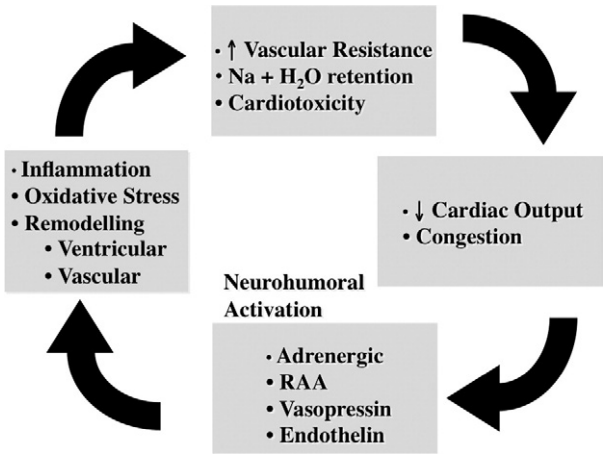

Figure 1. Vicious cycle of neurohumoral over activation in congestive heart failure.

Initially, β-blockers were considered to be contraindicated in the treatment of patients with HF. However, the publication of a large number of studies indicating that β-blockers not only reduced the morbidity and mortality of patient with HF and left ventricular dysfunction but also resulted in improvement in left ventricular function led to the recommendation that these medications should be given to all patients with HF who can tolerate them.[9] β-Blockers need to be started at low doses and uptitrated to therapeutic doses as tolerated. Initially, β-blockers can reduce systemic blood pressure; however, over a few months, the improvement of left ventricular function that accompanies their introduction reverses this reduction, and may even lead to an eventual increase in systemic blood pressure.[14] Perhaps not surprisingly, the beneficial effects of β-blockers appear to be greatest in patients with the greatest baseline heart rate.[15] This observation led to the Systolic Heart Failure Treatment With I_f Ivabradine (and outcomes in chronic heart failure) (SHIFT) study in which patients with HF who had resting heart rates >70 beats/min, despite maximal medical therapy, received a medication that reduced heart rate, ivabradine.[16] In the SHIFT study, ivabradine reduced the combination of cardiovascular death and HF hospitalizations, supporting the concept that the reduction of heart rate <70 beats/min is important in patients with HF.

Despite these successes, there have been many interventions that were tried and found to be unsuccessful and even harmful in the therapy of patients with HF and left ventricular dysfunction. Interventions that were found to be unsuccessful include those that have inotropic properties[17,18] and those that have attempted to temper the inflammatory process that accompanies HF.[19] Other interventions that were surprisingly found to be unsuccessful include the use of newer diuretics,[20] vasopressin antagonists,[21] endothelin receptor blockers,[22] and strong central sympatholytic agents.[23]

A number of important studies in the therapy of HF are presently under way and may end up adding new tools to the therapy of patients with HF. Many of these studies are for patients with acute HF, or in patients with HF and preserved left ventricular ejection fraction, subjects who are not part of this review. The Aliskiren Trial to Minimize OutcomeS in

Table 1. Newer approaches to therapy in heart failure—successful, unsuccessful, and in evaluation

Recent successful interventions
Eplerinone in mild to moderate chronic heart failure (EMPHASIS-HF trial)[13]
Ivabradine in moderate heart failure with a heart rate ≥ 70 bpm (SHIFT trial)[16]
Cardiac resynchronization in mild to moderate congestive heart failure (RAFT trial)[31]
Brain natriuretic peptide–guided therapy in congestive heart failure (meta-analysis)[42]
Recent unsuccessful interventions
Levosimendan in acute heart failure (SURVIVE trial)[18]
Rolofyline in acute heart failure (PROTECT trial)[20]
Tolvaptan in acute heart failure (EVEREST trial)[21]
Endothelin receptor blockers (ENABLE)[22]
Central sympatholytics (PROFILE trial)[23]
Maintaining sinus rhythm in patients with atrial fibrillation and heart failure (AF-CHF trial)[33]
Surgical left ventricular reconstruction (STICH trial)[40]
Ongoing studies
Direct renin inhibition (ATMOSPHERE trial)[24]
Combined neutral endopeptidase inhibitor–angiotensin II receptor blocker (PARADIGM-HF trial)[25]
Reduction of uric acid with allopurinol (EXACT-HF trial)[27]
Warfarin vs aspirin in reduced ejection fraction (WARCEF trial)[28]
Coronary revascularization vs medical therapy alone in congestive heart failure (STICH trial)[37]

Patients with HEart failuRE (ATMOSPHERE) study is assessing whether the addition of a direct renin inhibitor, a novel way of inhibiting the RAAS early in its pathway, will improve outcome in patients with chronic systolic HF who are already receiving optimal care.[24] The study on the safety and efficacy of LCZ696 compared to enalapril on morbidity and mortality of patients with chronic HF (PARADIGM-HF) is evaluating the benefits of enhancing endogenous vasodilator systems in HF by adding a neutral endopeptidase inhibitor to an ARB (in combination) to patients already on optimal medical therapy.[25] In the PARADIGM-HF study, the investigators have attempted to avoid the shortcomings of the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) study[26] by using a drug with a longer half-life and giving it twice a day. Also, because it uses an ARB instead of an ACEI in addition to an neutral endopeptidase inhibitor, the drug used in PARADIGM-HF appears to have little risk of angioedema compared with omapatrilat. The Using Allopurinol to Relieve Symptoms in Patients With Heart Failure and High Uric Acid Levels (EXACT-HF) study is evaluating the benefits of high-dose allopurinol in patients with HF and high uric acid levels. The hypothesis is that this intervention will result in a powerful antioxidant effect that will in turn result in improved cardiovascular outcomes.[27] Finally, the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) Trial is comparing the use of Coumadin (warfarin) vs aspirin in patients with HF, left ventricular dysfunction, and no clear indication for Coumadin.[28]

Electrophysiologic Devices and Rhythm

For nearly 10 years, the major advances in the therapy of patients with HF have come as a result of the introduction of electrophysiologic devices that have been found to improve both morbidity and mortality.[29] The first devices found to be beneficial were the implantable cardioverter-defibrillators (ICDs). These devices were developed in the hope of reducing the frequency of sudden death, the cause of death in nearly 50% of patients with HF. ICDs were found to significantly reduce mortality in patients with HF and left ventricular dysfunction regardless of whether the patient had documented underlying malignant ventricular arrhythmias. Thereafter, the introduction of cardiac resynchronization devices was found to reduce both morbidity and mortality in patients with HF, left ventricular dysfunction, and wide QRS complexes. These devices were developed in the hope of reducing the dyssynchronous ventricular contractions thought to be contributing to the HF of patients with wide QRS complexes. Dyssynchronous contraction of the left ventricle renders its contraction much less effective and has been shown to contribute to adverse left ventricular remodelling and mitral regurgitation. Cardiac resynchronization therapy (CRT) proved to not only reduce morbidity and mortality but also reverse some of the adverse left ventricular remodelling that accompanies HF and to reduce the severity of mitral regurgitation in a large number of patients.[30] Initially, CRT was limited to patients with more severely symptomatic HF; however, more recently, the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT) has extended the benefits of CRT to patients with minimally symptomatic HF, a left ventricular ejection fraction ≤ 30% (mean 22%) and a QRS width ≥ 120 msec (mean 158 msec).[31]

Atrial fibrillation is an important cardiac disease that has been rapidly increasing in frequency as the population ages and is seen in > 10% of patients > 70 years old. Atrial fibrillation is also seen in nearly 50% of patients with HF.[32] The loss of the atrial kick, and the irregular, and thus frequently inefficient, left ventricular filling periods, which are characteristic of atrial fibrillation, are thought to contribute to a further reduction in cardiac output and pulmonary congestion. The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) study evaluated a strategy of maintaining sinus rhythm vs a strategy of rate control of atrial fibrillation in patients with HF and chronic or paroxysmal atrial fibrillation.[33] Surprisingly, rhythm control showed no benefit over rate control. Multiple hypotheses have been put forth to attempt to explain these findings; however, at this time, these all remain speculative. The results of the SHIFT study indicating benefit in maintaining a slower heart rate in patients with HF suggests that a slow regular heart rate with the presence of an atrial kick may yet prove beneficial. The development of successful ablative techniques for atrial fibrillation has led to the development of a proposal to compare the use of electrophysiologic ablation of atrial fibrillation to reinstitute sinus rhythm (rhythm control) to rate control. Although ablation of atrial fibrillation has been shown to be possible in patients with HF, multiple procedures are frequently required to improve success rates up to the 70%-80% range.[34] In addition, left atria size is a limiting factor for ablation of atrial fibrillation, this procedure generally being limited to patients with left atrial dimensions < 55 mm.

Cardiac Surgical Techniques

CABG has been an important intervention used to reduce the morbidity and mortality of patients with HF and advanced coronary artery disease.[35] In addition, in patients with significant and refractory symptoms of angina, CABG has proved to

improve quality of life. Although little data from clinical trials exist comparing the use of percutaneous coronary interventions (PCI) for dilating coronary arteries to CABG in patients with HF and left ventricular dysfunction, all registries in which both are performed would suggest that the more severe the coronary artery disease, the better are the results of CABG compared with PCI.[36] This is not to say that PCI rather than CAGB is not indicated in a significant proportion of patients with HF and coronary artery disease in need of intervention; however, it would appear that if at all possible, the more advanced the coronary artery disease, should the overall condition of the patient permit it, CABG is the revascularization technique of choice.

As the therapies of coronary artery disease and of HF have both greatly progressed since the publication of small studies identifying the superiority of CABG over medical therapy in patients with coronary artery disease and left ventricular dysfunction,[37] there is a need to reevaluate the role of CABG in a significant proportion of these patients. This is all the more important since the results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) study were released.[38] The COURAGE study, performed in patients with preserved left ventricular function and without a clear-cut indication for coronary revascularization (significant left mainstem coronary artery obstruction, or equivalent, or uncontrollable angina), demonstrated that patients did as well with modern medical therapy alone as with coronary revascularization in addition to modern medical therapy. The Comparison of Surgical and Medical Treatment for Congestive Heart Failure and Coronary Artery Disease (STICH) Study is now revisiting the role of CABG in patients with HF and coronary artery disease receiving optimal medical and clinical therapy[39] but without a clear-cut indication for CABG (significant left mainstem coronary artery obstruction, or equivalent, or uncontrollable angina).[37] Indeed, as the patient population eligible for CABG becomes older and more complex, the decision as to whether to proceed to CABG becomes more difficult and less clear. In addition to age, factors that need to be considered include the diffuseness of the coronary atherosclerosis, comorbidities, the extent of cardiac viability, the left ventricular ejection fraction, the extent of HF (NYHA class), previous CABG, and the extent of angina.

The STICH study has already evaluated the role of surgical ventricular reconstruction (SVR) in the therapy of patients with HF, left ventricular dilatation associated with anterior wall akinesis, a left ventricular ejection fraction of $\leq 35\%$, and coronary artery disease requiring CABG.[40] The SVR procedure consists of creating a smaller ventricle with a more normal shape via an endoventricular circuloplasty technique used to treat ventricular aneurysms and adapted to treat patients with dominant anterior wall akinesis/dyskinesis. It was thought that SVR, by reducing ventricular dilatation, would improve left ventricular function and lead to improved survival in these patients. Unfortunately, the addition of SVR to CABG and optimal medical therapy was found to have no benefit. The STICH group is presently evaluating whether subgroups of patients tended to improve or deteriorate with the addition of SVR. However, at this time, although resection of left ventricular aneurysms may be indicated in specific patients, as a rule, SVR appears to have little place in the therapy of patients with ischemic dilated left ventricular dysfunction and large anterior akinetic/dyskinetic scars.

The role of repair of mitral regurgitation in the therapy of patients with HF has not been rigourously tested in a clinical trial. That having been said, in patients with severe mitral insufficiency not due to coronary artery disease and amenable to repair, it is generally accepted that surgical repair of the mitral valve should be performed unless the overall condition of the patients prevents it.[41] When the mitral regurgitation is due to a previous MI, the indication for mitral valve repair is less clear and generally limited to the reduction of the mitral valve area with the insertion of a mitral valve ring, and in some cases to mitral valve replacement if CABG is being performed.[9] Occasionally, mitral valve surgery may be required to treat a flail mitral valve leaflet following an acute MI. Attempts at prospectively evaluating the role of mitral valve repair in clinical trials have unfortunately failed, and at least for now, recommendations are based on rather incomplete data. Repair of a grossly dilated and insufficient tricuspid valve at the time of CABG is also generally performed, but again, no prospective data exist to support the addition of this procedure in selected patients undergoing CABG.[9] The role of cardiac transplantation and mechanical circulatory support in the therapy of patients with refractory HF has been well established, and a discussion regarding their role is beyond the scope of this paper.[9]

Biomarkers and Pharmacogenomics

Clinical trials have identified a number of interventions that have proven beneficial in improving both the quality and length of life of patients with HF. These trials carefully selected the inclusion and exclusion criteria for enrollment in order to optimize the chances of benefit and to minimize the risks to patients. Despite these careful selection criteria, even in studies where the intervention proved beneficial to the overall population enrolled, a significant proportion of patients did not benefit to the same extent as others, and in some cases they even deteriorated. This variability in outcomes appears to be greater for patients at the fringes of the selected enrolment characteristics of the clinical trials that established benefit.

Clinicians have long carefully evaluated the clinical and laboratory characteristics (phenotype) of their patients in order to judge whether they were more or less likely to benefit from a given intervention. The importance of such an approach is clear, but it does not always give the anticipated results such that there has been a search for biomarkers that could better identify patients more or less likely to improve with a given intervention.[42] Over the last few years, circulating biomarkers such as brain natriuretic peptides (BNP or N-terminal-pro-BNP) and high-sensitivity cardiac troponins (hs-cTns) (ie, markers of hemodynamic stress and cardiac injury) have been used to improve risk stratification and to help guide therapy in patients with HF.[43] A number of other circulating biomarkers have also been found to be associated with the pathophysiologic processes involved in HF as well as with prognosis.[42] Although the association of these biomarkers with prognosis in HF is well established, evidence of their response to various therapeutic interventions and their potential for identifying patients most or least likely to benefit from a given intervention is still lacking. For this to be properly done, their benefit would have to be prospectively assessed for its added value to that of

the careful clinical phenotyping of the patients. Pharmacogenomics as a tool for identifying patients most or least likely to benefit from a given intervention has also received increasing interest.[44] Early studies found single nucleotide polymorphisms (SNPs) to be predictive of the response of patients to certain therapies; however, follow-up studies were frequently unable to reproduce these provocative findings.[44] Indeed, we now better appreciate the complexity of genetic variations that can influence a patient's response to a given intervention. Multiple SNPs within a given system can upregulate or downregulate responses, haplotypes (a group of alleles located on a given chromosome that are transmitted together) may be better markers of drug response than SNPs, as can a whole host of downstream factors that can influence the response to a given drug or intervention. Until we can identify genetic patterns within patients that are predictive of a response, pharmacogenomics will not begin to attain its clinical potential. As with newer circulating biomarkers, the additive value of pharmacogenomics needs to be assessed prospectively in the context of the careful clinical phenotyping of the patient and to the addition of circulating biomarkers that have been proved to be helpful.

Conclusions

Over the past 25 to 30 years, the therapy of HF has markedly progressed. The introduction of medications that attenuate neurohumoral overactivation has had a major beneficial impact on patient outcomes and quality of life. More recently, the introduction of devices such as ICDs and CRT in appropriate patients has also prolonged and improved quality of life. The value of coronary revascularization, in particular CABG, is beyond question in a significant proportion of patients with HF and coronary artery disease; however, as the age and complexity of patients increase, and the benefits of optimal medical therapy become clearer, the role of CABG in a large number of patients with HF and coronary artery disease is becoming less clear. Adding SVR to CABG has proved to be disappointing, and although there is a consensus that mitral valve repair is indicated in some patients with severe mitral regurgitation, its role in many patients remains uncertain and unproved. Finally, although we remain at the dawn of the era of personalized medicine with the incorporation of circulating biomarkers, such as BNP, in the therapeutic decisions involving patients with chronic HF, much work need to be done prior to their use in clinical practice. The same can be said for the use of pharmacogenomics in guiding the care of patients with HF.

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