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Scientific Update™

Advances in the Treatment of End-Stage Heart Failure

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Chronic heart failure (CHF) is a leading cause of morbidity and mortality in the Western world.[1] In the United States, CHF afflicts over 4 million people.[2] In patients with end-stage CHF, clinical decompensation occurs frequently, resulting in recurrent hospital admissions. This places an enormous burden on health care delivery systems.[3,4] The report from this symposium will review some of the pathophysiologic mechanisms as well as potential novel therapeutic approaches in patients with end-stage CHF.

Medical management of the decompensated heart failure patient: an overview

In patients with CHF and systolic dysfunction, angiotensin-converting enzyme inhibitors (ACEI), ß-blockers, and possibly spironolactone, are the only agents that have been demonstrated to prolong survival and reduce hospital admissions in patients with CHF (Table 1).[5-9] With the exception of the reports on enalapril in the CONSENSUS study[5] and spironolactone in the recent RALES study,[9] few clinical trials had enrolled enough patients with end-stage CHF (i.e. those with New York Heart Association [NYHA] class IV symptoms) to draw meaningful conclusions, including those of ß-blockers, which reported favorable effects on survival. On the other hand, trials that used non-digitalis inotropes or vasodilators in patients with advanced CHF have invariably demonstrated detrimental effects.[10-12] Furthermore, a considerable number of the trials that found detrimental or no effects were never published.

CHF is a very complex syndrome, with both peripheral and cardiac factors contributing to disease progression. Agents that exert profound short-term or long-term hemodynamic effects may turn out to be detrimental in the long run to patients with advanced heart failure. Yet in these sick patients, hemodynamic improvement is often the principal goal of therapy. Digoxin has been shown to reduce all-cause hospitalizations and hospitalizations due to heart failure although it has a neutral effect on total mortality.[13] Although the Food and Drug Administration has only approved the use of digoxin in patients with NYHA II and III symptoms, subgroup analysis of the DIG study has shown that patients with NYHA class IV symptoms also benefit from the use of digoxin. Diuretics remain the standard therapy for patients with congestive symptoms. Those with refractory symptoms often benefit from the use of combination diuretic therapy.[14] Direct acting vasodilators such as hydralazine-nitrate combination may provide additional symptom relief.

Major clinical trials currently underway are studying different classes of agents in patients with advanced CHF. The role of ß-blockers in the treatment of patients with advanced CHF remains unclear. The completion of the COPERNICUS study will hopefully answer the question of whether the ß-blocker carvedilol will improve survival in these patients. Although used widely in many centers, the role of continuous or intermittent intravenous inotrope infusion in patients with advanced CHF remain controversial, in part because of the concern raised by chronic oral inotrope therapy[10,11] as well as the lack of controlled data. The Outcome of Prospective Trial of Intravenous Milrinone for Exacerbation of Chronic Heart Failure (OPTIME) is a prospective randomized placebo-controlled trial designed to determine whether outcome can be improved if treatment includes early administration of intravenous (IV) milrinone in patients with acute

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Table 1. Pharmacologic agents that have been shown irrevocably to improve survival in patients with chronic heart failure

	Agent	Trial	Percent of patients with NYHA class II	III	IV
ACE inhibitors	enalapril	CONSENSUS			100
	enalapril	SOLVD	57	31	2
ß-blockers	bisoprolol	CIBIS-II		83	17
	metoprolol CR/XL	MERIT-HF	41	56	3
Aldosterone antagonists	spironolactone	RALES		70	30

exacerbation of CHF. Recruitment for this study is almost complete. The ACTIVE IN CHF study has a design very similar to OPTIME, except it will examine OPC41061, a V_2 vasopressin receptor antagonist. Finally, a *novel* therapeutic approach in patients with end-stage CHF may be to combine the use of inotropic and ß-blockade therapy. Two multi-center trials designed to examine this approach, the PRimacor (milrinone lactate) for Optimization of Beta-blocker Efficacy (PROBE) and the EMPOWER studies, are currently underway. The objective of the PROBE study is to compare the efficacy and safety of IV administration of milrinone versus placebo in stabilizing patients hospitalized with NYHA functional Class III/IV congestive heart failure (CHF) in order to facilitate the initiation of oral ß-blocker therapy.

From compensated to decompensated heart failure: molecular mechanisms

A hallmark of heart failure is the presence of an initial period of compensation which is invariably followed by decompensation and the development of the end-stage heart failure phenotype. At the cellular level, the transition from compensated to decompensated heart failure has been associated with alterations in calcium homeostasis, down-regulation of ß-adrenergic receptors, myocyte dysfunction, ongoing myocyte loss, and extracellular matrix remodeling.[15,16]

In recent years, a number of biologically-active peptides including norepinephrine, angiotensin II, endothelin-1, aldosterone, and the pro-inflammatory cytokines have been implicated as molecules whose physiologic actions may contribute to disease progression of the failing heart.[16] The pro-inflammatory cytokines, such as tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), can hasten the progression of CHF through their multiple biologic properties. Indeed, *in vitro* and *in vivo* studies have demonstrated that exposure of myocytes to TNF-α and IL-1ß and overexpression of TNF-α in transgenic mice recapitulate many of the biochemical abnormalities that characterize the end-stage failing heart.[17-18] These abnormalities in Ca homeostasis occur via down-regulation of the expression of phospholamban and Ca ATPase, down-regulation of receptor-effector signaling via the receptor-G protein-adenylyl cyclase complex (through increased activity of Gi), increased extracellular remodeling, enhanced expression of inducible nitric oxide synthase (iNOS), and also induction of apoptosis, or programmed cell death.[17,19-21]

Patients with advanced CHF have elevated circulating TNF-α levels.[22] A novel approach to treating patients with advanced CHF is therefore to antagonize TNF-α. Etanercept, a soluble p75 TNF receptor fusion protein that binds to TNF and functionally inactivates this cytokine, has recently been shown to improve functional status in patients with severe CHF.[23] Two multi-center trials of the effect of etanercept on clinical outcomes which have identical protocols are currently ongoing – one conducted in North America (the RENAISSANCE study) and one in Europe (the RECOVER study).

It is interesting to note that several pharmacologic agents that have been explored for use in CHF have also been shown to inhibit the production of cytokines. These agents include vesnarinone, milrinone, pentoxyline, immunoglobulin, and adenosine.[24] Of relevance to the treatment of patients with end-stage CHF is the observation that some of the phosphodiesterase-III (PDE-III) inhibitors, namely amrinone, pimobendan and vesnarinone, inhibit TNF-α production in human peripheral blood mononuclear cells.[25] Accordingly, the appropriate use of PDE-III inhibitors such as IV milrinone may provide a novel mechanism for benefit besides increasing cardiac contractility in patients with end-stage CHF.

Inotropes in the ß-blocker era

ß-blockers have now become standard treatment for patients with mild to moderate CHF. Although many patients improve on ß-blockade therapy, some do not benefit or may even deteriorate on the therapy.[26] This is especially important in patients with end-stage CHF. When patients on ß-blockade therapy decompensate, non-digitalis inotropic agents are often required. Unfortunately, ß-adrenergic agonists such as dobutamine may not produce the desirable hemodynamic effect in the presence of ß-blockers, and may indeed increase systemic vascular resistance via α-adrenergic stimulation.[27] Patients with end-stage CHF have impaired response to inotropic stimulation,[28] related in part to up-regulation of a subunit of the regulatory G-protein $G_{\alpha i}$.[29] This abnormality is reversed by

Table 2. Effects of phosphodiesterase (PDE) inhibitors and ß-blockers

	PDE inhibitors	ß-blockers	Combination
Heart rate	↑	↓	↓
Contractility	↑(hemodynamic)	↑(biologic)	↑
Filling pressures	↓	↓	↓
ß-receptor density	↔	↑	↑
Exercise tolerance	↑	↔	↑
Proarrhythmias	↑	↓	↔

selective $ß_1$ adrenergic receptor blockers such as metoprolol,[30] but not by mixed receptor blockers such as carvedilol. Unlike dobutamine, the PDE inhibitors such as milrinone retain full hemodynamic effect in the presence of ß-blockade.[27] Therefore, milrinone is preferred over dobutamine in the management of decompensation in patients on ß-blockade therapy, especially if they are using carvedilol.

Recently, the PDE inhibitors and ß-blockers were administered in combination in patients with refractory CHF.[31] The inotrope was administered first, to increase the tolerability to ß-blocker initiation by counteracting the latter's negative inotropic effect. A schematic representation of the effects of the PDE inhibitor, ß-blocker, and their combination is shown in Table 2. The net effect was a reduction in heart rate and an increase in ejection fraction, with promising preliminary data on survival. Withdrawal of PDE inhibition resulted in clinical deterioration in over half of the patients. Based on these encouraging preliminary data, placebo-controlled trials exploring the combination of PDE inhibitor and ß-blockade therapy are being initiated. The EMPOWER trial is a three-arm study that will examine the effects of the PDE inhibitor enoximone, the ß-blocker metoprolol, and their combination on 12-month mortality and morbidity in patients with advanced CHF. The PROBE study will assess the combination therapy of intravenous inotrope and metoprolol in 300 patients.

Pulmonary hypertension in heart failure

Pulmonary hypertension (PHT) is common in patients with CHF. Although the mechanisms for the development of PHT in CHF remain to be elucidated, this disease entity contributes to morbidity and mortality in CHF patients. Furthermore, in patients awaiting cardiac transplantation, the magnitude of PHT is the most critical factor determining operative benefit from an assist device or transplantation surgery. The presumed mechanisms for PHT in CHF include volume expansion, hypoxia, local ventilatory-perfusion mismatch, increased endothelin-1, mitral regurgitation, and reduced cardiac output. It is now known that nitric oxide (NO) is an important regulator of pulmonary vascular resistance in normal subjects as well as in patients with CHF.[32,33] In a recent study of patients with CHF, inhaled NO decreased pulmonary vascular resistance (PVR) to a greater extent than the maximally-tolerated dose of nitroprusside, with no change in mean arterial pressure but an increase in pulmonary capillary wedge pressure.[34] Furthermore, the decline in PVR was brought on predominantly by the increase in pulmonary capillary wedge pressure, with no change in mean pulmonary artery pressure and even a slight decline in cardiac output.[33] Left ventricular dP/dt was unchanged. In a canine model of pacing-induced CHF, inhaled nitric oxide also increased left-sided filling pressure but had no effect on the left ventricular relaxation time constant and diastolic pressure volume relation.[35] The data overall suggest, therefore, that NO has a primary vasodilator effect on the pulmonary circulation.

It is interesting to note that the PDE inhibitor milrinone, a drug commonly used in patients with advanced CHF, has been shown consistently to reduce PVR in patients undergoing assessment for cardiac transplantation.[36,37] An intravenous bolus dose of milrinone rapidly reduces PVR and is well tolerated even in those with low arterial pressure.[37] The agent has therefore been proposed to be used as a test for the reversibility of PHT in patients with end-stage CHF evaluated for transplantation.[37]

New horizons in surgical therapy for advanced heart failure

Cardiac transplantation remains the gold standard of surgical therapies for patients with advanced end-stage CHF. Despite its success, transplantation will always remain a rather limited option – in part because of limited donor availability.[38]

Established surgical procedures, as well as new and evolving ones that were considered contraindicated in the past are now being used successfully in patients with advanced CHF. Surgical revascularization for patients with low ejection fraction, presumably to recruit hibernating myocardium, is practiced commonly in some centers. Mitral valve repair for severe mitral regurgitation in dilated ventricles is also being pursued. Preliminary data suggest that the procedure can be performed with relatively low perioperative mortality. Direct surgical procedures to restore normal geometry and size to the failing heart, such as left ventricular reduction (Batista procedure), endoventricular patch plasty (Dor procedure), dynamic cardiomyoplasty and prosthetic external constraints are currently under clinical evaluation.

These procedures are based, however, on a relatively simplistic view that heart failure is solely a result of ventricular remodeling. The use of mechanical devices such as intra aortic balloon pump and ventricular assist devices (VAD) was originally limited primarily to critically ill patients awaiting cardiac transplantation (mechanical bridging). However, the use of VAD is now increasing as an alternative to cardiac transplantation in patients with end stage heart failure.[39] The Canadian Artificial Heart Program has developed the first totally implantable pulsatile VAD for implantation in the thoracic cavity. The REMATCH (Randomized Evaluation of Mechanical Assistance Therapy for Congestive Heart Failure) is a multi-center study currently underway in the United States. This important study will compare the effects of VAD use to conventional medical therapy in patients with end-stage CHF who are not eligible for cardiac transplantation.

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