PART THREE

Clinical Experiences

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Heart Failure and Dialysis: New Thoughts and Trends

Heart failure is a major public health problem and a leading cause of hospitalization in adults in the United States. Renal dysfunction is emerging as a critical feature of patients hospitalized with heart failure and as a strong predictor of increased mortality. Despite the challenges and unique problems of patients with heart failure who have end-stage renal disease, evidence-based data regarding optimal management of these patients are limited. Here, we explore recent advances in the understanding of cardiorenal interactions and future directions in management strategies for patients with congestive heart failure on dialysis.

Key words
Congestive heart failure, end-stage kidney disease, adenosine antagonists, vasopressin antagonists, stem cells

Introduction

Congestive heart failure (CHF) is a chronic progressive disorder that accounts for substantial morbidity and mortality. Approximately 5 million Americans have heart failure, and these patients are at significant risk for decompensation and resulting hospitalization (1). From 1990 to 1999, the annual number of hospitalizations for heart failure as a primary diagnosis increased from approximately 810,000 to more than 1 million and for heart failure as a primary or secondary diagnosis from 2.4 million to 3.6 million. In 2001, heart failure was listed as the primary cause of death in nearly 53,000 patients (2).

Renal dysfunction is commonly seen in patients with heart failure, and the prevalence of chronic kidney disease (CKD) in these patients is 36% – 50% (3). Among patients with end-stage renal disease (ESRD), up to 64% present with heart failure at the time of initiation of dialysis (4). With heart failure and end-stage renal disease both reaching epidemic proportions in the U.S. population, optimal management strategies need to be further explored.

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Discussion

Cardiorenal interactions

Congestive heart failure causes progression of renal disease, and conversely, worsening of kidney disease can lead to cardiac damage. This strong interconnection between cardiac and renal dysfunction, causing amplified damage to individual organs, has been linked to various potential mechanisms. Recently implicated is the modified Guytonian theory that describes a feedback loop involving the renin–angiotensin system (RAS), nitric oxide balance, the sympathetic nervous system, and inflammation (5). This highly interactive model and its underlying mechanisms promote accelerated atherosclerosis, cardiac remodeling, and progression of renal disease to the detriment of cardiac function and long-term survival.

Activation of RAS by low perfusion pressure is a normal regulatory mechanism of the body, maintaining blood flow to vital organs. But in patients with heart failure, the resorptive and hemodynamic actions of angiotensin II (A-II) can be associated with deleterious effects. Activation of nicotinamide adenine dinucleotide phosphate (NADPH)–oxidase by A-II leads to formation of reactive oxygen species (ROS) that cause oxidative stress (6). Furthermore, A-II leads to vascular inflammation by activating nuclear factor kappa B, which is a potent stimulator of chemotactic and adhesion molecules (5).

Nitric oxide, which is vital to endothelial function and regulation of extracellular fluid balance, is inhibited in the milieu of A-II–induced ROS production (7), resulting in impaired renal regulatory mechanisms and fluid retention.

Together with increased oxidative stress, inflammation is found in patients with concomitant ESRD and CHF. Although Zebrack and colleagues showed a nice correlation between coronary artery disease and renal insufficiency, little information is available to

demonstrate a correlation between inflammation and patients with combined ESRD and CHF (8).

Excess sympathetic nervous system (SNS) activity also plays an important role in long-term regulation of extracellular fluid volume and blood pressure. Recently, excessive catecholamine exposure was proposed to accelerate organ failure in patients with both ESRD and CHF (5). Thus, SNS activity has emerged as a key therapeutic target in patients with CHF.

Management strategies

CURRENT THERAPEUTIC INTERVENTIONS

Many current treatments for CHF have undergone only limited study in patients with advanced CKD or ESRD. Most trials of CHF medications either excluded patients with a serum creatinine level above 2 mg/dL or did not report a subgroup analysis. Because of a lack of information and theoretical concerns, many agents—such as angiotensin converting-enzyme (ACE) inhibitors and aldosterone inhibitors—are underutilized in patients with heart failure. However, new data are emerging to suggest favorable results with these agents in carefully monitored patients who have coexistent CHF and CKD.

In patients with heart failure, ACE inhibitors can improve survival. The Cooperative North Scandinavian Enalapril Survival Study reported similar survival benefits in patients with heart failure with or without renal dysfunction (9). The Joint National Committee Guidelines on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure also advocate ACE inhibitors as first-line therapy for the management of hypertension in patients on dialysis (10). But ACE inhibitors can be associated with a risk of hyperkalemia, and their use should be discontinued in the presence of recurrent or refractory hyperkalemia. In addition, because of inhibition of bradykinin degradation by ACE inhibitors, cases of anaphylaxis have been reported in patients on hemodialysis exposed to synthetic membranes. Angiotensin receptor blockers have also been shown to be beneficial in the treatment of heart failure, although they are not superior to ACE inhibitors (11).

Beta blockers can reduce mortality in patients with heart failure. A randomized controlled trial by Cice *et al.* reported a 21.6% absolute reduction in 2-year mortality in patients with heart failure and renal dysfunction who received carvedilol. A lower rate of recurrent hospital admission was also observed (12).

Aldosterone receptor antagonists (for example, spironolactone) have been studied and are potentially safe in patients with heart failure and ESRD, but no convincing data show any survival advantage (13). No published studies with eplerenone are available, and that agent is currently contraindicated in patients with ESRD.

Recent data from the Anemia in Chronic Heart Failure study demonstrated that treatment of even mild anemia can be crucial in patients with heart failure (14). However, patients with both heart failure and ESRD receiving aggressive treatment for anemia have not realized the same benefit (15). Given the nature of the foregoing studies, further investigations in a randomized format are underway.

Despite the proven role of cardioprotective drugs, Berger *et al.* reported significant underutilization of these medications in patients with heart failure and renal dysfunction (16). Thus, conventional treatment of heart failure by cardiologists, nephrologists, and internists is associated with many risk–reward decisions that lack the luxury of excellent evidence on which to base a decision.

DIALYSIS AND ULTRAFILTRATION

According to the Acute Decompensated Heart Failure National Registry, patients with heart failure exacerbations experience prolonged hospitalizations, with 42% of patients being discharged with unresolved symptoms and 70% with inadequate weight loss, leading to high rates of readmission (17). In patients with ESRD, the ineffectiveness of diuretic therapy leaves dialysis as the only option for removing excess extracellular fluid volume. And despite the role of dialysis as a major modality for optimizing extracellular fluid volume, no large head-to-head randomized controlled trials are available to assist treating physicians in choosing a mode of dialysis [hemodialysis or peritoneal dialysis (PD)]. Further, patients with heart failure are sensitive to intravascular volume shifts, and only a small window makes the difference between a state of pulmonary vascular congestion and one of hypotension. Extracorporeal ultrafiltration (UF) has been reported to be the therapy of choice for short-term management of patients with severe fluid overload (17), but PD may be the therapy of choice for long-term treatment of patients resistant to traditional

medical therapy for heart failure (18). However, most of these conclusions derive from observational studies, which may be affected by selection bias.

New frontiers: pharmacologic and molecular advances

INOTROPIC THERAPIES

Several emerging therapies are now under evaluation in patients with heart failure. These include the myosin activators, which have had limited clinical trials largely in phase I exposures (19). At the time of writing, data regarding the potential long-term use of these agents were not available. Other agents undergoing preclinical testing are the Na^+,K^+-ATPase inhibitors (19). In animal models, these agents appear promising, but researchers in the field of heart failure have a large "medicine cabinet" of promising preclinical agents that are failing to help heart failure patients. Our suspicion is that it will take many years before these agents reach the population of patients with heart failure and CKD.

ADENOSINE A1 RECEPTOR ANTAGONISM

Selective adenosine A1 receptor blockade has recently been proposed to be associated with improvement in diuresis and with maintenance or improvement of glomerular filtration. The direct renal actions of adenosine include reduced glomerular filtration, perhaps by dilation of postglomerular vessels or by vasoconstrictive effects. Similar effects have been seen when intravenous adenosine is given. These actions suggest the possibility that an adenosine antagonist may be able to reduce afferent arteriolar pressure and cause diuresis and maintain or improve glomerular filtration. Gottlieb and coworkers recently reported that, in 17 patients, a selective adenosine A1 receptor antagonist produced diuresis comparable to that achieved with furosemide, but a significantly lesser reduction in glomerular filtration rate (20). These studies have limited experience with patients having CKD, but we believe that they may be the next class of agents available for use.

VASOPRESSIN ANTAGONISTS

Vasopressin antagonists increase production of the aquaporin-2 channel and thereby increase water excretion through the kidney. Initial clinical trials conducted with tolvaptan met with early positive results that were not long-lasting (21). Currently, whether the vasopressin antagonists will become standard treatment for patients with heart failure is unclear. The role that this class of agents may play in patients with CKD is similarly unclear.

STEM-CELL THERAPY

The concept of the heart as an organ composed of terminally differentiated myocytes incapable of regeneration is being challenged. Experimental studies suggest that stem cells can exert beneficial effects on the failing heart by transdifferentiating into cardiac cell types or by providing a source of cardioprotective paracrine factors. A variety of stem and progenitor cell populations could potentially be used for cardiac repair. Each cell type has its own profile of advantages, limitations, and practicability issues in specific clinical settings. Many investigators have therefore chosen a pragmatic approach by using unfractionated bone marrow cells (BMCs), which contain various stem and progenitor cell populations, including hematopoietic stem cells, endothelial progenitor cells, and mesenchymal stem cells.

Clinical trials evaluating the efficacy of stem-cell therapy for improvement of cardiac function have been conducted mainly on patients with ischemic heart failure, acute myocardial infarction, and coronary artery disease who lack revascularization options. None of these trials have included patients with ESRD (Table 1).

The BOOST (Bone Marrow Transfer to Enhance ST Elevation Infarct Regeneration) trial, a recently conducted randomized clinical trial in patients presenting with acute ST elevation myocardial infarction, reported that BMC transfer resulted in 6% improvement in left ventricular ejection fraction at 6 months, which is equivalent to the additional benefit of percutaneous coronary intervention over thrombolysis. However, the latest long-term follow-up results from BOOST failed to show any additional benefit in left ventricular function at 18 months for treatment as compared with placebo (22). That finding shows that BMC transfer accelerates recovery of left ventricular function, although the benefit may not be sustained in the long term.

A similar trial in patients with acute ST elevation myocardial infarction was conducted by Lunde *et al.* (23). Those authors performed an intracoronary injection of autologous mononuclear BMCs in 47 subjects and studied the impact on global left ventricular

TABLE 1 Clinical trials that have evaluated the efficacy of stem-cell therapy for improvement of cardiac function

	BOOST (22)	*BMCs after AWMI (23)*	*REPAIR-AMI (24)*
Study type	RCT	RCT	RCT
Patients (*n*)	60	100	204
Cells/route	IV BMCs	IC BMCs	IC BMCs
Time after MI (days)	4	4–7	5–7
Endpoint	EF change	EF change	EF change
EF method of measurement	Cardiac MRI	SPECT and echo	LV contrast angiography
Time points	3.5 days, 6 and 18 months	4–7 days, 6 months	5–7 days, 4 months
Change in EF	6 months, 18 months	6 months	4 months
p Value	<0.05, NS	NS (SPECT or echo)	0.05

BOOST = Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration trial; BMCs = bone marrow–derived cells; AWMI = anterior wall myocardial infarction; AMI = acute myocardial infarction; RCT = randomized control trial; IV = intravenous; IC =intracoronary; EF = ejection fraction; MRI = magnetic resonance imaging; SPECT = single-photon emission computed tomography; echo = echocardiogram; LV = left ventricle; NS = nonsignificant.

function. Although this series was small, the results were negative. No significant improvement in left ventricular function as assessed by two-dimensional echocardiography, single-photon emission computed tomography, and cardiac magnetic resonance imaging was detected.

Schachinger and colleagues also recently reported the results of the randomized placebo controlled REPAIR-AMI trial, evaluating the effects of intracoronary administration of autologous progenitor cells after acute myocardial infarction (24). They found that, at 1 year, intracoronary infusion of BMCs was associated with a reduction in the combined clinical endpoint of death, recurrence of myocardial infarction, and any revascularization procedure. A recent study by Assmus and co-workers (25) also reported that intracoronary infusion of progenitor cells is safe and feasible in patients with healed myocardial infarction and is associated with significant improvement in the left ventricular ejection fraction after 3 months.

Thus, these small studies have so far generated some hope for the future management of patients with CHF. But variable results and the preliminary nature of the foregoing research point to a great need for larger trials that can evaluate the safety and efficacy of stem-cell therapy.

Conclusions

The management of CHF is complex, and the therapeutic environment is changing. Major advances have been made that are improving the quality of life and survival of patients with this debilitating and high-mortality disease, but considerable room for improvement remains, particularly in patients with ESRD and CKD. Patients on dialysis are especially vulnerable to the development and exacerbation of CHF. Few agents under study appear to have major beneficial effects in this growing patient population. Cardiologists and nephrologists must work together to improve care in these patients using both current and unconventional approaches.

References

1 American Heart Association. Heart disease and stroke statistics: 2005 update. Dallas, TX: American Heart Association; 2005.
2 Hunt SA, Abraham WT, Chin MH, *et al.* ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2005;112:e154–235.
3 Silverberg D, Wexler D, Blum M, Schwartz D, Iaina A. The association between congestive heart failure and chronic renal disease. Curr Opin Nephrol Hypertens 2004;13:163–70.
4 Avorn J, Bohn RL, Levy E, *et al.* Nephrologist care and mortality in patients with chronic renal insufficiency. Arch Intern Med 2002;162:2002–6.
5 Bongartz LG, Cramer MJ, Doevendans PA, Joles JA, Braam B. The severe cardiorenal syndrome: "Guyton revisited." Eur Heart J 2005;26:11–17.
6 Griendling KK, Minieri CA, Ollerenshaw JD, Alexander RW. Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. Circ Res 1994;74:1141–8.

7 Ortiz PA, Garvin JL. Interaction of O_2^- and NO in the thick ascending limb. Hypertension 2002;39:591–6.
8 Zebrack JS, Anderson JL, Beddhu S, *et al.* Do associations with C-reactive protein and extent of coronary artery disease account for the increased cardiovascular risk of renal insufficiency? J Am Coll Cardiol 2003;42:57–63.
9 The CONSENSUS Trial Study Group (Cooperative North Scandinavian Enalapril Survival Study). Effects of enalapril on mortality in severe congestive heart failure. N Engl J Med 1987;316:1429–35.
10 Chobanian AV, Bakris GL, Black HR, *et al.* The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 2003;289:2560–72.
11 Pitt B, Poole–Wilson PA, Segal R, *et al.* Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. Lancet 2000;355:1582–7.
12 Cice G, Ferrara L, D'Andrea A, *et al.* Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. J Am Coll Cardiol 2003;41:1438–44.
13 Covic A, Gusbeth–Tatomir P, Goldsmith DJ. Is it time for spironolactone therapy in dialysis patients? Nephrol Dial Transplant 2006;21:854–8.
14 Go AS, Yang J, Ackerson LM, *et al.* Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure: the Anemia in Chronic Heart Failure: Outcomes and Resource Utilization (ANCHOR) Study. Circulation 2006;113:2713–23.
15 Singh AK, Szczech L, Tang KL, *et al.* Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355:2085–98.
16 Berger AK, Duval S, Krumholz HM. Aspirin, beta-blocker, and angiotensin-converting enzyme inhibitor therapy in patients with end-stage renal disease and an acute myocardial infarction. J Am Coll Cardiol 2003;42:201–8.
17 Costanzo MR, Saltzberg M, O'Sullivan J, Sobotka P. Early ultrafiltration in patients with decompensated heart failure and diuretic resistance. J Am Coll Cardiol 2005;46:2047–51.
18 Khalifeh N, Vychytil A, Horl WH. The role of peritoneal dialysis in the management of treatment-resistant congestive heart failure: a European perspective. Kidney Int Suppl 2006;70(Suppl 103):S72–5.
19 deGoma EM, Vagelos RH, Fowler MB, Ashley EA. Emerging therapies for the management of decompensated heart failure: from bench to bedside. J Am Coll Cardiol 2006;48:2397–409.
20 Gottlieb SS, Brater DC, Thomas I, *et al.* BG9719 (CVT-124), an A1 adenosine receptor antagonist, protects against the decline in renal function observed with diuretic therapy. Circulation 2002;105:1348–53.
21 Gheorghiade M, Gattis WA, O'Connor CM, *et al.* Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. JAMA 2004;291:1963–71.
22 Meyer GP, Wollert KC, Lotz J, *et al.* Intracoronary bone marrow cell transfer after myocardial infarction: eighteen months' follow-up data from the randomized, controlled BOOST (bone marrow transfer to enhance ST-elevation infarct regeneration) trial. Circulation 2006;113:1287–94.
23 Lunde K, Solheim S, Aakhus S, *et al.* Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. N Engl J Med 2006;355:1199–209.
24 Schachinger V, Erbs S, Elsasser A, *et al.* Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. N Engl J Med 2006;355:1210–21.
25 Assmus B, Honold J, Schachinger V, *et al.* Transcoronary transplantation of progenitor cells after myocardial infarction. N Engl J Med 2006;355:1222–32.

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