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# New approaches to detect and manage edema and renal insufficiency in heart failure

## ■ ABSTRACT

Earlier detection of edema and renal insufficiency, before overt decompensation, is fundamental to further advances in altering the natural history of heart failure. Progress is being made in the earlier detection of these complications through the use of new devices that monitor for hemodynamic compromise and through monitoring of select cardiac and renal biomarkers. In addition, diuretic-sparing approaches to heart failure management, novel drug classes, new devices, and nonpharmacologic therapies are emerging to reduce reliance on diuretic therapy and manage edema with less renal compromise.

## ■ KEY POINTS

Implantable devices are being developed to enable remote monitoring of intracardiac filling pressures and impedance in an effort to better guide outpatient heart failure therapy and avoid edema.

B-type natriuretic peptide, cardiac troponin T, and cystatin C show promise in clinical trials for identifying cardiac and renal distress in heart failure patients prior to organ damage.

As more heart failure patients are managed with neurohormonal antagonists, including the investigational adenosine type 1 receptor antagonists and vasopressin receptor antagonists, discontinuation of chronic diuretic therapy may be increasingly possible.

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**A**LTHOUGH CLINICIANS are increasingly able to reduce mortality and delay disease progression in patients with heart failure, too often these attempts come too late to have an effect. We do not yet fully understand the mechanisms that promote edema and renal insufficiency in heart failure, and we have not had satisfactory methods to proactively detect these complications in heart failure patients. As a result, we often identify patients at risk for edema and renal insufficiency only after these complications have already wreaked havoc on patients' clinical status.

Although diuretic therapy can manage edema and congestion effectively in patients with heart failure, it is commonly associated with renal insufficiency and other adverse effects, as discussed in the previous articles in this supplement.

A key challenge before us is how to identify sooner those heart failure patients who are at risk for edema and renal insufficiency. New devices and the use of biomarkers are showing promise for this purpose. Moreover, new strategies are emerging to more safely manage edema and congestion in heart failure, in the form of new, more kidney-friendly medications as well as devices and even invasive procedures. This article briefly reviews these emerging approaches and the rationale behind their development.

## ■ 'ACUTE' HEART FAILURE IS NOT ALWAYS SO ACUTE

The broad objectives of heart failure therapy are to:

- Alter the natural history of the disease, in terms of reducing mortality and delaying disease progression
- Lessen the disease burden and costs, in terms of improving quality of life, reducing

symptoms and complications, and reducing hospitalizations.

In terms of clinical presentation, acute heart failure is defined as either the new onset (within hours to days) of symptoms of congestion and heart failure, or worsening of the signs and symptoms of previously stable heart failure.

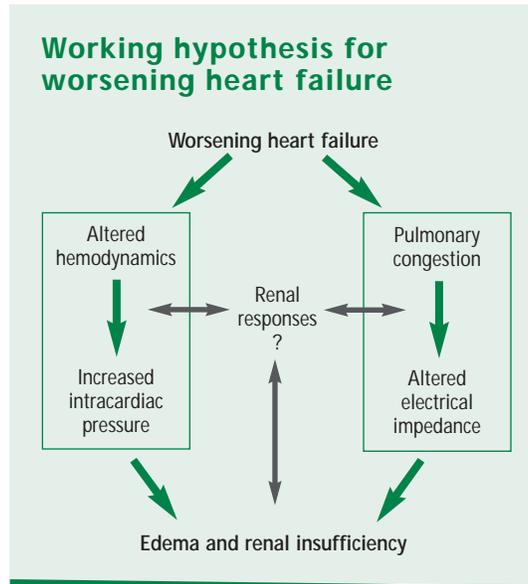
In real-world practice, heart failure often is characterized according to where the patient is seen and treated, with the disease being deemed acute heart failure if we encounter the patient in the hospital. This tendency is unfortunate, since the evolution of fluid retention is not necessarily “acute” and could be detected sooner and managed better if we routinely monitored patients for it in the outpatient setting.

In a questionnaire-based study of 87 consecutive patients hospitalized for heart failure, Schiff and colleagues found that the median duration of symptom worsening (edema, weight gain, dyspnea) was 7 to 12 days prior to hospitalization.<sup>1</sup> They concluded that “there is a time window between symptom exacerbation and admission during which earlier access and intervention might prevent hospitalization.” This is the premise of the many emerging strategies for early detection of edema and renal insufficiency.

**Figure 1** illustrates the working hypothesis of how heart failure worsens during this time window. The worsening is believed to contribute to alteration in hemodynamics, as discussed in the previous articles in this supplement, as well as both pulmonary and peripheral congestion. The ultimate result is edema and renal insufficiency, although the mechanisms of their development are not well understood. At the same time, the physiologic variables involved in their development can be detected in a proactive manner, and emerging devices and techniques are making the detection of these variables increasingly efficient.

#### ■ STRATEGIES FOR EARLIER DETECTION OF DECOMPENSATION

Earlier detection of decompensation, before overt presentation, is fundamental to further advances in altering the natural history of heart failure. Progress in earlier detection has focused on monitoring for hemodynamic



**FIGURE 1.** Progression of heart failure is believed to involve alterations in hemodynamics and pulmonary and peripheral congestion. Edema and renal insufficiency are among the consequences, but their development is not fully understood.

compromise and on monitoring for select biomarkers.

#### Hemodynamic monitoring to guide therapy

There are two main targets in monitoring for hemodynamic compromise: rising intracardiac filling pressures and elevations in intrathoracic fluid volumes (or impedance). The past decade has seen a number of important advances in this area, which are outlined below.

**Measuring intracardiac filling pressures.** The randomized, single-blind COMPASS-HF trial assessed the clinical utility of an implantable hemodynamic device (Chronicle, Medtronic, Inc., Minneapolis, MN) in the management of heart failure. This investigational device allows remote monitoring of right ventricular systolic and diastolic pressure, estimated pulmonary artery pressures, and many other hemodynamic variables.

The study included 274 patients with New York Heart Association (NYHA) class III or IV heart failure. All patients had the device implanted, but data collected by the device were shared with the treating physician to guide therapy for only half of the patients (“full-access” group); the other half (control group) received usual care. The primary end-

The evolution of fluid retention is not necessarily ‘acute’

point was the need for treatment for heart failure decompensation.

Results of the COMPASS-HF trial were presented at the 2005 scientific session of the American College of Cardiology.<sup>2</sup> There was no statistically significant difference in the primary endpoint between the groups at 6 months, but post hoc analysis revealed a significant reduction in heart failure-related hospitalizations in the full-access group compared with the control group (relative risk = 0.79; 95% confidence interval [CI], 0.64 to 0.98;  $P = .029$ ). The benefit in avoiding hospitalization was limited to patients with class III heart failure. Although these post hoc findings must be considered only hypothesis-generating, they suggest considerable promise for the utility of an implantable hemodynamic monitor.

Additional investigational devices for remote hemodynamic monitoring have not yet been assessed in large clinical trials, although studies are planned or under way.

**Impedance cardiography.** Another area of hemodynamic monitoring involves measurement of impedance, or the resistance of tissue to an electrical current. Impedance cardiography is a noninvasive means of obtaining continuous measurements of hemodynamic data based on the notion that variation in the impedance to flow of a high-frequency, low-magnitude alternating current across the thorax generates a measured waveform from which hemodynamic measures can be calculated. Interest has arisen in the use of impedance cardiography to estimate thoracic body fluid status or total fluid volumes.

Several impedance cardiographic monitors are now commercially available, each with its own algorithm. However, a lack of standardized definitions and the many potential confounders have posed challenges to broad application of impedance cardiographic monitoring in the clinical setting.

Promising results for the predictive utility of impedance cardiography in patients with heart failure were reported from the prospective PREDICT study of 212 patients who had had an episode of decompensated heart failure in the preceding 3 months.<sup>3</sup> Every 2 weeks for 6 months, blinded impedance cardiographic and clinical variables were collected from all

patients; the BioZ ICG Monitor (CardioDynamics, San Diego, CA) was used for assessment of impedance. In multivariate regression analysis that included numerous baseline and clinical variables, a composite impedance score emerged as the strongest predictor of a heart failure event (all-cause death or a heart failure-related hospitalization or emergency room visit) in the 14 days after any given study visit ( $P < .0002$ ). Visits at which patients had a high-risk impedance score were 7.7 times more likely to be followed by a heart failure event within 14 days than were visits at which patients had a low-risk impedance score (95% CI, 5.5 to 10.4). This significant predictive ability of impedance cardiography extended to 90 days after a study visit. These preliminary results are the basis of a larger pivotal trial (PREVENT-HF) that is commencing in 2006.

New device-based impedance measurements have provided a more consistent assessment of intrathoracic impedance (InSync Sentry CRT-D, Medtronic, Inc.). In the MID-HeFT study of 33 patients with NYHA class III or IV heart failure, intrathoracic impedance was inversely correlated with pulmonary capillary wedge pressure and fluid balance and decreased up to 1 to 2 weeks prior to hospital admission for fluid overload.<sup>4</sup> **Figure 2** illustrates the algorithm used by the device employed in this study.

In the future, it is conceivable that physicians and patients will be able to monitor fluid status in a manner analogous to self-monitoring of glucose or blood pressure levels. How well impedance data may guide therapy is currently unknown but will be assessed in upcoming trials.

#### Use of biomarkers

The other major front in hastening the detection of impending decompensation involves the use of novel biomarkers to assess cardiac and renal distress prior to organ damage. These biomarkers include those that signify cardiac distress, such as B-type natriuretic peptide (BNP) and troponin, and those that signify renal distress, such as cystatin C.

**BNP** is a polypeptide secreted by the heart's ventricles in response to myocyte

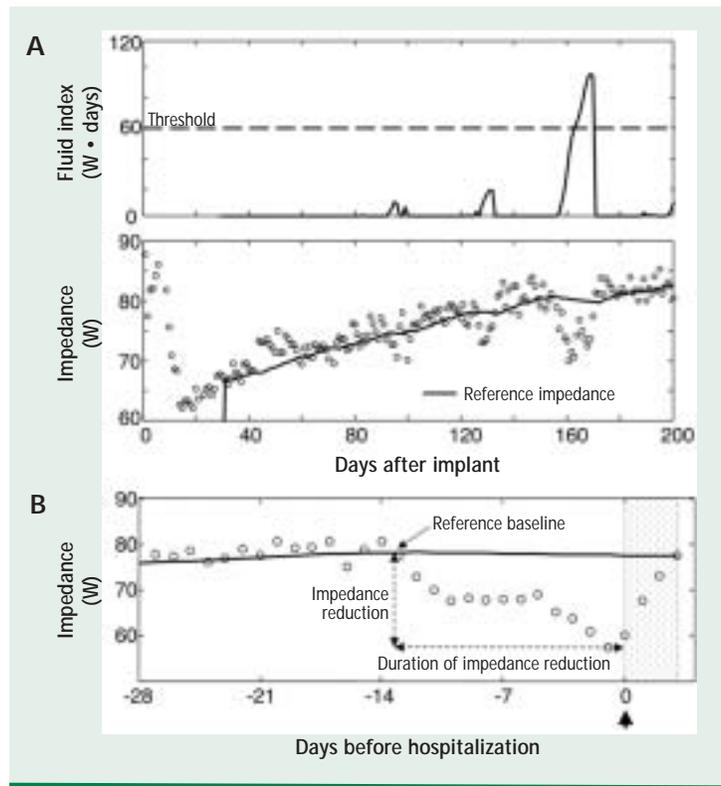
Impedance and hemodynamic monitors may allow proactive monitoring of fluid status

stress. It is a useful cardiac marker in a number of heart failure settings, as it has demonstrated diagnostic utility in acute dyspnea,<sup>5,6</sup> prognostic value in patients with chronic congestive heart failure and systolic dysfunction in the outpatient setting,<sup>7-9</sup> and prognostic value following discharge after hospitalization for severe decompensation.<sup>10</sup>

Interest also has arisen in a potential role for BNP-guided therapy in patients with chronic heart failure. Data from a small preliminary randomized trial showed that BNP-guided treatment of heart failure reduced the incidence of total cardiovascular events and delayed the time to a first event compared with intensive therapy guided by standard clinical assessment.<sup>11</sup> Several large, prospective outcomes trials are now under way or are being planned to further define the potential role of BNP-guided therapy in chronic heart failure.

Although BNP-guided therapy holds promise, it presents several challenges. First, the several BNP assays that are now commercially available show variation in their measurement of absolute BNP levels, with variances of as much as 30 pg/mL between different assays despite similar diagnostic performance.<sup>12</sup> Such variation means that any BNP-guided approach to therapy would have to ensure consistent use of the same assay in all treatment and laboratory settings or the harmonization of values from different assays. Second, there is the potential for confusion, particularly among clinicians, between BNP and the inactive compound N-terminal pro-BNP, levels of which may be much higher than BNP levels without causing concern. Finally, findings from recent small studies indicate that the potential utility of BNP levels in guiding therapy requires further investigation. In a retrospective study of 39 patients with severe heart failure, O'Neill and colleagues found that BNP levels did not accurately or consistently predict serial hemodynamic changes.<sup>13</sup> In a pilot study of 10 men hospitalized for pulmonary catheter-guided treatment of congestive heart failure, James and colleagues found that changes in blood volume do not correlate well with changes in BNP.<sup>14</sup>

**Troponin T** is a protein component of thin myofilaments that is released with



**FIGURE 2.** (A) Operation of an algorithm for detecting decreases in impedance over time. A fluid index (top panel) is calculated from differences between measured impedance (circles) and reference impedance (solid line) accumulated over time (second panel). Threshold is then applied to fluid index to detect sustained decreases in impedance. (B) Example of impedance reduction before heart failure hospitalization (day 0; arrow) for fluid overload and impedance increase during intensive diuresis during hospitalization (shaded portion). Reprinted, with permission, from reference 4.

myocyte damage. In addition to utility for the diagnosis of coronary artery disease and myocardial infarction, cardiac troponin T levels have been shown to predict prognosis in patients with decompensated heart failure. In a study of 84 patients with acute cardiogenic pulmonary edema, Perna and colleagues found that a troponin T level of 0.1 ng/mL or greater was associated with a significant reduction in 3-year survival (29% vs 76% in patients with levels < 0.1 ng/mL;  $P < .001$ ) and was a powerful independent predictor of mortality.<sup>15</sup> The mechanism of troponin T elevation in this setting is not well understood, and further studies are needed to better define both its specific clinical utility in this context and the variations among different commercially available assays observed specifically in the setting of heart failure.

**Cystatin C** is a novel marker of glomerular filtration rate whose emergence in the heart failure literature underscores the interrelationship between the kidney and the heart in heart failure progression. Cystatin C is a cysteine protease inhibitor that is produced by all nucleated cells. Its production is stable and serum levels are independent of body mass. Unlike creatinine, cystatin C is not cleared; it is freely filtered by the glomerular membrane and then metabolized by the kidneys.

An elevation in serum cystatin C has been shown to be an independent predictor of cardiac events in patients with heart failure.<sup>16</sup> In fact, the Cardiovascular Heart Study has demonstrated that cystatin C is superior to creatinine both in predicting incident heart failure in the elderly and in predicting mortality in elderly patients with heart failure.<sup>17,18</sup> Although the mechanism by which cystatin C predicts risk for heart failure or progression of heart failure is unclear, this biomarker holds considerable promise for improving risk stratification and guiding therapy.

**Cystatin C is superior to creatinine in predicting mortality in heart failure**

#### ■ IMPROVING STRATEGIES TO LIMIT CARDIORENAL COMPROMISE

In addition to earlier detection of decompensation, other approaches and therapies are emerging to help us avert or better manage edema and renal insufficiency in heart failure.

##### Diuretic-sparing strategy

The previous articles in this supplement have detailed the rationale for diuretic therapy in heart failure as well as the adverse effects, both electrolytic and metabolic, of diuretic therapy in this setting. Most concerning is the finding that chronic therapy with a non-potassium-sparing diuretic raises the risk of arrhythmic death and all-cause death in patients with heart failure, as demonstrated in the SOLVD database<sup>19</sup> and other heart failure data sets.<sup>20</sup>

Although these analyses did not show such an increase with the use of potassium-sparing diuretics,<sup>19,20</sup> they underscore whether it might make sense to forgo diuretic therapy in some patients to reduce their risk of developing renal dysfunction. More than a decade ago, Grinstead and colleagues demonstrated that diuretic therapy can be safely discontinued in approximately 30% of patients with stable

heart failure.<sup>21</sup> As more and more patients are managed with neurohormonal antagonists, this “peeling off” of chronic diuretic therapy may be increasingly worthy of consideration.

##### New drug classes

A diuretic-sparing approach is likely to be more feasible as additional drug classes emerge. Two novel classes have shown recent progress in development for heart failure management.

**Adenosine type 1 (A<sub>1</sub>) receptor antagonists** promote excretion of excess fluid and sodium in animals and humans without major changes in glomerular filtration. These effects have been confirmed in patients with congestive heart failure.<sup>22</sup> Several A<sub>1</sub> receptor antagonists are in development for various indications (including KW-3902, from NovaCardia, Inc.; and BG-9928, from Biogen Idec), with several clinical trials under way for their use in heart failure.

**Vasopressin receptor antagonists.** Development of vasopressin receptor antagonists was prompted by the realization that levels of arginine vasopressin are elevated in heart failure and are believed to result in myocardial hypertrophy and vasoconstriction as well as water retention and hyponatremia. These agents offer the promise of preventing left ventricular dysfunction while also yielding an acute improvement in congestion and hyponatremia. As detailed by Gheorghide later in this supplement,<sup>23</sup> a number of trials of vasopressin receptor antagonists in heart failure have been reported or are under way.

##### New devices and nondrug interventions

The most important nonpharmacologic advances in managing edema and renal insufficiency include ultrafiltration and targeted renal therapy, which were detailed by Francis earlier in this supplement.<sup>24</sup> In addition, highly invasive modalities such as continuous aortic flow augmentation<sup>25</sup> are being investigated for use in the intensive care unit for patients with severely acute decompensation and other complications.

#### ■ SUMMARY

Current strategies that aim to “salvage” deteriorating clinical status in patients with heart failure are inadequate, largely because

we do not understand the optimal targets of therapy and we have not had effective ways to proactively detect edema and renal insufficiency. New devices and the use of biomarkers show promise, however, for improving our ability to monitor for and

avert edema and renal insufficiency. Simultaneously, novel drug classes and emerging nonpharmacologic therapies offer the potential to reduce the use of diuretic therapy and manage heart failure with less renal compromise.

## ■ REFERENCES

- Schiff GD, Fung S, Speroff T, McNutt RA. Decompensated heart failure: symptoms, patterns of onset, and contributing factors. *Am J Med* 2003; 114:625–630.
- Bourge RC, Abraham WT, Aaron MF, et al, for the COMPASS Investigators and Coordinators. Chronicle Offers Management with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF): ambulatory hemodynamic guided management of heart failure [abstract]. Program and abstracts of the American College of Cardiology Annual Scientific Session 2005; March 6–9, 2005; Orlando, FL. Late-breaking Clinical Trials II.
- Abraham WT, Trupp RJ, Mehra MR, et al, for the PREDICT Investigators. Prospective Evaluation of Cardiac Decompensation with Heart Failure by Impedance Cardiography Test: the PREDICT multicenter trial [abstract]. *Circulation* 2004; 110(Suppl III):III-597. Abstract 2775.
- Yu C-M, Wang L, Chau E, et al. Intrathoracic impedance monitoring in patients with heart failure: correlation with fluid status and feasibility of early warning preceding hospitalization. *Circulation* 2005; 112:841–848.
- Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002; 347:161–167.
- Logeart D, Saudubray C, Beyne P, et al. Comparative value of Doppler echocardiography and B-type natriuretic peptide assay in the etiologic diagnosis of acute dyspnea. *J Am Coll Cardiol* 2002; 40:1794–1800.
- Tsutamoto T, Wada A, Maeda K, et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. *Circulation* 1997; 96:509–516.
- Koglin J, Pehlivanli S, Schwaiblmair M, et al. Role of brain natriuretic peptide in risk stratification of patients with congestive heart failure. *J Am Coll Cardiol* 2001; 38:1934–1941.
- Berger R, Huelsman M, Strecker K, et al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. *Circulation* 2002; 105:2392–2397.
- Logeart D, Thabut G, Jourdain P, et al. Predischarge B-type natriuretic peptide assay for identifying patients at high risk of readmission after decompensated heart failure. *J Am Coll Cardiol* 2004; 43:635–641.
- Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* 2000; 355:1126–1130.
- Rawlins ML, Owen WE, Roberts WL. Performance characteristics of four automated natriuretic peptide assays. *Am J Clin Pathol* 2005; 123:439–445.
- O'Neill JO, Bott-Silverman CE, McRae AT 3rd, et al. B-type natriuretic peptide levels are not a surrogate marker for invasive hemodynamics during management of patients with severe heart failure. *Am Heart J* 2005; 149:363–369.
- James KB, Troughton RW, Feldschuh J, Soltis D, Thomas D, Fouad-Tarazi F. Blood volume and brain natriuretic peptide in congestive heart failure: a pilot study. *Am Heart J* 2005; 150:984e1–984e6.
- Perna ER, Macin SM, Parras JI, et al. Cardiac troponin T levels are associated with poor short- and long-term prognosis in patients with acute cardiogenic pulmonary edema. *Am Heart J* 2002; 143:814–820.
- Arimoto T, Takeishi Y, Niizeki T, et al. Cystatin C, a novel measure of renal function, is an independent predictor of cardiac events in patients with heart failure. *J Card Fail* 2005; 11:595–601.
- Sarnak MJ, Katz R, Stehman-Breen CO, et al. Cystatin C concentration as a risk factor for heart failure in older adults. *Ann Intern Med* 2005; 142:497–505.
- Shlipak MG, Katz R, Fried LF, et al. Cystatin-C and mortality in elderly persons with heart failure. *J Am Coll Cardiol* 2005; 45:268–271.
- Domanski M, Norman J, Pitt B, et al. Diuretic use, progressive heart failure, and death in patients in the Studies Of Left Ventricular dysfunction (SOLVD). *J Am Coll Cardiol* 2003; 42:705–708.
- Cooper HA, Dries DL, Davis CE, Shen YL, Domanski MJ. Diuretics and risk of arrhythmic death in patients with left ventricular dysfunction. *Circulation* 1999; 100:1311–1315.
- Grinstead WC, Francis MJ, Marks GF, Tawa CB, Zoghbi WA, Young JB. Discontinuation of chronic diuretic therapy in stable congestive heart failure secondary to coronary artery disease or to idiopathic dilated cardiomyopathy. *Am J Cardiol* 1994; 73:881–886.
- 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; 105:1348–1353.
- Gheorghide M. The clinical effects of vasopressin receptor antagonists in heart failure. *Cleve Clin J Med* 2006; 73(Suppl 2):S24–S29.
- Francis G. Acute decompensated heart failure: the cardiorenal syndrome. *Cleve Clin J Med* 2006; 73(Suppl 2): S8–S13.
- Konstam MA, Czernska B, Bohm M, et al. Continuous aortic flow augmentation: a pilot study of hemodynamic and renal responses to a novel percutaneous intervention in decompensated heart failure. *Circulation* 2005; 112:3107–3114.

'Peeling off' chronic diuretic therapy may be increasingly worth considering

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