Review

Devices in Heart Failure

Potential Methods for Device-Based Monitoring of Congestive Heart Failure

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Congestive heart failure has long been one of the most serious medical conditions in the United States; in fact, in the United States alone, heart failure accounts for 6.5 million days of hospitalization each year. One important goal of heart-failure therapy is to inhibit the progression of congestive heart failure through pharmacologic and device-based therapies. Therefore, there have been efforts to develop device-based therapies aimed at improving cardiac reserve and optimizing pump function to meet metabolic requirements. The course of congestive heart failure is often worsened by other conditions, including new-onset arrhythmias, ischemia and infarction, valvulopathy, decompensation, end-organ damage, and therapeutic refractoriness, that have an impact on outcomes. The onset of such conditions is sometimes heralded by subtle pathophysiologic changes, and the timely identification of these changes may promote the use of preventive measures. Consequently, device-based methods could in the future have an important role in the timely identification of the subtle pathophysiologic changes associated with congestive heart failure. ***(Tex Heart Inst J 2008;35(2):166-73)***

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Congestive heart failure (CHF), long one of the nation's most serious medical problems, contributes to approximately 250,000 deaths each year. About 2% of the total population has CHF, and it accounts for about $20 billion annually in health-care expenses. In the United States alone, heart failure accounts for 6.5 million days of hospitalization annually.[1,2] The mean length of hospital stay for a CHF-related admission is approximately 14 days.[1]

One important goal of heart-failure therapy is to inhibit the progression of CHF through pharmacologic and device-based therapies. Accordingly, there have been intensive efforts to develop device-based therapies aimed at improving cardiac reserve and optimizing pump function to meet metabolic requirements. The fairly indolent course of CHF is often worsened by overriding perturbations, including new-onset arrhythmias, ischemia and infarction, valvulopathy, decompensation, end-organ damage, and therapeutic refractoriness, which have an impact on outcomes. For example, mortality rates are 34% higher in CHF patients who have atrial fibrillation than in patients who have CHF alone.[3]

The onset of conditions known to worsen patients' prognoses is sometimes heralded by subtle pathophysiologic changes. The timely identification of such changes can enable preventive measures, and device-based methods should have an important role in this process.

The purpose of the present review is to survey the pathophysiologic processes that can now be monitored by mechanical devices and to provide information about predicting the onset of a condition that can aggravate CHF. In the interest of brevity (in dealing with a vast subject), we will discuss only those select pathologic conditions that occur frequently in CHF patients and adversely affect outcomes. Table I provides a summary of devices and procedures that have the potential of predicting these adverse events.

New-Onset Atrial Fibrillation

Atrial fibrillation (AF) and CHF tend to coexist, and the prevalence of AF increases in parallel with the severity of CHF.[4] Atrial fibrillation may affect as few as 5% of CHF patients with mild disease[3] and as many as 50% with New York Heart Association (NYHA) functional class IV symptoms.[5] In a study of 1,470 Framingham participants who developed AF, CHF, or both, 382 (26%) developed both, and 41% of that number had CHF first.[6] These statistics correlate with reports of AF prevalence published elsewhere.[7] Although some studies have shown variability in the asso-

TABLE I. Devices in Heart Failure

Condition	Device or Procedure	How Future Events Are Predicted
Atrial fibrillation	Periodic 2D echocardiography	Measures increased atrial diameter (>40 mm), low left ventricular fractional shortening, left ventricular wall thickness
Right ventricular dysfunction	Periodic 2D echocardiography	Measures RVWT ≥0.8 mm, RVEDD >6 mm, TAPSE <1.6 mm, PAAT/CL ratio <0.08
Nonischemic cardiomyopathy	Electrical impedance spectroscopy	Measures changes in myocardial resistance secondary to ischemia
	Intracardiac electrocardiography	Measures changes in myocardial resistance secondary to ischemia
CAD/ischemia	Peak endocardial acceleration	Measures changes in myocardial resistance secondary to ischemia
	Coronary sinus thermometry	May show increased coronary sinus temperature with ischemic/obstructive CAD
	Ballistocardiography	Noninvasively records the stroke volume of the heart for calculating cardiac output
	Seismocardiography	Noninvasively records cardiac vibrations and measures acute and chronic changes in left ventricular function
	Strain-rate imaging	Measures the timing and extent of myocardial deformation and provides more reliable information about the sequence of myocardial contraction in the presence of delayed electrical activation
Cardiac decompensation	Noninvasive impedance cardiography	Measures TFC and changes in thoracic electrical impedance as a consequence of TFC
	OptiVol®	Monitors thoracic impedance through biventricular pacemaker electrodes and gives a general indication of the fluid balance of patients; helpful in predicting impending volume overload
	HeartPOD™	Measures left atrial pressures and provides an indirect estimate of PCWP in impending decompensation
	Hypothermia	May serve as a univariate predictor of in-hospital death in patients with CHF decompensation and may also serve to predict CHF decompensation
	Chronicle®	Measures right ventricular pressures and estimated pulmonary artery diastolic pressure through a lead implanted in the right ventricular outflow tract
Sudden cardiac death	Implantable defibrillators	Primary and secondary prevention
	Signal-averaged electrocardiography	Risk stratification
	T-wave alternans	Risk stratification
	Heart rate variability	Risk stratification

CAD = coronary artery disease; CHF = congestive heart failure; PAAT/CL = pulmonary artery acceleration time/cycle length; PCWP = pulmonary capillary wedge pressure; RVEDD = right ventricular end-diastolic dimension; RVWT = right ventricular free-wall thickness; SCD = sudden cardiac death; TAPSE = tricuspid excursion; TFC = thoracic fluid content; 2-D = 2-dimensional

ciation between AF and increased death, other studies have shown that AF plays an important role in predicting death.[8,9] The impact of AF on CHF death (Fig. 1) is particularly significant if the CHF is mild[10] or if cardiac decompensation is present.[11]

The development of AF in CHF patients can be explained by impaired hemodynamics, an altered neurohumoral state, and an acute rise in atrial pressure, all of which promote electrical and structural remodeling and elicit mechanoelectrical feedback within the

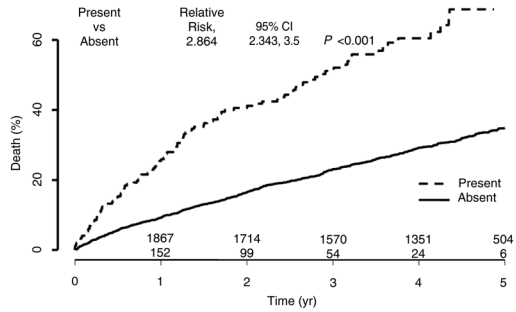

Fig. 1 *New-onset atrial fibrillation is associated with increased risk of death in congestive heart failure. (Reprinted with permission from Swedberg K, Olsson LG, Charlesworth A, Cleland J, Hanrath P, Komajda M, et al. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. Eur Heart J 2005; 26[13]:1303-8.)*

atria.[12,13] Structural remodeling, including fibrosis and dilatation, is, at some level, mediated by humoral factors such as angiotensin.[10] Potent profibrotic molecules such as angiotensin II, which circulate abundantly in the bloodstreams of CHF patients, promote the dispersion of atrial impulse conduction and re-entry by altering the atrial ultrastructure.[14]

In a prospective study conducted in Framingham participants to determine which impaired mechanics of cardiac activity lead to AF, an analysis of echocardiographic data showed that increased atrial diameter, increased left ventricular wall thickness, and low left ventricular fractional shortening were predictive of AF.[15] The study's conclusions, however, were reached on the basis of periodic echocardiographic measurements and lacked information on serial changes in the described echocardiographic values. Therefore, the study was inconclusive in describing rates of change and cut-off points in the echocardiographic measurements of interest. However, others have shown that left atrial diameters >40 mm are indeed associated with increased risk of AF.[16]

It should be noted that cardiac biometry varies with an individual's height; therefore, in clinical practice, it may not be feasible to apply cut-off points. Rates of change in variables that one predictive of future AF may be a more effective indication and afford a better standard. Measurement of such variables and their rates of change could be achieved with continuous monitoring devices, which could prove useful in the early identification of high-risk patients.

New-Onset Right Ventricular Dysfunction

Right ventricular dysfunction may constitute the "common final pathway" in the progression of CHF.[17] However, there are no clear data to describe the epidemiology and pathophysiology of right ventricular dysfunction and how it complicates the prognoses of patients with pre-existing left ventricular dysfunction. Inferences can be made from studies that recruited patients with isolated left ventricular dysfunction, in whom right ventricular dysfunction could develop as their disease progressed.[18] The anatomically united ventricles exhibit mechanical coupling, in which the performance of one ventricle has an effect on the other. This mechanical interdependence is another means by which a pathologic process can be diffused.[19,20]

A study by Mariano-Goulart and associates[21] determined that there is a correlation between high levels of brain natriuretic peptide and right ventricular dysfunction. That study compared plasma brain natriuretic peptide (BNP) levels in patients who had isolated left ventricular dysfunction with levels in patients who had biventricular dysfunction and found that right-sided heart failure contributed substantially to the elevation of BNP. The authors concluded that important BNP increases in patients with "isolated" left ventricular dysfunction should indicate a high risk of right ventricular dysfunction. From the results of another study, by Ahmed and colleagues,[22] it may be inferred that approximately 35% of CHF patients have isolated left ventricular dysfunction. Therefore, a fairly large population of patients with lone left-sided failure may eventually develop right ventricular dysfunction during the course of their disease.

Other studies of the prognostic impact of right ventricular dysfunction reveal its importance in predicting functional capacity and short-term outcomes in CHF patients.[23-27] In a prospective study of the role of right ventricular ejection fraction (RVEF) in predicting short-term outcomes in 142 ambulatory patients who were awaiting cardiac transplantation, an RVEF <24% was found to be predictive of a greater death rate.[28] In addition, survival and symptoms are worse in patients with dilated cardiomyopathy and biventricular failure than in patients whose RVEF is close to normal (>35%).[25] In another study, RVEF together with NYHA classification and functional capacity were predictive of survival in patients with mild-to-moderate CHF symptoms.[23] Right ventricular function remains important in predicting functional capacity and short-term outcomes, particularly in very ill patients for whom the left ventricular ejection fraction (LVEF) is not as reliable for predicting those same outcomes (Fig. 2). The evaluation of right ventricular systolic and diastolic function provides complementary information, with a very high power to stratify the prognoses of patients with heart failure.[26]

Despite its powerful prognostic implications, the right ventricle is not as well studied as the left.[17] Data on right ventricular pathophysiology have been drawn from animal models of right ventricular dysfunction. Hardziyenka and coworkers[24] studied the progressive changes in selected echocardiographic variables that preceded

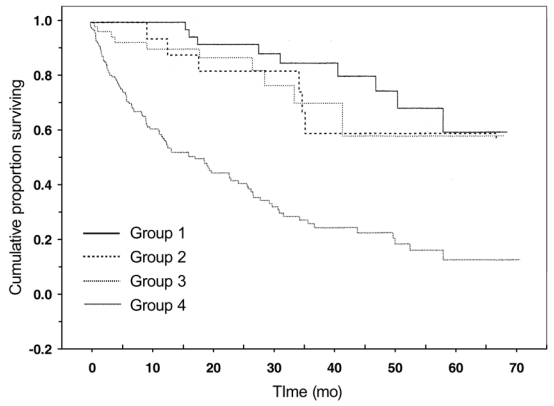

Fig. 2 *Right ventricular dysfunction in congestive heart failure. Group 4 = depressed right ventricular ejection fraction (RVEF) and elevated pulmonary arterial pressure (PAP). Group 1 = preserved RVEF and normal PAP. Groups 2 and 3 = at least one factor (RVEF or PAP) is impaired. (Reprinted with permission from Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol 2001;37[1]:183-8.)*

right-sided heart failure in rats. All variables deteriorated progressively: right ventricular free-wall thickness, ≥0.8 mm; right ventricular end-diastolic diameter, >6 mm; tricuspid excursion, <1.6 mm; and pulmonary artery acceleration time normalized to cycle length (PAAT/CL ratio), <0.08. Interestingly, the deterioration preceded the development of overt right-sided heart failure and followed a distinct temporal sequence. The investigators concluded that these variables were useful in predicting the onset of right ventricular failure in rats and that their applicability to human beings should be investigated.[24]

These methods and variables may be used for device-based monitoring that could facilitate the prediction of right ventricular dysfunction before the onset of overt right-sided heart failure in patients with pre-existing disease.

New-Onset Ischemia in Nonischemic Congestive Heart Failure

There is a distinct paucity of data on the incidence of new-onset coronary artery disease in patients who already have a diagnosis of nonischemic CHF. Coronary artery disease (CAD) is a real and possibly under-recognized phenomenon in nonischemic CHF. For heart-failure patients in whom the ischemic portion of the disease has escaped notice, there is risk of future ischemia and infarction. The risks of ischemic complications in these patients and the affect on outcomes are unknown,[29] as is the contribution of CHF to atherogenesis and CAD. Vague estimates of the incidence of ischemia and infarction in nonischemic CHF patients may be made on the basis of data available from some clinical trials.[30,31] However, these estimates have inherent limitations—mainly that the diagnostic methods used in classifying CHF populations into ischemic and nonischemic subgroups yield high numbers of false positives for ischemia.[32] In addition, an ischemic episode can appear to be sudden cardiac death (SCD) in the already-weakened heart. In such cases, a diagnosis is made only at autopsy, which is not routinely performed. In a search of the medical literature, we found no studies other than clinical trials that provided data on the epidemiology of new-onset CAD in nonischemic CHF patients. The manifestation rate of CAD averaged 7% to 12% per lesion per year.[33,34]

Although devices that detect electrical and mechanical changes in the heart may show the presence of ischemia, there are other potential detection methods for use in implantable devices. Electrical impedance spectroscopy, for example, measures changes in myocardial resistance that are secondary to ischemia. This method has been used in the diagnosis of several diseases, including breast cancer, cervical cancer, and tumors of the urothelium, in addition to myocardial ischemia.[35] Repolarization abnormalities are also often used for diagnosing ischemia, and these changes are measurable through intracardiac and intracoronary approaches. Intracardiac electrocardiography (ECG) has been found to be more sensitive than surface ECG and to show ischemic responses earlier, even in the presence of intraventricular conduction delays (for example, left bundle-branch block).[36] Electrocardiography performed with electrodes placed within the coronary arteries also provides increased sensitivity and specificity.[37] Other methods of detecting ischemia include peak endocardial acceleration measurement, coronary sinus thermometry, ballistocardiography, seismocardiography, and strain-rate imaging.[38-42]

Guidelines for the clinical monitoring of CAD are well defined in the medical literature. At the same time, considerable work is being done to decrease morbidity and death associated with ischemia. Real-time, device-based monitoring, although not routinely used, may be beneficial in high-risk patients, particularly those whose hearts are already compromised and least able to sustain a superimposed myocardial insult.

Decompensation

Cardiac decompensation is a "period of broken compensation" associated with "embarrassed circulation"[43] and characterized by reduced cardiac output, hypoperfusion, tissue congestion, and an increased pulmonary capillary wedge pressure. Numerous precipitating factors may worsen cardiac function and volume status, resulting in an episode of acute decompensation.[44] However, a large number of decompensation cases (up to 34%) occur in the absence of identifiable precipitating factors.[45,46] Outcomes after hospitalization for de-

compensation are poor: mortality rates are 37% for men and 30% for women after 1 year of follow-up.[47] Rates of rehospitalization range from approximately 30% within 60 days after discharge[45] to 44% at 6 months.[48]

The period between symptom onset and hospitalization is usually characterized by a gradual deterioration, which may be as short as 3 days among elderly patients[49] or as long as 2 weeks among younger patients.[50] This period could provide an important "window" for monitoring values that are predictive of decompensation, and the development of mechanical devices that are capable of such monitoring could lead to improved outcomes. Noninvasive impedance cardiography uses changes in thoracic electrical impedance to measure thoracic fluid content,[51] and studies have shown that this technology is effective in predicting the increased near-term (14-day) risk of recurrent decompensation, impending hospitalization, or SCD.[52] OptiVol® (Medtronic, Inc.; Minneapolis, Minn), a system used in conjunction with biventricular pacemakers, monitors thoracic impedance through pacemaker electrodes; it is currently being tested in clinical trials (MiD-HeFT and FAST). The HeartPOD™ can be percutaneously implanted inside the left atrium, where it directly measures left atrial pressures and can monitor impending decompensation as signaled by rapid increases in pulmonary capillary wedge pressure and left atrial pressure. It can also provide information about the appropriate titration of medications until left atrial pressures are optimized.[53] The device is currently being investigated in a clinical trial (HOMEOSTASIS) that is aimed at showing the efficacy of frequent-dose titration on the basis of left atrial pressure variation.

Low body temperature is a novel indicator of poor prognosis in CHF patients. Our team has shown that low body temperature is a univariate predictor of in-hospital death in patients with decompensation.[54] The prognostic role of body temperature in predicting death in CHF patients has been published elsewhere.[48] Extensive work is now being done to identify the predictive role of low body temperature in various clinical settings. Data have shown that CHF patients who experience a decrease in body temperature over time require rehospitalization.[55] On the basis of existing data and ongoing work, body-temperature monitoring may gain acceptance as an inexpensive but sensitive method for device-based monitoring in CHF patients.

The Chronicle® (Medtronic) is an implantable device that is programmed to measure right ventricular pressures and to estimate pulmonary artery diastolic pressure through a lead implanted in the right ventricular outflow tract.[56] Results from initial studies are encouraging.[57] Right ventricular hemodynamic monitoring with Chronicle® modestly reduced CHF-related events by 22% (P=NS). A subset of CHF patients with NYHA functional class III symptoms benefited most from Chronicle®, with a 41% reduction in CHF-related events (P <0.05).[58]

Acute decompensation in CHF is a life-threatening condition. Although our ability to predict future decompensation in patients is limited, the use of some mechanical devices for measuring certain physiologic variables may prove invaluable for predicting which patients are most at risk in the near-term.

Sudden Cardiac Death

Sudden cardiac death accounts for 300,000 to 400,000 deaths in the United States each year.[59] A large number of deaths in CHF patients can be attributed to SCD (almost 30% in dilated cardiomyopathy).[60] In a study of more than 3,000 consecutive patients who underwent cardiopulmonary resuscitation for SCD, the survival rate was 1.4% until hospital discharge.[61] In addition, up to 80% of SCD survivors may have anoxic encephalopathy.

The advent of implantable cardioverter-defibrillators (ICDs) has had a beneficial effect on outcomes. Several clinical trials have shown improved freedom from all-cause mortality after ICD implantation.[62] In the Multicenter Automatic Defibrillator Implantation Trial (MADIT), there was a 56% reduction in death among patients who had an ICD.[63]

Two noninvasive electrocardiographic tools are being used clinically for identifying patients at risk of SCD: signal-averaged electrocardiography and T-wave alternans (Fig. 3).[64]

One measurable mechanism for possible device-based monitoring is a reduction in heart rate variability, in response to alterations in autonomic tone. Heart rate variability is studied by time-domain or frequency-

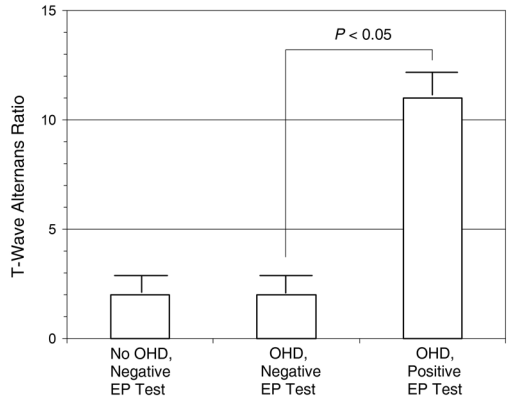

Fig. 3 *Significantly elevated T-wave alternans ratios in patients susceptible to inducible ventricular arrhythmias. (Reprinted with permission from Rosenbaum DS, Jackson LE, Smith JM, Garan H, Ruskin JN, Cohen RJ. Electrical alternans and vulnerability to ventricular arrhythmias. N Engl J Med 1994;330[4]:235-41.)*

OHD = organic heart disease; EP Test = electrophysiologic stimulation of arrhythmias

domain analysis. Vagal tone on the heart can be measured by indices of heart rate variability that are derived by frequency-domain analysis—that is, low-frequency and high-frequency power domains. The frequency domains may then be used in the diagnosis of reduced vagal tone or increased sympathetic tone on the heart, both of which are arrhythmogenic disorders.[65] Heart rate variability must be considered with the absolute values of both low and high frequency to determine what factor contributes to the autonomic misbalance and potential arrhythmogenesis.

Conclusions

Despite advances in the management of CHF patients, clinical practice still lacks the monitoring and diagnostic methods that have substantial specificity and sensitivity: for example, acute decompensated heart failure is still diagnosed by physical examination. Optimal management of CHF would reduce death and morbidity, but such management requires close monitoring of CHF patients, with the objective of preventing the conditions known to affect outcomes adversely. The development of devices designed to predict complications by measuring the subtle pathophysiologic processes involved in CHF may provide the foundation for future monitoring and diagnostic methods.

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