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Implantable Cardiovascular Sensors and Computers: Interventional Heart Failure Strategies

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Abstract

Despite evidence-based medical and pharmacologic advances the management of heart failure remains challenging, whether in the ambulatory setting where daily weight monitoring has failed, or in the inpatient setting where readmission rates and morbidity remains high. There is an urgent need to develop strategies to reduce hospitalizations and readmission rates for heart failure in general. There may be a shift in the paradigm with respect to the treatment of heart failure, which may usher in an era of invasive heart failure therapies and specialists. Experimental invasive devices and monitors have the potential to be game-changing therapies, and cardiac resynchronization therapy has evolved beyond just resynchronization and has the potential to provide important real-time hemodynamic feedback.

Keywords

Heart failure; Hemodynamic monitoring; Cardiac resynchronization; Cardiac contractility modulation; Baroreceptors activation therapy; Impedance monitoring; Implantable cardiovascular sensors and computers

Introduction

Clinical management to prevent acute decompensation and/or hospital admission in the ambulatory heart failure (HF) population remains challenging. Despite current treatments and disease management approaches, rates of hospitalization for heart failure have improved little. Using recent Medicare administrative data, the unadjusted all-cause 30-day readmission rate is approximately 23 % [1], and among beneficiaries of Medicare, 27 % of discharged patients with HF are readmitted to the hospital within 30 days [2]. Hospital discharges for HF have remained essentially unchanged from 1997 to 2007 (966,000 and 990,000, respectively). Data from ambulatory medical utilization estimates for 2007 showed that the number of visits for HF was 3,434,000 [3]. Improvements in outpatient management of patients with chronic HF are needed to address the increasing burden of worsening HF that requires hospitalization. Frequent monitoring of these high risk patients is imperative,

and with the development of wireless and remote technology, sometimes by invasive means, regular monitoring is now possible. The purpose of this review is to highlight new and safe invasive technologies to monitor and to manage our ever-growing HF population.

Rationale for an Invasive Approach

There has been increased interest recently incorporating noninvasive telemonitoring into the ambulatory setting to assist in the management of advanced HF. Obviously this is an attractive approach for patients as it spares them from an invasive procedure. Unfortunately, this approach has yielded inconsistent results, and thus invasive strategies are now being viewed as a more viable option. With respect to the noninvasive approach, a recent large meta analysis examining randomized control trials (RCT) and observational cohort studies suggested there may be a role for remote telemonitoring for reducing death, hospitalizations, and hospitalizations for heart failure, with a 17 % and 47 % reduction in the risk of death for RCT and cohort studies respectively [4]. But 2 recent prospective RCT contradict these findings. Telemonitoring by means of a telephone-based interactive voice-response system that collected daily information about symptoms and weight that was reviewed by the patients' clinicians demonstrated no significant difference regarding readmission or death at 180 days for any cause, and the secondary endpoints of hospitalizations for HF, number of days in the hospital, and number of hospitalizations did not reach statistical significance [5]. European studies have not been able to show a benefit with remote noninvasive monitoring either [6]. The failure of these noninvasive approaches to telemonitoring in HF may be the insensitivity of the parameters measured for predicting worsening HF, in particular, the sensitivity of daily weight monitoring for predicting HF hospitalization is on the order of 20 % [7, 8]. In addition, worsening of HF symptoms may occur late in the course of decompensation leading to hospitalization [9], limiting the opportunity to respond to these changes on an outpatient basis. Often over-looked is the overall poor patient adherence to noninvasive remote monitoring systems which may also limit their utility [5]. At this time the exact role of noninvasive telemonitoring remains undefined and as a standalone strategy may be insufficient for improving outcomes [10].

Implantable Hemodynamic Monitoring and Other Interventional Approaches to Heart Failure Management

An alternative approach to monitoring the status of ambulatory HF patients and preventing potential hospitalizations may involve implantable devices capable of providing real time hemodynamic data to the clinician. There are several different devices that have the capability of providing clinical information. Several trials have evaluated a variety of parameters to assess filling pressures directly in an ambulatory setting; these investigational devices include right ventricular (RV), pulmonary artery (PA), and left atrial pressure (LAP) sensors. Also on the horizon are new exciting therapeutic technologies such as Cardiac Contractility Modulation (CCM) and Baroreflex Activation Therapy (BAT). Finally, some devices combine therapy delivery with monitoring technologies including the diagnostic features found in implantable cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillator (ICD) devices, which may add modest value to monitoring of symptoms and daily weight alone.

RV Sensors

It has been demonstrated that estimating pulmonary artery end-diastolic pressure (ePADP) using micromanometers in the RV and pulmonary artery is safe and feasible [11]. RV pressure at the time of pulmonary valve opening was equal to ePADP. With the ability to estimate the ePADP from the RV being demonstrated, a multicenter, prospective,

nonrandomized study using a long-term implantable device designed to record ongoing RV pressures, heart rate (HR), and pressure derivatives was conducted. The implantation procedure was similar to a single lead permanent pacemaker system. The device continuously measured RV systolic and diastolic pressures (RVSP and RVDP), ePADP, dP/dt, HR, activity, and temperature. Thirty two patients with New York Heart Association (NYHA) class II-III HF received the device. RVSP increases occurred on average 4 ± 2 days before the exacerbations requiring hospitalization. Hospitalizations before using the device data for clinical management averaged 1.08 per patient-year and decreased to 0.47 per patient-year after hemodynamic data were used [12]. Using the same implantable RV sensor, a prospective, multicenter, randomized, single-blind trial was conducted and enrolled patients with NYHA class III or IV HF. This study, however, did not find a significant difference in the primary efficacy endpoint of reduction in HF events (defined as hospitalizations, emergency or urgent care visits requiring intravenous therapy) with a 21 % reduction in the RV sensor group compared with the control [13]. These early studies nevertheless laid the foundation for exploring invasive means to manage HF patients.

LAP Sensors

Ambulatory monitoring of direct LAP with an investigational implantable device has been shown to be well tolerated, feasible, and accurate during short and long-term follow-up [14, 15]. The LAP monitoring system consists of an implantable sensor lead coupled with a subcutaneous antenna coil, a patient advisory module (PAM), and the clinician's personal computer software. The sensor system is implanted into the atrial septum oriented to the left atrium (LA), comprises a sealed sensor module with a titanium pressure sensing membrane and circuitry for measuring and communicating LAP, temperature, and intracardiac electrogram. The implant is powered and interrogated through the skin by 125-kHz radiofrequency wireless transmissions from the PAM. During interrogation, physiologic waveforms are captured and stored in the memory of the PAM. The results from early studies showed that the LAP measurements were within $5 \pm$ mm Hg of simultaneous PCWP readings via right heart catheterizations [15]. A prospective, observational, first-in-human study of this LAP sensor, the HOMEOSTASIS trial, suggests that it has the potential to improve hemodynamics, symptoms, and outcomes in advanced HF. Forty patients with NYHA class III or IV HF had the LAP device implanted. Using a physician-directed, patient self-management approach, pressure-guided therapy decreased the mean LAP from 17.6 to 14.8 mmHg ($P < 0.003$). The frequency of readings > 25 mmHg was reduced by 67 % ($P < 0.001$). Improvements in LVEF and NYHA class were also observed [16]. The results from the HOMEOSTASIS trial are promising and further multicenter RCTs are needed to confirm these results.

PA Sensors

From an invasive HF perspective, an implantable PA sensor is a new and potentially game-changing technology. These devices are wireless and can be placed directly into the PA during a right heart catheterization, hence it is less invasive than RV and LAP sensors. The PA sensor is a coil and a pressure sensitive capacitor encased in a capsule. The device has no leads or batteries. Two nitinol loops at the ends of the capsule serve as anchors in the PA. The coil and capacitor form an electrical circuit that resonates at a specific frequency, and pressure applied to the sensor causes deflections of the pressure-sensitive surface, resulting in a characteristic shift in the resonant frequency. Electromagnetic coupling is achieved by an external antenna which is held against the patient's body. The antenna provides power to the device, continuously measuring its resonant frequency, which is then converted to a pressure waveform [17]. Dual anti-platelet therapy is required for the first month after device implantation (Aspirin and Clopidogrel), and after the first month Aspirin alone is sufficient [17]. The CHAMPION study was a RCT of 550 patients that received PA pressure

(PAP) sensors in addition to standard of care (access group) vs standard of care alone in a control group (no access group). After 6 months of follow-up significantly fewer HF-related hospitalizations were reported in the PAP sensor group compared with the control group. During the entire follow-up, the treatment group had a 37 % reduction in HF-related hospitalizations compared with the control group (Fig. 1). The device proved to be very safe as freedom from device-related or system-related complications was 98.6 % and overall freedom from pressure-sensor failures was 100 % [18•]. This was the first positive RCT of implantable hemodynamic monitoring in patients with moderately symptomatic heart failure [18•].

Cardiac Contractility Modulation

In the failing heart, the ability of the plasma membrane calcium current to trigger calcium release from the sarcoplasmic reticulum (SR) is reduced. This defect appears to reside in a change in the relation between SR calcium-release channels and sarcolemmal calcium channels. Beta-Adrenergic stimulation can overcome the defect in hypertrophic but not failing heart cells. Once compensatory mechanisms to increase inotropy fail excitation-contraction, coupling defects may contribute to HF [19]. Seminal work by Dr. Houser's lab demonstrated that calcium transients and contractions induced by action potentials at 0.5 Hz exhibit phasic and tonic components, known as cardiac contractility modulation (CCM) signals [20]. These signals can prolong the action potential and secondarily increase SR calcium loading and cycling, thus CCM signal stimulation can be used to enhance myocardial contractility [21]. Early studies in humans revealed that this new technology is both safe and feasible [22]. The implanted device resembles a dual chamber pacemaker in that a right atrial and 2 right ventricular leads are placed transvenously. The device can deliver nonexcitatory CCM signals at preset times, and is delivered during the absolute refractory period of the cardiac cycle [22]. The device was initially tested in 13 class III NYHA HF patients. CCM signals were delivered 3 h daily over 8 weeks (3-h phase) and 7 h daily over the next 24 weeks (7-h phase). At the end of the study period no patient died or required a heart transplant, and there were no device related complications. The left ventricular ejection fraction (LVEF), 6 min walk time, and NYHA class all significantly improved [22]. While the results were promising, this was not a controlled or blinded study. Subsequent studies in humans have demonstrated that CCM signal treatment reverses the cardiac maladaptive fetal gene program and normalizes expression of key SR calcium cycling and stretch response genes [23]. A randomized, double blind, crossover study of CCM in NYHA class II-III patients with an LVEF <35 % was performed in Europe. At the conclusion of 3 months, CCM treatment was shown to be safe and the study met its co-primary endpoints by demonstrating statistically significant improvements in peak oxygen consumption and Minnesota Living with Heart Failure Questionnaire (MLWHFQ) scores in patients receiving CCM therapy [24]. The Fix Heart Failure 5 (FIX-HF-5) study was a US multicenter unblinded RCT using CCM therapy with optimal medical therapy (OMT) vs OMT alone [25]. Ultimately FIX-HF-5 enrolled 428 patients with NYHA class III or IV HF, with a narrow QRS complex and LVEF $\geq$ 35 %. Roughly half of the patients were enrolled in the treatment arm (CCM with OMT) and half in the OMT arm. Efficacy was assessed by the primary end point of ventilatory anaerobic threshold (VAT), as well as peak VO₂ (pVO₂), and MLWHFQ at 6 months. While VAT did not improve at 6 months, once again CCM therapy was shown to be safe, and a potential subgroup of responders was identified (LVEF $\geq$ 25 % and NYHA class III symptoms) [26•, 27]. The ultimate role of this exciting new technology for HF is still being defined.

Baroreflex Activation Therapy

In a canine model of HF, carotid sinus baroreceptor activation was shown to improve global left ventricular function and partially reverses left ventricular remodeling both globally and

at cellular and molecular levels [28•]. Possible explanations for this beneficial effect include a reduction in sympathetic activity and normalization of the cardiac β -adrenergic receptor signal transduction pathway, and attenuation of the enhanced activity of the peripheral renin-angiotensin-aldosterone-system [28•]. This therapy, also known as baroreflex activation therapy (BAT) may be useful in human HF patients, especially those with HF with preserved ejection fraction (HFPEF). Left ventricular hypertrophy is common in this cohort of patients, and BAT therapy for hypertension has demonstrated echocardiographic regression of left ventricular hypertrophy [29, 30]. An active implantable medical device has been developed to electrically provide BAT through the stimulation of carotid baroreceptors. This device resembles a pacemaker system and consists of a pulse generator implanted in the pectoral region of the chest and 1 carotid sinus leads which are connected to the pulse generator via wires and to the carotid sinus by an electrode [31•]. BAT therapy can be individually tailored to meet the patient's needs via an interactive device programming system. Thus, with compelling echocardiographic data and animal studies, it is possible that BAT could succeed at improving outcomes in HFPEF where medical therapies have failed. The Health Outcomes Prospective Evaluation for Heart Failure with EF $\geq 40\%$ (HOPE4HF) trial is an international prospective RCT where subjects will be randomized in a 2:1 ratio to receive BAT plus medical management or to receive medical management alone. The primary efficacy endpoint will be measured by the time from randomization to cardiovascular death or HF event, defined as a HF hospitalization or an emergency department or clinic visit requiring intravenous therapy for the treatment of HF [31•]. A positive result with the HOPE4HF trial will provide the first evidence based therapy for the management of HFPEF.

The Evolving Role of Cardiac Resynchronization Therapy for Invasive HF Treatment

Introduction and the Evidence for CRT

CRT is thought to improve the LVEF and functional status by minimizing regional left ventricular delay caused by prolonged ventricular conduction, thereby reducing mitral regurgitation and left ventricular reverse remodeling, while increasing cardiac output and stroke volume [32]. This technology incorporates the traditional leads used in ICD implantation (Right atrial and Right Ventricular leads), but via the coronary sinus an additional lead is placed into the left ventricle to achieve resynchronization. The first large prospective double-blind study of CRT in patients with moderate-to-severe (NYHA class III and IV) HF and a prolonged QRS interval was the MIRACLE study. This landmark trial led to the approval of the first CRT device in the U.S. and demonstrated that patients who received CRT experienced statistically significant improvements in the distance walked in 6 min, functional class, quality of life, time on the treadmill during exercise testing, peak VO_2 , and cardiac structure and function (reverse remodeling), compared with control subjects. In addition, fewer patients in the group assigned to CRT than control patients required hospitalization for the treatment of HF [32]. The COMPANION trial was able to demonstrate that CRT decreased the combined risk of death from any cause or first hospitalization and, when combined with an implantable defibrillator, significantly reduced mortality [33]. The CARE-HF study provided the important information that in patients with CRT alone, CRT was still able to improve symptoms and the quality of life of patients while simultaneously reducing the risk of death when compared with standard medical therapy [34]. At the present time there is no data supporting the role of CRT in patients with a QRS interval <120 milliseconds and severe symptomatic HF, although this is currently being studied further, as many patients will have evidence of dyssynchrony despite a normal QRS interval [35]. The indications for CRT are expanding rapidly with possible new indications for this therapy being discovered. Recent studies show that CRT, when combined with

OMT, reduces the risk for HF hospitalization, and improves ventricular structure and function in NYHA functional class II and NYHA functional class I patients with previous HF symptoms [36]. While much of the initial focus of CRT has been on symptomatic NYHA class III-IV HF, research has demonstrated that CRT combined with an ICD may decrease the risk of HF events in relatively asymptomatic patients with a low ejection fraction and wide QRS complex [37•]. More recent data suggests that CRT may result in major structural and functional reverse remodeling at 1 year, with the greatest changes occurring in patients with a nonischemic cause of HF [38]. And while data up to this point indicate the use of CRT as adjunctive therapy in advanced HF with a QRS >120 milliseconds and NYHA class III-IV HF, recent data suggests a reduction in death may be seen in patients with NYHA class II HF who receive CRT in addition to medical therapy and an ICD [39]. While some authors suggest there may be a role for CRT in NYHA class III or IV HF with a LVEF >35 % [40], at this time the FDA approved indications for CRT covers patients with NYHA class III-IV HF, LVEF ≤ 35 %, and a QRS ≥ 120 ms, with updated approvals in September 2010 and April 2012 to include patients with left bundle branch block and NYHA class II or ischemic class I HF with an LVEF ≤ 30 % and a QRS duration ≥ 130 ms based on MADIT-CRT data [41] and NYHA class II HF, LVEF ≤ 30 %, left bundle branch block, and a QRS duration ≥ 130 ms based on REVERSE and RAFT [39].

Impedance Monitoring

Intrathoracic Electrical Impedance

CRT and ICD devices have the potential to provide physiological data that physicians can use to manage their HF patients in the ambulatory setting. Using these devices, physicians may be able to detect pulmonary congestion secondary to an increase in filling pressures and possible hemodynamic deterioration by intrathoracic impedance monitoring. When an electrical current is passed across the lung, accumulation of intrathoracic fluid during pulmonary congestion will form a better conductance, thereby causing a corresponding decrease in impedance. At this time there are specialized implantable defibrillators which use the RV coil electrode-to-device case pathway to create a current. The resulting voltage (and therefore calculated intrathoracic impedance) is acquired from the RV coil electrode. There are data that has demonstrated an inverse correlation between intrathoracic impedance and pulmonary capillary wedge pressure, and between intrathoracic impedance and net fluid loss during hospitalization [42]. Moreover, a decrease in impedance was noted before the onset of symptoms and hospital admission for pulmonary fluid overload [42]. Studies to date have assessed different values, and in all they have proven to be sensitive but not very specific for the assessment of HF [8, 43]. However, the sensitivity of intrathoracic impedance appears to be much greater than that seen with daily weight monitoring (Fig. 2) [8]. Another possible limitation of this therapy is that intrathoracic impedance may be affected by several noncardiac factors, such as pulmonary structural and functional diseases, resulting in false positive as well as false negative readings (hence the reduced specificity of this technology).

Intracardiac Electrical Impedance

Intracardiac impedance measurement between the RV and LV lead electrodes with cardiac resynchronization may be a better physiological alternative than intrathoracic impedance [44]. Animal models using the LV lead and CRT therapy suggests that impedance vectors employing a LV lead are highly responsive to physiologic changes during HF [45]. Overall impedance monitoring is limited by the inflammatory reaction that occurs around the lead early after implant, thereby affecting measurements, as most studies did not record data during the first 30 days after implantation. The ideal duration of time to begin recording data

has yet to be defined. Further studies, especially in humans, are needed to validate and define the implications of this promising therapy.

Heart Rate Variability

Using CRT and ICD technologies, prognostic information can be obtained regarding heart rate variability (HRV). HRV is a physiological marker of cardiac autonomic control. A low or decreasing HRV is indicative of high sympathetic and low parasympathetic tone, a physiology that is undesirable in HF patients. HRV as calculated by an implanted CRT device can be defined as the standard deviation of 5 min median atrial-to-atrial intervals (SDAAM). SDAAM <50 ms when averaged over 4 weeks was associated with a greater than 3-fold mortality risk. SDAAM decreased a median of 16 days before hospitalization and returned to baseline after treatment. Automated detection of decreases in SDAAM was 70 % sensitive in detecting cardiovascular hospitalization, but with 2.4 false-positives per patient-year of follow-up [46].

CRT and Diagnostic Parameters

A recent prospective, multicenter observational study in patients receiving CRT was performed to determine the utility of combined HF device diagnostic information to predict clinical deterioration of HF in patients with left ventricular systolic dysfunction. The devices used in this study had the capability to continuously monitor, record, and, display various HF device diagnostic parameters, such as atrial fibrillation (AF) duration, ventricular rate during AF, the fluid index from intrathoracic impedance, night heart rate, HRV, the percentage of time of pacing in CRT, and appropriate ICD shocks. The parameters that most commonly triggered the algorithm were low activity, low fluid index as measured by impedance, and low HRV. Patients with a positive combined HF device diagnostics had a 5.5-fold increased risk of HF hospitalization with pulmonary signs or symptoms within the next month [47]. Changes in HF device diagnostic parameters based on a combined algorithm can stratify HF patients for subsequent HF events into high and low risk. The results from this study may provide us with another potential tool in our armamentarium from an invasive HF perspective.

Conclusions

HF is a complex disease process and while novel research has led to a better clinical understanding of human sinus node disease, AF, ventricular tachycardia, and HF mechanisms, translating these discoveries to new therapies for human HF has yet to come to fruition [48, 49]. Invasive HF monitoring devices and therapies, some of which are still in the investigational stage, represent a new way of approaching the treatment of HF. Now may be the time to think beyond traditional therapies and medications and pursue invasive strategies for HF, which is only increasing in prevalence as the population continues to age [50]. CRT and ICD devices have many possible uses beyond resynchronization, and implantable sensors have the potential to help us manage HF more effectively in the ambulatory setting. Cardiologists and HF specialist should familiarize themselves with these technologies as invasive HF therapy has become established and new sensor technologies are on the near horizon.

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Fig. 1.

Cumulative HF hospitalizations during the entire period of randomized single-blind follow-up in the CHAMPION trial, demonstrating a marked reduction in HF hospitalizations with the use of a PA pressure monitoring system. (Reproduced with permission from: Abraham WT, Adamson PB, Bourge RC, et al.; for the CHAMPION Trial Study Group. Wireless pulmonary artery hemodynamic monitoring in chronic heart failure: a randomized controlled trial. *Lancet*. 2011;377:658–66) [18•]

Fig. 2.

Event detection performance curves demonstrate relationships between sensitivity to worsening heart failure events and unexplained detection rates. Performance was evaluated for a range of fluid index thresholds (30–180 ohm days) as well as weight thresholds. Arrows indicate nominal thresholds (60 ohm days; 3 lb in 1 day or 5 lb in 3 days). (Reproduced with permission from: Abraham WT, Compton S, Haas G, et al. On behalf of the FAST Study investigators. Intrathoracic impedance vs daily weight monitoring for predicting worsening heart failure events: results of the fluid accumulation status trial (FAST). *Congest Heart Fail.* 2011;17:51–5 [8])