Implantable Sensors for Heart Failure

Faisal M. Merchant, MD; G. William Dec, MD; Jagmeet P. Singh, MD, PhD

Heart failure (HF) affects more than 5 million Americans, and acute decompensated heart failure (ADHF) has emerged as the leading cause of hospitalization among people over the age of 65 years.1 Importantly, HF is a leading public health concern, and hospitalization expenses related to management of ADHF impose a substantial financial burden on the health care system. Additionally, readmission rates after hospitalization for ADHF may be as high as 50% at 6 months,2 and insights from the ADHERE registry suggest that a majority of patients admitted with ADHF have a history of heart failure.1 These data demonstrate that the majority of patients admitted with ADHF are known to the medical system and to medical providers, thereby creating an opportunity for upstream strategies that may be capable of detecting early HF destabilization and implementing therapies to reestablish the patient and avert hospitalization. The anticipated changes in the health care system—with a focus on bundled payments for disease management—will necessitate robust disease management programs to optimize therapy and minimize recurrent admissions once patients have been diagnosed with HF. Perhaps even more importantly, averting repeat episodes of ADHF is likely to have a stabilizing effect on the progression of HF and may improve long-term morbidity and mortality.

The transition from chronic HF to ADHF involves perturbations in multiple intersecting processes including neurohormonal circuits, inflammatory mediators, cardiorenal interactions, and myocardial performance. Concurrently, derangements in comorbid illnesses such as coronary disease, atrial and ventricular arrhythmias, and hypertension also contribute to the pathophysiology of ADHF.3 Ultimately, these multiple pathways lead to an elevation in ventricular filling pressures and signs of vascular congestion, which, in concert with symptoms from impaired cardiac output, lead to the clinical constellation of ADHF. This pathophysiologic paradigm highlights multiple opportunities for detecting early changes in the processes that lead to ADHF with the goal of upstream interventions to reestablish the patient and prevent hospitalization. For example, subtle changes in ventricular filling pressures or markers to detect early vascular congestion may serve as important targets for heart failure monitoring. Even more proximal perturbations in neurohormonal pathways or myocardial performance may be amenable to monitoring with advanced sensor systems and may ultimately prove to be even more effective in aborting the ADHF cascade.

The concept of outpatient monitoring for early detection and treatment of ADHF is not new. However, the question of which parameters to monitor and what specific detection strategies should be used to prevent hospitalization has not been adequately addressed. Symptoms such as orthopnea and physical examination signs such as pulmonary rales, peripheral edema, and elevated jugular venous pressure reflect increased ventricular filling pressures and vascular congestion and are often used for the diagnosis of ADHF. However, these findings have relatively poor sensitivity for detecting acute decompensation, particularly among patients with chronic HF syndromes.4 Additionally, these findings are often relatively late-stage manifestations reflecting substantially elevated ventricular filling pressures. As such, dependence on symptoms and physical examination findings alone has proven ineffective in averting ADHF hospitalizations. Serial monitoring of body weight has some utility in outpatient HF monitoring with increases in body weight detectable as early as 30 days before ADHF hospitalization.5 Serial assessment of body weight has been incorporated with other clinical and physiological parameters (ie, symptoms, activity logs, blood pressure, heart rate, and oxygen saturation) into multidisciplinary remote patient monitoring programs to facilitate early detection of ADHF and prevent recurrent hospitalizations. Most of these remote monitoring systems include either patient-directed interventions in response to a change in a monitored parameter or direct contact (often via telephone) with a health care provider to provide instructions on which interventions to undertake (ie, change in medication or dietary regimen). However, despite the increasing use of remote monitoring systems and the enhanced use of technology to facilitate remote monitoring and decision support, results have been variable. A meta-analysis of randomized clinical trials of remote monitoring for HF patients suggested reductions of ≈17% in total mortality, 7% in all-cause hospitalization, and 29% for ADHF hospitalization.6 Although these results suggest a modest but significant improvement in patients randomly assigned to remote monitoring, given the burgeoning HF epidemic, far more robust strategies such as advanced sensor technology will be neces-

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Implantable Sensors

The rapidly expanding role of cardiac implantable electronic devices (CIEDs) in HF patients presents an opportunity to broaden the paradigm of outpatient HF monitoring. Traditional roles for CIEDs in HF have focused on electrophysiological applications including pacing, antiarrhythmic therapies, and cardiac resynchronization. However, emerging technologies designed to couple various biological sensors to CIEDs have opened the door to novel HF monitoring strategies that can take broader advantage of the implantable devices. In the simplest terms, in a closed system a “sensor” is an element that is attached to a device that detects a change and signals to an “effector” to initiate a response. In the paradigm of HF disease management, the sensor could take a number of different forms including the patient, a health care provider, or the device itself. The use of implantable sensors has several advantages over other monitoring paradigms. For example, self-monitoring systems in which the patient acts as the “sensor” to detect changes in HF status are limited by several factors including subjectivity, variable patient ability, and often poor sensitivity for detecting subtle changes during the early destabilization process. Other strategies include frequent in-clinic monitoring in which the health care provider can act as the “sensor” during face-to-face contact. However, this strategy is logistically challenging, highly dependent on patient compliance with frequent clinic visits, and again limited by the poor sensitivity of symptoms and physical examination findings for detecting early destabilization. In contrast, implantable sensor strategies have several theoretical advantages including continuous monitoring, objectively measured metrics without the bias of subjective assessment, and the capability of providing a patient-specific clinical profile that can be analyzed serially overtime with relative ease.

The concept of device-based monitoring and intervention represents a major opportunity for improving outcomes in chronic HF disease management. This article begins with a discussion of implantable sensor strategies that are already in various stages of clinical testing and then expands to a discussion of future horizons in sensors for HF monitoring (Table).

Electrophysiologic Sensors

Because most currently available CIEDs are used for electrophysiological applications, it makes sense that much of the work on sensor strategies has also focused on monitoring electrophysiological parameters. In the simplest terms, presently available implantable pacemakers and defibrillators are capable of sensing atrial and ventricular arrhythmias and under certain circumstances, initiating therapy (either pacing or defibrillator shocks) in a closed loop system in which both sensor and effector functions are contained within the device. Although detecting and treating rhythm disturbances may have a stabilizing effect in HF patients, monitoring other electrophysiological parameters may play a more important role in predicting and preventing episodes of ADHF. For example, increases in mean heart rate have been demonstrated before episodes of ADHF and generally return back to baseline after treatment during hospitalization. Such heart rate trends are easily sensed by an implantable device, and, when coupled to either a patient-based or a health care provider–based effector to initiate therapy, have the potential to avert hospitalization. Similarly, cardiac autonomic tone as measured by short-term heart rate variability (HRV) is a powerful predictor of sudden cardiac death and total mortality in patients with chronic HF. HRV can be measured from CIEDs with atrial leads by determining the standard deviation of 5-minute median atrial-atrial intervals; SDANN, standard deviation of 5-minute median ventricular-ventricular intervals; LV, left ventricle; RV, right ventricle; HRV, heart rate variability; RV, right ventricle; LV, left ventricle; ePAD, estimated pulmonary artery diastolic pressure; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal proBNP; ANP, atrial natriuretic peptide; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; hsCRP, high-sensitivity C-reactive protein.

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SDAAM indicates standard deviation of 5-minute median atrial-atrial intervals; SDANN, standard deviation of 5-minute median ventricular-ventricular intervals; LV, left ventricle; RV, right ventricle; HRV, heart rate variability; RV, right ventricle; LV, left ventricle; ePAD, estimated pulmonary artery diastolic pressure; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal proBNP; ANP, atrial natriuretic peptide; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; hsCRP, high-sensitivity C-reactive protein.
HRV to all patients. Extension of these findings and the potential for customized detection thresholds based on individual patient trends holds promise for further improving the sensitivity and specificity of these algorithms. Additionally, cardiac resynchronization therapy (CRT) improves HRV among clinical responders, with a shift in autonomic control away from sympathetic dominance,11–13 suggesting that HRV monitoring may also play an important role in predicting response to therapy. Future work will be necessary to determine whether specific interventions on the part of either the patient, health care provider, or device can be used to implement therapy in response to a sensed change in HRV and avert an episode of ADHF.

Beyond prediction of short-term risk of ADHF, measurement of HRV from CRT devices is also a significant predictor of long-term mortality such that patients demonstrating the lowest baseline HRV have significantly worse long-term outcomes.10,14 Recent work has suggested that device-derived HRV along with heart rate and physical activity data can be used to risk-stratify patients with HF and CIEDs15 (Figure 1). In this manner, implantable sensors may also play an important role not only in predicting short-term risk of destabilization but also in refining long-term risk stratification.

**Hemodynamic Sensors**

Fundamental to the pathophysiology of ADHF is an elevation of ventricular filling pressures and therefore, much of the focus of chronic HF disease management has centered on achieving the lowest ventricular filling pressures possible without compromising cardiac output or further activating neurohormonal cascades. Serial monitoring of intracardiac and pulmonary pressures may be useful in optimizing medical and device-based therapy. However, to date, obtaining such hemodynamic data has required repeated invasive right heart catheterization (RHC), which is not feasible as part of an outpatient disease management program, particularly given the rapidly increasing numbers of patients with chronic HF. Other options for assessing ventricular filling pressures include noninvasive surrogates such as natriuretic peptide testing or Doppler echocardiography indices. However, correlation between these noninvasive markers and invasive assessment of pulmonary capillary wedge pressure has been modest.16 Serial natriuretic peptide testing has shown promise for improving outcomes in chronic HF management,17,18 but results have not been consistent19,20 and readmission rates remain high. With this background, the opportunity for continuous monitoring of intracardiac pressures via implantable sensors is an attractive option. From an implantable device perspective, coupling a pressure transducer to the right ventricle (RV) lead of a pacemaker or defibrillator provides the simplest form of continuous intracardiac pressure monitoring. Early work demonstrated the feasibility and safety of long-term RV pressure monitoring and also documented excellent correlation between pressure measurements obtained from the implantable sensor and serial invasive RHC measurements out to 1 year.21 Additionally, resting pressure measurements obtained from the RV sensor between midnight and 4 AM correlate most closely with resting supine hemodynamic data at the time of RHC,22 allowing direct extrapolation of the vast clinical experience with chronic HF management, based on invasive hemodynamic data. Perhaps most importantly, a validated technique has been developed for deriving estimated pulmonary artery diastolic (ePAD) pressure from the first derivative of the RV pressure curve (RV dP/dt max), thus allowing a closer surrogate of left atrial filling pressures to be extrapolated from an RV pressure sensor.23

A commercially available implantable pressure sensor (Chronicle IHM, Medtronic Inc, Minneapolis, Minn) has been tested across a range of clinical settings. Early data suggested that the use of a continuous RV pressure sensor may reduce ADHF hospitalizations.24 A subsequent randomized trial of 274 patients with New York Heart Association (NYHA) class III or IV heart failure demonstrated a nonsignificant 21% reduction in HF events among patients randomly assigned to continuous hemodynamic monitoring.25 A secondary efficacy analysis from this study did demonstrate a significant 36% relative risk reduction in the time to first HF hospitalization among patients implanted with the Chronicle IHM (P=0.03) (Figure 2). Failure to meet the primary efficacy end point may have been related to a lower-than-expected event rate in the control cohort and suggests that future studies, potentially with increased statistical power, will be necessary to more clearly define the utility of implantable hemodynamic monitoring in this patient population. Additionally, beyond attempting to reduce HF hospitalizations, data from studies on continuous RV and ePAD pressure monitoring have also yielded important insights into the pathophysiology of HF with reduced versus preserved ejection fraction (EF), demonstrating important differences in baseline ventricular filling pressures and ventricular distensibility between the groups.26 Patients in both EF groups demonstrated significant increases in ePAD before episodes of ADHF, although the number of days of advanced notice was significantly less (19.3±17.3 versus 29.1±22.3, P<0.05) and the rate of rise in filling pressures was significantly greater in patients with preserved EF compared with those with low EF. These findings may have important implications for tailoring

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**Figure 1.** Prognostic utility of a risk score based on 4 simple sensor-derived parameters (SDANN, HRV footprint, HR, and physical activity) to risk-stratify HF patients for long-term mortality. From Singh et al.15
chronic HF management strategies for patients in different EF subgroups.

Conceptually, continuous measurement of RV and extrapolated pulmonary pressures from an RV transducer represents the most straightforward form of implantable sensor-based hemodynamic monitoring. However, most patients admitted for ADHF have pulmonary congestion caused by elevated left atrial pressure. Therefore, continuous monitoring of left atrial pressure (LAP) may provide a more robust target for implantable sensor-based strategies. The HeartPOD (St. Jude Medical Inc, Minneapolis, Minn) is a permanently implantable LAP sensor inserted during transseptal cardiac catheterization (Figure 3). The LAP sensor is coupled via a subcutaneous antenna to a hand-held patient advisor module, which contains a range of patient alerts with reminders to take medications or obtain additional LAP recordings. Additionally, the patient advisor module is able to generate a customized patient prescription for several different parameters including medication dosage, activity level, sodium and fluid intake, and physician contact. The prescription is a physician-directed, patient self-management program that is customized on the basis of LAP measurements. In an early stage safety/efficacy observational study, 40 patients with NYHA class III or IV HF were implanted with the LAP sensor and followed for a median of 25 months. All patients underwent successful device placement without any major device-related complications. LAP-guided therapy resulted in improvements in several important efficacy end points including reductions in mean daily LAP, improvements in functional capacity, and higher doses of neurohormonal antagonists with reductions in daily diuretic requirements. Additionally, elevations in LAP were clearly identifiable during the month before episodes of ADHF, suggesting that continuous LAP monitoring may be effective in reducing HF hospitalizations. Although not specifically designed to assess reductions in hospitalizations or other clinical end points, landmark analysis from this study also demonstrated a significant improvement in event-free survival (death or ADHF hospitalization) during the period of LAP monitoring compared with the observation period of standard HF therapy (event-free survival: 95% versus 77%, \(P=0.012\)) (Figure 4). Further studies will be necessary to validate the impact of LAP sensors on clinical outcomes.

Another emerging technology for implantable hemodynamic sensors is direct pulmonary pressure measurement via an implantable pulmonary artery (PA) pressure transducer (Champion, CardioMEMS, Atlanta, Ga). In a pivotal trial recently reported in preliminary form, 550 patients with class III HF were randomly assigned to PA pressure monitoring or standard care. In a pivotal trial recently reported in preliminary form, 550 patients with class III HF were randomly assigned to PA pressure monitoring or standard care. The safety profile of the PA sensor was
Early studies content in the interpositioned pulmonary tissue and signals a across the thoracic cavity reflects an increase in tissue fluid

Monitoring system (Medtronic Inc, Minneapolis, Minn) uses invasive impedance cardiography. The OptiVol Fluid Status
devices can and the RV coil, Z can be measured in a safe and reproducible manner and yields results comparable to noninvasive impedance cardiography. The OptiVol Fluid Status Monitoring system (Medtronic Inc, Minneapolis, Minn) uses a proprietary system that compares daily impedance measurements with a baseline reference value. The reference value is a slow-moving average of preceding impedance values. The
difference in impedance between the daily measurement and the reference value is summed to generate an OptiVol fluid index such that an increase in OptiVol fluid index corresponds to a cumulative decrease in impedance measurements, reflecting a gradual increase in pulmonary fluid content (Figure 5). Notably, a decrease in impedance is typically seen during the first several weeks after device implantation and is attributed to pocket edema and local inflammation. Impedance recordings during this early period are not used for clinical decision-making or for determining the reference impedance value.

A strong inverse correlation has been defined between intrathoracic impedance and pulmonary capillary wedge pressure and between impedance and net fluid loss among patients hospitalized for ADHF. Additionally, this work suggested that an OptiVol threshold of 60 Ω-days yielded the greatest diagnostic accuracy in predicting impending ADHF hospitalization without substantially compromising specificity by increasing the “false-positive” detection rate (ie, crossing the threshold without subsequent hospitalization). Several studies have demonstrated significant reductions in impedance preceding episodes of ADHF, with a sensitivity ranging from 60% to 77% using the 60 Ω-day threshold for predicting impending hospitalization with a relatively low false detection rate ranging from 0.2 to 1.5 alert events without hospitalization per patient-year. Additionally, at least 1 study has suggested that a strategy of audible device alerts based on impedance monitoring might reduce HF hospitalization. Although the published sensitivity rates of impedance monitoring for predicting ADHF suggest that this technology may be an important adjunct in HF management, the positive and negative predictive values have been relatively modest, compromised by both “false-positive” and “false-negative” events. Early studies have suggested that episodes classified as “false positives” are often due to very mild signs or symptoms of congestive HF and may in fact trigger changes in treatment but do not necessarily lead to hospitalization for ADHF. It is likely that many of these events are clinically relevant and therefore should not be classified as “false positives.” Analysis of “false-negative” events (ie, hospitalization for ADHF without crossing the impedance threshold) suggests that these events cluster in patients who present more often with signs of peripheral edema or symptoms of low cardiac output and less frequently with pulmonary congestion. These findings highlight one of the major challenges in evaluating the efficacy of sensor strategies and that is the lack of a true gold-standard for the diagnosis of ADHF that can be broadly applied to all patients. To date, most studies have relied on a combination of clinical evaluation and adjunctive testing (natriuretic peptides, chest radiography, RHC...) for adjudicating whether a hospitalization is due to ADHF or not. However, all methods for detecting ADHF, including clinical evaluation and natriuretic peptide testing, are imperfect and therefore pose a major limitation when serving as the gold standard for testing new diagnostic modalities. New technologies such as impedance monitoring or hemodynamic sensors that are designed to detect very early changes may be inappropriately penalized for detecting subtle changes in volume status or ventricular loading.

Numbers at risk:
Observation: 35 0
Titrations/Stability: 37 35 28 18 13 7

Figure 4. Landmark analysis from the HOMEOSTASIS study demonstrating trend toward improved event-free survival (death or ADHF hospitalization) during the period of left atrial pressure monitoring compared with the observational period of standard HF care (event-free survival: 95% versus 77%, P=0.012). Reprinted with permission from Circulation.28

Unit: Ω•days
conditions, which, although clinically important, may not necessarily lead to ADHF hospitalization. Addressing these limitations will be a major challenge in future clinical studies evaluating the efficacy of new heart failure technologies.

Initial work in impedance monitoring has focused on measurements between the device can and right-sided leads, reflecting electric conductance across the heart, lungs, and other interpositioned tissues, thus reflective of total thoracic

Figure 5. Clinical example of a patient implanted with a thoracic impedance monitor. Top panel demonstrates the onset of atrial fibrillation (red line). Bottom panel demonstrates a progressive decrease in thoracic impedance after the onset of atrial fibrillation with a corresponding increase in the OptiVol fluid index, suggesting a significant increase in pulmonary fluid content. In this example, both the atrial fibrillation and the pulmonary edema probably will need to be addressed to restore homeostasis.
impedance. However, with biventricular device platforms, numerous other vectors are available for measuring impedance between the device can, right atrium, right and left ventricles. Studies in a dog model of pacing-induced heart failure have suggested that although all measured vectors demonstrate a consistent reduction in Z as HF develops, left ventricle (LV)-dependent vectors demonstrated the fastest rate of change and the greatest magnitude of change. Specifically, Z measured from the LV-can vector demonstrated the closest correlation with LV end-diastolic volume and left atrial pressure, probably reflecting a drop in impedance because of both increased pulmonary water content and progressive LV cavity dilation, both of which would tend to improve electric conductance. In other animal models, intracardiac impedance measured between the LV and RV leads in a CRT platform has also been closely correlated with end-diastolic volume, end-diastolic pressure, stroke volume, and LV dP/dt max. Furthermore, in patients undergoing CRT device implantation, intracardiac impedance (LV-RV) is more closely correlated with echocardiographic changes in LV volume than intrathoracic impedance (RV-can). These findings suggest that changes in LV volume and pressure conditions may produce a more profound change in impedance along the LV-RV vector, encompassing only cardiac tissue, as opposed to the RV-can vector, which encompasses a larger area of noncardiac tissue and may be less sensitive to minute changes in LV loading conditions. Dynamic changes in interlead or lead-can impedance, accompanying the volumetric changes of the LV during systole and diastole, may also have the potential to provide a close correlate for cardiac output. However, this strategy has not been tested in clinical settings.

Beyond trying to predict impending episodes of ADHF by serving as a surrogate for LV pressure and volume conditions, intracardiac impedance sensors may also play a role in device optimization for patients undergoing CRT device implantation. Measurement of intracardiac impedance has been closely correlated with invasive LV stroke volume measurements as a technique to guide LV lead position in patients undergoing CRT device implantation. Similarly, intracardiac impedance has been shown to compare favorably with both echocardiography and invasive hemodynamic pressure measurement to guide atrioventricular (AV) and interventricular (VV) delays during CRT.

Although the primary focus of impedance monitoring for developing HF sensors has centered on detecting changes in lung water content and LV loading conditions, thoracic impedance has also played a long-standing role in measuring minute ventilation (MV) to guide rate-responsive cardiac pacing. Changes in thoracic impedance over the course of the respiratory cycle can be used to measure tidal volume and MV and correlate closely with directly measured MV from the flowmeter of a respiratory gas analysis system. Impedance-based monitoring of MV has been incorporated into algorithms to predict the risk of impending ADHF and may play a complimentary role in sensor-based heart failure monitoring strategies.

**Other Sensor Modalities**

Physical activity level can also be incorporated into sensor monitoring strategies by extrapolating data from accelerometer signals, which are already incorporated into many CIEDs for modulating heart rate during exercise. Physical activity level can be estimated by integrating the accelerometer-detected activity counts in each minute. A minute is considered “active” if the counts exceed a threshold that corresponds to a walking rate of approximately 70 steps per minute, and a low activity threshold has been defined as less than 1 hour of activity per day averaged over a 1-week period. Physical activity level has been incorporated into sensor-based monitoring strategies to predict short-term risk of ADHF, long-term mortality, and clinical response to CRT.

Continuous monitoring of cardiac output (CO) via an implantable sensor can also be performed with a high degree of accuracy. Most implantable sensors have used a technique of measuring oxygen saturation from a photosensitive diode and then extrapolating CO from the venous oxygen saturation based on the Fick equation. Several studies have demonstrated the feasibility of continuous CO monitoring based on mixed venous oxygen saturation in the RV and have demonstrated close correlations with invasive CO measurements across a broad range of oxygen saturation levels. Although combining both continuous pressure monitoring and CO monitoring from a single sensor located in the RV is feasible, additional studies are needed to define the incremental value of continuous CO monitoring in addition to pressure monitoring. In general, as clinical HF management has tended to focus less and less on CO as a diagnostic and therapeutic target and more and more on ventricular filling pressures and neurohormonal status, the importance of CO monitors as part of a sensor-based HF management strategy remains unclear.

Another modality for CIED mounted sensors is peak endocardial acceleration (PEA), which measures the maximum amplitude of the vibrations produced by the first heart sound by using an implantable micro accelerometer mounted within the tip of a conventional pacemaker lead. PEA is strongly correlated with changes in LV and RV contractility (dP/dt max) during inotrope infusion but not during pacing-induced chronotropic stimulation, suggesting that monitoring PEA might serve as a useful surrogate for changes in myocardial contractility. Additionally, PEA sensors have also been used to guide device optimization in patients receiving CRT, and studies have suggested that AV and VV optimization using PEA may be equivalent to echocardiography-based algorithms and LV dP/dt max algorithms.

**Multimodality Sensor Strategies**

Heart failure is a highly complex disease entity representing the interplay of perturbations in multiple processes including myocardial contractility, systemic inflammation, neurohormonal activation, and volume retention. As such, multimodality sensor-based strategies that are designed to monitor several different aspects of the HF cascade may prove more useful than monitoring any one individual parameter. As proof of this concept, recent studies have demonstrated the incremental value of monitoring several different parameters.
using CIEDs. The PARTNERS-HF study prospectively followed patients receiving CRT devices to multimodality monitoring including detection of atrial fibrillation and ventricular response rate, thoracic impedance monitoring with the OptiVol system, patient activity level, nocturnal heart rate trends, heart rate variability (SDAAAM), overall percentage of CRT pacing, and defibrillator therapies. The multimodality algorithm used a diagnostic threshold of abnormal measures on at least 2 of the 7 monitored parameters during a single monitoring period to predict impending ADHF. Several important insights emerged from this well-monitored cohort. First and perhaps most importantly, the use of a diagnostic algorithm based on multimodality criteria significantly improved the ability to predict impending ADHF hospitalization within the subsequent 30 days when compared with algorithms based on monitoring thoracic impedance alone (hazard ratio, 5.5 versus 2.7, \( P < 0.0001 \)). Additionally, there were significant improvements in the predictive capability of the multimodality algorithm when the frequency of monitoring was increased from quarterly to monthly to semimonthly, lending support to the notion that more frequent monitoring is more effective. This capability to increase the frequency of monitoring is one of the major advantages of implantable sensor strategies.

Another study assessed the complementary nature of both ePAD pressure monitoring via an RV pressure sensor and thoracic impedance monitoring. Measurements of ePAD and Z demonstrated a modest inverse correlation, particularly in the 14 and 30 days before an HF event. Importantly, impedance remained relatively constant until ePAD crossed a particular threshold at which point, presumably, compensatory mechanisms to regulate lung water accumulation were exhausted and \( Z \) began to fall. These observations highlight the primary role of increased cardiac filling pressures in triggering episodes of ADHF and suggest that multiple sensor strategies might be optimally employed by using a temporal sequence whereby hemodynamic/pressure-based sensors are used for early monitoring/prevention and impedance-based sensors are used for early detection/treatment (Figure 6). In this paradigm, early increases in cardiac filling pressures could be treated with intensified neurohormonal blockade with the goal of preventing ePAD from crossing the threshold whereby lung water begins to accumulate. If that threshold is crossed, as detected by a concurrent drop in impedance, diuretics may become necessary, in addition to neurohormonal antagonists, with the goal of averting ADHF hospitalization.

**Opportunities for Future Sensor Development**

Several opportunities exist for enhancing the role of implantable sensors in HF management. As discussed earlier, perturbations in multiple neurohormonal and inflammatory cascades contribute to ADHF. More sophisticated sensor technologies may be capable of detecting these very early pathophysiologic changes and using them to target upstream therapy. For instance, numerous biomarkers are significantly altered in both acute and chronic HF including blood chemistries (electrolytes, glucose, pH), natriuretic peptides (ie, B-type natriuretic peptide [BNP], N-terminal proBNP, atrial natriuretic peptide),\(^53\) inflammatory makers (ie, tumor necrosis factor-\( \alpha \), interleukin-6, interleukin-1),\(^54\) oxidative stress markers (ie, myeloperoxidase),\(^55\) and collagen turnover/extracellular matrix peptides (ie, C-terminal propeptide of collagen type 1, matrix metalloproteinase, tissue inhibitor of matrix metalloproteinases).\(^56\) Additionally, using metabolomic technologies, novel pathways are being implicated in the pathophysiology of HF and may identify markers that are capable of detecting even more subtle alterations in the failing heart such as changes in myocardial signaling and energetics.\(^57\) These observations open the door to novel implantable sensors that are capable of measuring circulating levels of metabolites from multiple interacting pathways and providing an earlier, more sensitive profile of impending HF destabilization. Such metabolite-based sensors may also enable the monitoring and treatment of coexistent comorbidities such as ischemic heart disease and diabetes in the HF patient.

Opportunities also exist for improvements in the design of sensors. For instance, the use of biocompatible materials may enhance the longevity and safety of implanted devices, which can remain in situ for decades. Similarly, the use of novel energy scavenging technologies to power sensors using sources such as motion or temperature gradients may overcome many of the constraints of currently available CIEDs, which are limited by finite battery lifetime and size.\(^58\)

Perhaps the most important challenge for the future of sensor-based strategies is developing tools to directly couple implantable sensors to equally robust effectors. To demon-
strate an important improvement in clinical outcomes, the information gathered from an implantable sensor will need to be coupled to an effector that is capable of instituting therapy in a rapid and robust manner. To date, most sensor strategies have transitioned clinical information to a health care provider, who is then responsible for “closing the loop” by implementing an appropriate therapeutic intervention. This strategy has several limitations including the potential for time lags between the sensed event and the implementation of the appropriate intervention. Additionally, a health care provider is still required to interpret the data and make appropriate clinical decisions, which, in light of the burgeoning HF epidemic, may require substantial resources. Alternatively, information from implanted sensors may be relayed directly to the patient, who then serves as the primary effector. However, patient-driven strategies suffer from variability in patient capability and compliance and also require relatively simple decision-making algorithms such that a large percentage of patients are capable of interpreting the information from the sensor and implementing an appropriate therapeutic strategy. Perhaps the greatest potential for CIEDs in HF management lies in the ability to directly couple both sensor and effector functions within the device. This strategy would allow for a truly “closed-loop” system, which would completely eliminate dependence on human factors. Additionally, the sensor-effector unit could work in an iterative fashion with the sensor able to measure the response to a particular intervention and then make further changes based on the dynamic nature of chronic HF.

As proof of concept, currently available rhythm management devices are capable of sensing changes and implementing therapy (ie, antitachycardia pacing in response to sensed ventricular tachycardia) within an iterative and closed-loop system. Similar systems could be developed for other aspects of HF disease management. For instance, there is great interest in the development of microelectromechanical systems capable of controlled drug delivery via an implantable device. It is conceivable that the timely and potentially localized delivery of various pharmacological agents (vasodilators, diuretics, antiarrhythmics) could serve as a useful treatment modality for chronic HF management. Similarly, devices may soon be capable of modulating the AV interval, altering LV-RV pacing timings, or even delivering other forms of treatment such as cardiac contractility modulation in response to a drop in myocardial contractility (detected by a PEA sensor) or an elevation in filling pressures (measured by an LAP sensor). Ultimately, to realize their true impact, implantable sensor strategies will need to be coupled to equally robust effector strategies to truly stabilize the HF disease process and improve patient outcomes.

The expanding role of implantable sensors is leading to a paradigm shift in HF management. Implantable sensors will become part of routine clinical care, and, when coupled with remote monitoring, will allow the practice of a more personalized form of medicine. Sensor strategies will continue to evolve, and in addition to facilitating risk stratification and predicting risk of ADHF, will enable early, automated therapeutic interventions and improve clinical outcomes.

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