Optimizing heart failure therapy with implantable sensors

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A B S T R A C T

Heart failure (HF)-related hospitalization is associated with significant mortality and morbidity and can be prevented by early intervention. Implantable sensors detect early pathophysiological changes in HF, using an accelerometer, a paced electrogram, impedance and pressure sensors in implanted intracardiac leads, or stand-alone devices. Such sensors monitor daily activity, QT and ST intervals, pulmonary fluid, and intracardiac pressures at various points. Sensor data are available either by patient's or physician's regular interrogation, or using remote patient monitoring. Different sensors have different levels of sensitivity and specificity for HF detection, and they have the ability to antedate HF exacerbation and thereby allow for the initiation of intervention to avert decompensation. Clinical studies suggest that alone or in combination, such sensors have a greater beneficial impact than conventional therapy on acute HF outcome.

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doi:10.1016/j.joa.2012.02.003
1. Importance of heart failure

Acute decompensated heart failure (ADHF) refers to a clinical condition of worsening HF with dyspnea, often with evidence of fluid overload [1]. This is generally triggered by 1 of the 4 main factors: atrial fibrillation, anemia, hypertension, and medication/dietary indiscretion. About 5 million Americans suffer from HF [2]. In the 1991–1994 Connecticut Medicare beneficiaries review [3], ADHF necessitating hospitalization was found to be associated with an in-hospital mortality of 8%. Importantly, of the 17,448 survivors, 44% were readmitted once, with 18% of these patients being admitted due to recurrent HF. Overall, 24% died within 6 months of the first clinical manifestation of ADHF, and 53% either died or were readmitted during the study period. Thus, prevention of ADHF can have significant prognostic value for the patient, in addition to reducing the cost of HF management.

2. Limitations of symptoms, signs, and investigations

While dyspnea is the commonest presenting symptom for hospitalization in ADHF, it occurs relatively late in association with hemodynamic and fluid status changes. Adamson et al. [4] implanted a right ventricular (RV) sensor to measure RV systolic and diastolic pressure during HF exacerbation in 32 patients. At a mean of 4 ± 2 days before admission, RV systolic pressure started increasing in the case of 9/12 HF events. Overall, there was an increase in the RV systolic pressure by 25 ± 4% and in the heart rate, by 11 ± 2% during ADHF. These findings suggested that pressure changes are the mechanisms responsible for initiating HF exacerbation. Similarly, a study using an implantable intrathoracic impedance sensor to assess pulmonary fluid revealed that fluid overloading occurs at 18.3 ± 10.1 days before dyspnea occurred [5]. Thus, dyspnea is a late event and does not allow time for the clinician to start or for the patient to seek appropriate intervention and thereby avert hospitalization.

The cardinal physical signs of congestive HF are as follows: a third heart sound, pulmonary crackles, raised jugular venous pressure, and pedal edema. However, these signs have poor sensitivity in detecting HF. In a study [6] of 50 patients with raised pulmonary arterial wedge pressure (PAWP; ≥ 22 mmHg), lung crackles were identified in only 19% of the patients, while a raised jugular venous pressure and peripheral edema were present in 50% and 20% of patients, respectively. While a third heart sound was heard in most cases, it was also detected in those with a low PAWP. The combination of these signs has a sensitivity of 58% and specificity of 100% for diagnosing congestive HF. However, physical examination of jugular pressure is reported to be both difficult and inaccurate [7].

In a recent study [8], 134 patients with ADHF were compared with a case-matched group of non-hospitalized patients. Body weight gain 1 week before hospitalization was associated with an increased risk of hospitalization. However, while daily body weight measurement is recommended in most HF guidelines, body weight is a non-specific parameter and may be influenced by the amount of intake and several other factors.

Radiological evidence of ADHF tends to appear late. HF management is reported to be facilitated by a brain natriuretic peptide (BNP)-guided approach; in a study on HF therapy guided by the levels of N-terminal BNP (TIME-CHF) [9], 499 patients who were aged ≥ 60 years and had systolic HF were randomized. Titration to achieve an N-terminal BNP level of ≤ 2 times the upper limit was compared to conventional management without BNP guidance. There was no difference in the survival rates between BNP-guided therapy and conventional therapy (41% versus 40%), and both groups had a similar degree of improvement in the quality of life (QOL). However, the secondary endpoint of HF-related hospitalization was significantly reduced (72% versus 62%), and the outcomes were better in the 60- to 75-year-old patients than in those aged ≥ 75 years.

3. Does ambulatory monitoring prevent HF decompensation?

While vigilant monitoring of symptoms and signs (and BNP levels) is useful, it does not guarantee the accurate prediction of ADHF. On the other hand, frequent monitoring of some of these signs and symptoms and the use of external physiological (and implantable) data have been tested. A meta-analysis of both cohort (2354 patients) and randomized trials (6258 patients) [10], with 6–12 months of follow-up revealed a significantly lower rate of deaths and hospitalizations in patients receiving BNP-guided therapy than in those receiving conventional therapy. The Cochrane Database Systematic Review [11] examined 25 studies and 5 abstracts and has suggested that telephonic support and telemonitoring are effective in reducing all-cause mortality, HF-related hospitalization, and treatment...
cost; improving the QOL; and increasing the frequency of evidence-based prescription.

The Randomized Trial of Phone Intervention in Chronic HF (DIAL) trial [12] randomized 1518 outpatients to either nurse-led, telephone-based intervention or conventional treatment. Weight, diet, and medication compliance were monitored, and nurse specialists adjusted the diuretics doses according to certain specified criteria. Patients were instructed to call 3 times at a frequency of once every 14 days and, thereafter, at a frequency depending on the severity of HF. This protracted study followed the patients for up to 3 years after trial completion. The primary endpoint (death or HF-related hospitalization) was lower in the intervention than in the conventional arm, with the main benefit being a reduction in hospitalization (28.5% versus 35.1%, at 3 years). An educational effect and adherent to the above 3 supervised areas were considered the main reasons for improvement. The Telemedical Interventional Monitoring in HF (TIM-HF) trial [13] also randomized stable Class II or III HF patients with a history of HF-related hospitalization during the last 2 years to either conventional care or remote data monitoring (ECG, blood pressure, and body weight); the latter involved the transferece of the collected data via a personal digital assistant to the monitoring center daily, followed by physician-led response. Over a median follow-up period of 26 months, there was no difference in the frequency of HF-related hospitalization or death, nor in the overall QOL score. However, physical functioning improved. The study documented an 81% compliance in ≥70% daily transmission of data. The Telemonitoring in Patients with HF (TELE-HF) trial [14] randomized 1653 patients who were recently admitted with ADHF. Daily telephone-based interactive voice-response systems on symptoms and weight were reviewed by the patients’ physicians. At the end of 180 days, there was no significant difference in the primary endpoint of death and HF-related hospitalization between the telephone-based intervention group and the conventional care group (52.3% versus 51.5%, respectively). Again, this study shows only a 55.1% adherence to interventional therapy at the end of 26 weeks among the 85.6% of patients who made at least 1 call.

The different efficacies of telemonitoring reported between meta-analyses and prospective studies may be attributable to the differences in the severity of HF in the patients involved in the studies, the types of clinical variables measured, and the interventions offered. Important drawbacks of these studies are sub-optimal compliance of subjects and lack of rapid therapeutic intervention. Furthermore, these studies have mainly been limited to easily measurable clinical variables that occur relatively late in the course of ADHF. Many patients with left ventricular (LV) dysfunction require implantable cardiac implantable electronic devices (CIEDs), either for arrhythmia prevention or therapy (ICD) or HF treatment (cardiac resynchronization therapy, [CRT] or CRT device with defibrillator [CRT-D]); this opens the possibility of adding implantable sensors for HF monitoring in these devices. The use of implantable sensors will allow continuous monitoring of physiological parameters without the intensive use of manpower. Furthermore, the ability of these sensors to detect early physiological changes before ADHF may open a window for averting HF-related hospitalization. They can also facilitate the evaluation of the hemodynamics at different body positions and on an ambulatory basis and may obviate the need for invasive monitoring when the patient is admitted for HF therapy.

4. Monitoring of pathophysiological changes in HF

Three possible pathophysiological areas for HF monitoring can be defined: monitoring of electrical remodeling, mechanical remodeling, and neurohormonal changes occurring with HF (Table 1). Electrical remodeling in either the atrium or ventricle will result in changes in the normal automaticity, conduction properties, and refractory period and predisposition to atrial fibrillation (AF) and ventricular tachyarrhythmias. The occurrence of arrhythmias is routinely monitored and treated by CIED, both by pacing and defibrillation. The effective refractory period (ERP) can be monitored by physician-activated electrical stimulation through a programmer. Intra- and inter-chamber conduction timings in HF are important; progressive PR and QRS duration prolongation occur with a worsening of HF [15]. A wide LBBB QRS complex is associated with ventricular dyssynchrony and impairs LV function.

The initiating event of HF is most often systolic LV dysfunction. This will affect the sizes of the right and left ventricles, and their systolic and diastolic functions. Early recognition of these changes by monitoring may allow pharmacological or interventional approaches to reverse the changes before clinical HF develops; this may be possible in patients such as those already implanted with a device, such as a pacemaker, which enables long-term monitoring of HF.

However, the major immediate clinical consequence of HF is ADHR, which arises because of fluid overload

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### Table 1

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<th>Monitoring for heart failure pathophysiology.</th>
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<td><strong>Electrical remodeling</strong></td>
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<td>Atrium</td>
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<td>Ventricle</td>
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<tr>
<td>Conduction</td>
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</table>

| **Mechanical remodeling** | **Examples** |
| Atrium | Size, function, structure |
| Ventricle | Size, function, structure |
| Pressure changes | End-diastolic pressure, pulmonary artery pressure (and wedge pressure), venous pressure, left atrial pressure |

| **Neurohormonal changes** | **Examples** |
| Sympathovagal imbalance | Heart rate variability |
| Renin–angiotensin–aldosterone system | BNP |

*BNP*—B-type natriuretic peptide.
*ERP*—effective refractory period.
(particularly in the lungs), and the monitoring of pressure and volume statuses of the lungs and appropriate therapy can prevent ADHF.

Finally, many neurohormonal changes develop secondary to the compensating mechanisms of HF. While not easily measurable directly, these changes may be reflected through heart rate variability and electrical repolarization, which can be assessed by parameters such as the QT interval. This will be an interesting new area for monitoring and therapy guidance.

5. Sensors for heart failure (Table 2)

Sensors for HF monitoring can be classified according to the technical instrumentation. Table 2 summarizes the sensors that have been used or proposed to monitor the events of HF. The paced QRS enables the determination of the QT duration. In addition, the QRS width, measured as the ventricular depolarization gradient, has been proposed as a sensitive marker of catecholamine [16]. These sensors have long been used as surrogate markers of sympathetic activity, which increases with exercise.

High percentage of biventricular pacing is necessary to deliver effective CRT [17] and is a good marker of HF decompensation. AF and ventricular tachyarrhythmias can either be a consequence or trigger event of HF that can easily be recognized and treated. Heart rate variability (HRV) can be measured in patients not yet rendered pacing-dependent, and this factor is a well-established prognostic marker because it reflects the level of sympathovagal imbalance [18]. Reduction of HRV antedates HF events.

Piezoelectric crystals are used to monitor body motion. Decreased body activity is an intuitive consequence of HF exacerbation.

Impedance refers to low, stimulating alternating currents that are of non-cardiac origin and are injected and recorded between pacing electrode pairs. When impedance was applied between RV and LV leads, the lead configuration will encompass part of the left ventricle, thereby enabling the measurement of the intraventricular volume and contractility. When the impedance is applied between an intracardiac lead and the CIED casing, respiratory parameters such as the respiratory rate and minute ventilation can be monitored; these parameters are affected by tachypnea occurring in ADHF. This electrode configuration can also detect pulmonary fluid status, serve as a marker of pulmonary edema, and monitor the respiratory rate.

More direct measurements are now possible with pressure sensors instrumented in the RV, pulmonary artery (PA), or in the left atrium (LA). Since central hemodynamic changes are the precipitating events of ADHF, pressure sensors that measure LA, PA, and RV pressures have been developed and investigated. Recent developments and clinical applications of some of these sensors are summarized below.

5.1. Activity monitoring

Kadhiresan et al. [19] reported the use of externally attached accelerometers at the chest wall to monitor walking distance in HF patients. Using an acceleration threshold of 50 mG, a walking speed of 2 mph (approximately = 2.8 METS) can be detected in a group of 30 patients. The activity log index so defined was closely related to the walking distance of these patients, and the index was higher in the CRT-on phase than in the CRT-off phase. Similarly, the number of times per day when physical activity was greater than a threshold of 70 steps/min was determined by an implanted accelerometer sensor [20], and the trend of the activity level was similar to that of HRV during ADHF and correlates with the NYHA class at baseline. Although a crude index, activity is a good reflection of the general well-being of a HF patient. It is a readily available sensor in most CIEDs, and uses minimal battery energy. In addition, the absence of activity usually signifies the patient is at rest and allows other measurements, such as respiratory parameters, to be determined in the baseline state. An activity sensor is used in conjunction with other sensors for HF monitoring.

5.2. Heart rate variability

In patients with HF, neurohormonal activity predicts the cardiovascular outcome. HRV is an indirect measure of autonomic tone and predicts both sudden and non-sudden cardiac death [21,22]. HRV has been proposed to not only prognosticate HF severity but also serve as a guide for the treatment and prediction of ADHF.

In a randomized study of 50 patients with an implanted CRT device [23], HRV was measured in the atrial sensing mode (VDD at 30 bpm) in either the CRT-on or CRT-off mode. HRV, measured as the SD of the atrial cycle length of all atrial sensed beats, was significantly higher in the CRT-on than in the CRT-off arm (25% higher) and in patients receiving a beta-blocker than in those not receiving it (27% higher).

In the Boston Scientific device, HRV is measured by the SDANN. SD of the intrinsic intervals in the 288 five-minute segments of a day is measured and averaged over a week. If the percentage of intrinsic beats is less than 67% for 24 h, the data for that day is discarded. Using the

<table>
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<th>Table 2</th>
<th>Classification of heart failure-monitoring sensors according to the technical realization.</th>
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<tr>
<td><strong>Sensors</strong></td>
<td><strong>Parameters</strong></td>
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<tr>
<td>Piezoelectric/accelerometer</td>
<td>Activity level</td>
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<td>Paced electrogram</td>
<td>QT</td>
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<td>Impedance</td>
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<td>Minute ventilation</td>
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<td>Pulmonary fluid</td>
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<td>Left ventricular volume and function</td>
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<td>Special leads</td>
<td>Pulmonary arterial and wedge pressures</td>
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<td></td>
<td>Right ventricular pressure</td>
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<td></td>
<td>Left atrial pressure</td>
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<td>Myocardial contractility</td>
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SDANN in a cohort study of 113 HF patients receiving CRT, CRT resulted in a reduction in the ventricular heart rate and mean heart rate and an increase in SDANN (from 69 ± 23 ms to 93 ± 27 ms) after 3 months. Furthermore, lack of HRV improvement predicts non-responders to CRT [24].

With the Boston Scientific CRT device, the HRV can be plotted at each heart rate over a 24-h period, resulting in the so-called “foot-print” [25]. The normalized size of the foot-print is termed the foot-print number, and the graph and number give an easy understanding of the level of HRV: “the larger the better.” In another cohort study [26], HRV using either the SDANN or foot-print was used to predict mortality in 842 patients implanted with CRT during a 11.8-month follow-up period.

In the CRT RENEWAL study, a 436-patient cohort was evaluated for clinical scores derived on the basis of diagnostic data obtained 2 weeks after implantation. The patients were assigned scores on the basis of the following criteria: SDANN of <43 ms; mean heart rate, >74 bpm; foot-print number, <29; and activity percent, <5% from [27]. This scoring system was used to classify patients into low-, moderate-, and high-risk groups. When applied to a separate group of CRT recipients in the HF–HRV cohorts, this scoring system accurately predicted the mortality risk (low, 2.8%; moderate, 10.1%; and high, 13.4%) on the basis of tertiles of their scores.

In the Medtronic device, a long-term measure of HRV—the SD of a 5-min median AS–AS interval (SDAAM)—is used. The algorithm averages the 24-h SD of intrinsic atrial cycle length and will exclude the day’s data if the percentage of atrial pacing exceeds 80% or detects an atrial high-rate episode (AHRE). The change in SDAAM is compared to a rolling average of the preceding 6 months. The SDAAM, night-time heart rate, and activity level were used to predict outcome and HF-related hospitalization in a 397-patient cohort [28] (Fig. 1). A SDAAM of <50 ms predicts overall mortality, and the absolute value of SDAAM remains low in those who were either hospitalized or died. SDAAM declined from 76 ± 27 ms to 64 ± 26 ms at the time of hospitalization, and the change was apparent up to 3 weeks before the event. These data suggest that autonomic surveillance of parameters, such as the HRV, is a good method for both monitoring HF prognosis and predicting ADHF. HRV has limited value when the percentage of atrial pacing is high and during atrial tachyarrhythmias; additionally, its measurement is affected by medications.

5.3. Percent biventricular pacing

In a cohort retrospective analysis of 2 HF trials of CRT-D (1812 patients), Koplan et al. [17] analyzed the relationship between the percentage of biventricular pacing and the outcomes of death and HF-related hospitalization. A 44% reduction was noted in the event rates in those paced 100% of the time versus those paced for less than 92%. The main reason for an inadequate percentage of pacing was atrial arrhythmia. Thus, a high percentage of biventricular pacing of ≥98% is an important goal to achieve in patients with CRT.

In patients with AF, the 12-lead Holter System may be needed to monitor “true” complete biventricular capture using a template-matching system because of fusion complexes [29].

5.4. Right ventricular pressure

PA pressure and PAWP monitoring have been shown to be effective for tailored therapy in patients admitted with advanced HF [30]. Early attempts have been made to continuously record PA pressure on an ambulatory basis [31,32]. An implantable pressure sensor has been incorporated into a pacing electrode with a preliminary application for rate-adaptive pacing [33]. This sensor is a hermetically sealed piezoelectric crystal with a diaphragm facing the blood stream. Early experiences have shown the continuous recording of RV pressure by connecting this electrode to an implanted hemodynamic monitor [34,35]. The Medtronic Chronicle IHM (Model 9520) is a non-pacing, implantable pulse generator capable of external radiofrequency connection and integration in a web-based system. Piezoelectric activity from a passively fixed lead in the RV outflow tract is sampled up to once every 2 s timed to the sensed unipolar RV electrogram. It has been shown that PA diastolic pressure can be estimated at the time of the maximum positive RV dp/dt [36]. Pre-implant calibration pressure is required to facilitate absolute pressure measurement.

5.4.1. Feasibility study

In one study [37], serial Swan-Ganz catheterizations at 3, 6, and 12 months after implant showed a small baseline error of <1 mmHg 12 months after the implantation. Furthermore, the accuracy of pressure measured is not affected by body posture. Adamson et al. [4] studied 32 HF patients who underwent implantation of Chronicle IHM. They found that long-term RV pressure was stable in most...
patients. During a total of 36 volume-overload events, RV systolic pressure increased by 25 ± 4%; heart rate, by 11 ± 2%; and estimated PA diastolic pressure, by 26 ± 4%. Increases in one of the pressures occurred in 9/12 events among patients who underwent HF-related hospitalization, but in 9/24 events among non-hospitalized patients. During a volume-depleted state in 7 patients, RV pressure parameters were reduced. All patients returned to baseline levels after therapeutic intervention. A sustained increase in one of the pressures (> 20% from baseline) occurred in patients subsequently admitted, at a mean of 4.2 days before admission. When the device data were available to the monitoring physician, a reduction in HF-related hospitalization was subsequently observed. Zile et al. [38] compared the ongoing RV hemodynamics between systolic and diastolic HF patients during HF events. They found that RV diastolic pressure was elevated in both conditions, although there was a tendency for more rapid elevation of the pressure in diastolic HF, with less compliable ventricles, than during systolic HF. Thus, besides monitoring HF for intervention, the implantable pressure device enables an understanding of HF pathophysiology that was hitherto impossible.

5.4.2. Clinical outcome study

The Chronicle Offers Management to Patients with Advanced Signs and Symptoms of HF (COMPASS-HF) Study [39] prospectively randomized 274 NYHA Class III or IV HF patients to receive conventional care or therapy guided by Chronicle-derived RV pressure parameters. During a follow-up of 6 months, there was a statistically insignificant trend for reduction of either HF-related hospitalization or the need for intravenous diuretics (primary endpoint) by 21%. A post-hoc analysis showed a 36% prolongation in time to the final HF-related hospitalization in the Chronicle-guided treatment group (Fig. 2). A subgroup analysis [40] found a 20% insignificant reduction in HF events when diastolic HF patients were managed according to Chronicle-derived data. This will be of interest in future larger trials to prevent HF in diastolic HF, which has few proven therapies.

5.5. Other pressure sensors

5.5.1. Left atrial sensor

PA diastolic pressure is an indirect assessment of the filling LV pressure, and an increase in LA pressure precedes pulmonary congestion. This may allow a longer time window for physician intervention to avert ADHF.

The HeartPOD LA pressure monitoring device (St Jude Medical Inc.) comprises an implantable sensor lead that is attached to a coil antenna for telemetry of sensor signals (Fig. 3). The sensor is a pressure sensor with a titanium pressure sensing membrane of 3 × 7 mm². It is capable of measuring high-fidelity pressure and temperature, and electrogram recording. An external patient advisory module (PAM) sends a 125 KHz radiofrequency transmission to the antenna, which then captures 20-s sensor data. The PAM has 13 MB of memory and can store about data during data for 3 months, with 6 recordings per day.

In a single-center feasibility study [41], 8 patients underwent implantation of the LA pressure device using a transeptal approach from the femoral vein. All patients received dual antiplatelet therapy for 6 months (aspirin, 160 mg and clopidogrel, 75 mg per day). The device was calibrated over time using a Valsalva maneuver technique during which the expiratory pressure, as measured by the PAM, will equate to the LA pressure. Over a period of 6 months, the net drift was 0.2 ± 1.9 mmHg per month, although in 1 patient the drift was much more, probably due to malalignment of the sensor to LA walls.

The Hemodynamically Guided Home Self-Therapy in Severe HF Patient (HOMEOSTASIS) trial enrolled 40 patients with Class III to IV HF [42]. All patients underwent implantation of a LA pressure device, although sensor failure occurred in 4 patients. After a 3-month run-in period during which HF-related hospitalization, related events, and medication dosages were documented. Thereafter, LA pressure data were disclosed to the patients, who in conjunction with the physician, adjusted the diuretic dosages. Survival without HF events occurred in 61% at 3 years. Mean daily LA pressure therapy resulted in a fall of LA pressure (17.6 mmHg to 14.8 mmHg), reduction in elevated LA pressure frequency (events > 25 mmHg by 67%), and better NYHA Class, LVEF, and more frequent up-titration of angiotensin-converting enzyme inhibitors and reduction in diuretic dosages.

The HOMEOSTASIS trial is an interesting observational study in which the LA pressure parameter is treated similar to blood glucose parameters in a diabetic patient, and self adjustment of dosages of diuretics helped maintain a euvoletic state. Thus, the possibility of reduced clinical events may be due to the up-titration of angiotensin-converting enzyme inhibition by reducing the dose of diuretics, if LA pressure is low. Conversely, when LA
pressure increases, increasing the dose of diuretics would enable the administration of a larger dose of beta-blockers. As a result, the target doses of both drugs were achieved in 54% of patients as against only 27%, at baseline.

The LA pressure sensor is an interesting device that requires further study in prospective randomized trials. At present, there remain issues of sensor stability, ease of implant (subclavian implant tools are now available), and the risk of thromboembolism.

5.5.2. Pulmonary arterial pressure sensors
Diastolic PA pressure is a surrogate measure of PAWP. An implantable wireless PA pressure transducer (W-IHM) has been developed (Cardio-MENS, Atlanta, GA, USA) [43]; this device is capable of transmitting continuous PA pressure readings when powered by radiofrequency signals from the outside (Fig. 4A). The recordings of this device have been shown to correlate with direct PA pressure measured invasively and with echocardiographic Doppler data [44]. The cardioMENS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III HF Patients (CHAMPION) [45,46] trial investigated the use of such a sensor in 550 patients in the US. In this trial, 280 patients were randomized to be blinded to the sensor information and receive conventional treatment and 270 patients, in the active group in which PA pressure was measured daily by W-IHM; the latter group showed a significant (39%) reduction of HF-related hospitalization (Fig. 4B). The secondary endpoints of mortality, QOL, and duration of HF-related hospitalization were also improved. There was no device failure, and system-related complications only occurred in 8 patients, with 1% implant-related complications. All patients were either continued on warfarin or aspirin after 1 month of dual anti-platelet therapy. No episode of pulmonary infarction or embolism related to the sensor was reported.

The CHAMPION study is the first large study to confirm the role of implantable pressure sensor data to reduce HF morbidity. Unlike telemonitoring that involves only clinical and non-invasive HF parameters, the invasively derived PA pressure measurement allows the physician to adjust neurohormonal, diuretic, or vasodilator drugs, with an aim to reduce PA pressure. There were more changes in medications, and the benefits were observed both in the systolic and non-systolic HF groups. Other implanted PA pressure devices are also under development. For example, an external ultrasound-activated PA pressure sensor (InPressure, Remon Medical Technologies, Boston Scientific) which is fixed in the right PA and has a self-expanding wire mesh, has been tested in 31 patients with chronic HF (PAPIRUS study). Its pressure recordings are reported to be similar to data obtained by the Millar catheter [47].

5.6. Intrathoracic impedance for pulmonary fluid status
Dyspnea is the commonest presenting symptom for ADHF, and congestion or edema are the main underlying mechanisms for dyspnea. Increase in fluid in the lungs will decrease the transthoracic impedance, which can now be measured with an implantable device.

5.6.1. Device description
The concept of impedance to monitor pulmonary congestion is based on a canine experiment by Wang et al. [48]. The Medtronic OptiVol™ fluid management system uses transthoracic impedance to measure pulmonary fluid (Fig. 5). Low-voltage, non-stimulating currents are injected between the RV ICD electrode (e.g., InSyn Sentry) or RV bipolar electrode (e.g., Advixa) to the ICD or pacemaker casing between noon and 5 pm, at a time when the subject is presumably ambulant and upright. A sampling once every 20 s is made and the average obtained. The moving average of the impedance is used to establish a baseline impedance level against which any change can be compared. The algorithm is inactive for the first 34 days after device implantation to allow time for post-implant pocket healing and electrode stabilization. When pulmonary fluid has accumulated beyond a programmable threshold, an alarm is used to alert the patient (or the physician via remote monitoring).
5.6.2. Feasibility studies

The feasibility of using intrathoracic impedance to monitor fluid status has been tested in 34 patients with NYHA Class III or IV HF in the MID Heft Study [5]. A defibrillation lead in the RV apex is connected to a special pacemaker capable of injecting and sourcing impedance. The electrode pairs that connect the RV coil to the device case afford the best impedance signals.

During a follow-up of 20.7 ± 8.4 months, 25 adjudicated HF-related hospitalization events were recorded for 10 patients. Intrathoracic impedance started to decrease before worsening symptoms at 15.3 ± 10.6 days, whereas dyspnea was only reported during the 3 days before hospitalization. For 17 hospitalization events, pulmonary capillary wedge pressure was found to be significantly correlated with impedance (r = −0.61, p < 0.001), and impedance increased as fluid removal occurred with diuresis.

An algorithm for HF detection was derived from 6.2 patient-years of monitoring of 10 patients, and tested in the remaining cohort (Fig. 6). A 60 Ω·day was suggested to have a sensitivity of 76.9% at the expense of 1.5 false-positives per patient-year of monitoring. Early warning occurred at 13.4 ± 6.2 days of HF-related hospitalization events. This landmark study shows that intrathoracic impedance is correlated with pulmonary congestion and changes in a predictable manner as diuresis occurs, thereby facilitating acute monitoring. Furthermore, impedance changes days before ADHF and suggests its role in monitoring HF on an ambulatory basis.

5.6.3. Clinical outcome studies

The Italian OptiVol Study [49] on 532 HF patients reported a 67% detection rate of HF necessitating hospitalization or therapy adjustment. In the remaining patients in whom OptiVol alert was inactivated, HF-related hospitalization was significantly higher (20% versus 7%). The study also showed a false-positive detection rate of 0.5 per patient-year of follow-up.

Maines et al. [50] showed that a 12-week maturation period was required for the pocket and the leads in the de-novo implants, but substantially shorter adaptation period was required for the replacement group, suggesting that the adaptation is partly due to the leads or the algorithm itself. Interestingly, using the RV–LV impedance vectors, they showed that the impedance measured in the responders and non-responders were significantly different, with the biventricularly measured impedance being higher in the responders. This suggests that impedance may play a role in tracking responders to CRT.

In a multi-center study of 558 HF patients implanted with In Sync Sentry from 34 Italian centers, the device-recorded OptiVol fluid index of above 60 Ω·day was associated with a 36% increased risk of HF-related hospitalization over 326 ± 216 days of follow-up [51]. Multivariate analysis showed that in addition to the OptiVol fluid index, a higher percentage of days with low activity, low HRV, and increased

Fig. 5. Intrathoracic impedance measurement by an implantable system. Reproduced with permission [5].
night-time heart rate were independent predictors of hospitalization. In 62 patients for whom the OptiVol algorithm was used, prospective observational measurements of NT-pro-BNP, i.e., clinical HF statuses, were obtained over 27 ± 2 weeks [52]. There was a significant but weak relationship in all pooled change in impedance and change in NT-Pro-BNP levels over all the visits (r = 0.30, p < 0.001). However, the NT-pro-BNP level increased significantly when an OptiVol alert was associated with clinical signs of ADHF (89 ± 25% increase), whereas an insignificant increase was noted in the absence of such signs (25% increase). In patients receiving an alert, NT-Pro-BNP increased by more than 10% in most incidents. By the time of the patient's medical visit, impedance continued to fall, indicating a worsening HF status. In 42% of the cases, a device alert was not related to clinical signs of HF, although overall BNP increased significantly more than objective monitoring, or true false detection by OptiVol.

The usefulness of OptiVol in preventing HF was reported in a single center, case–control study in which 27 patients implanted with InSyn Sentry was compared to a clinically similar group of 27 patients with CRT-D without OptiVol [53]. In the former group, 12/27 patients had OptiVol alerts, resulting in intervention; and hospitalization occurred in only 1/27 over a year of follow-up. In contrast, 7/27 patients had HF-related hospitalization in the controlled patients treated with conventional CRT-D without the OptiVol algorithm. When coupled with remote patient monitoring (Medtronic Carelink, 20/28 (71%) OptiVol alerts in 67 patients could be remotely managed [54]. A temporal relationship has been reported between arrhythmias and OptiVol-measured fluid level. In a study [55], OptiVol threshold crossing > 60 O.day was related to a high risk of occurrence of AF. AF occurred in 43% before or 29% after OptiVol level crossing. This relationship was not verified in another study [56]. However, the latter study showed a higher prevalence of VT/VF at lower level of OptiVol 15–45 Ω day, suggesting that VT/VF occurred at the time of fluid index crossing. The ability of the fluid index to predict the occurrence of arrhythmia requires further study.

5.6.4. Algorithm considerations

Small et al. [57] investigated a cohort of 326 patients implanted with InSyn Sentry, who were followed up for almost a year. In the first 4 months (observational period), threshold crossing at the nominal 60 Ω.day occurred in 17 patients (22 ADHF episodes). The occurrence of threshold crossing predicted a 35% increase in hospitalization during the subsequent period. Furthermore, the following criteria are predictive of hospitalization: more than 3 threshold crossings per year or more than 30 days of threshold crossing per year. When a multivariate analysis was applied, only night-time heart rate remained predictive of ADHF in addition to the crossing of the OptiVol threshold. Thus, both the crossing of the threshold and the duration for which OptiVol level exceeds the programmed threshold are predictive of HF-related hospitalization.

The threshold for OptiVol alert has also been tested in 115 patients implanted with Medtronic InSyn Sentry CRT-D [58]. During a follow-up of 9 ± 5 months, 45 OptiVol alerts occurred in 30 patients; 15 of these alerts (33%) were correlated with clinical signs and symptoms of HF, and the authors suggested that the threshold be increased to 90 Ω.day to increase the specificity to 73%. The authors did not find any causes for false-positive alerts, but patients with HF had significantly higher OptiVol level versus those without. On the other hand, in the European InSyn Sentry Observational Study on 373 subjects [59], the level of 60 Ω.day was associated with a 60% sensitivity and 60% positive prediction of ADHF. This study documented that 9/53 (17%) events were not associated with an OptiVol alert, and in an additional 11 events, an increase in the OptiVol level occurred but did not exceed the programmed detection threshold. These studies confirm the usefulness of intrathoracic impedance in monitoring ADHF, but pointed out the need for fine tuning the detection algorithm and/or individual programming of the OptiVol detection level.

The SENSE-HF study is a prospective trial to assess the sensitivity and positive predictive value of implantable intrathoracic impedance to predict HF-related hospitalization [60]. The study comprises 3 phases and has completed recruitment in 2008. Phase I is a double-blind phase that focuses on retrospective analysis of the value
5.6.5. Advantages and limitations

The advantages of the intrathoracic impedance sensor are the relative ease of instrumention, which eliminates the need for additional leads or complexity of implantation. The battery energy expenditure is low. It has been relatively well-characterized in acute settings and for long-term monitoring. While it has a high sensitivity, its specificity may be limited as impedance in the vector used may be liable to alteration by a number of clinical events that do not indicate pulmonary congestion, such as the occurrence of pleural effusion or pneumothorax [61] (Table 3). However, some of the OptiVol alerts without clinical evidence of HF might represent spontaneous HF improvement due to delayed presentation, i.e., subclinical congestion, in addition to being false positive. Nevertheless, when combined with other sensors, intrathoracic impedance is useful for long-term and acute monitoring of HF (see below).

5.7. Intrathoracic impedance

Impedance signals derived from fully intracardiac electrodes reflect volume changes of the heart more closely than transthoracic impedance. Indeed, Salo et al. [62] reported the use of a tripolar RV lead to measure RV volume changes during the cardiac cycle, from which RV volume and contractility can be derived for rate-adaptive pacing. With the addition of a LV lead in CRT, more accurate measurement of LV volume is now possible for HF monitoring.

5.7.1. Unipolar impedance from the right ventricle

Unipolar impedance applied from the RV apex to the CIED casing samples a small region in the cardiac apex. This results in a signal that has been termed closed-loop stimulation (CLS) sensor. Since the majority of the current is dissipated over a distance of about 1 cm from the apex, the signal reflects the regional contractility of the ventricle rather than a change in stroke volume. While useful for rate-adaptive pacing, unipolar impedance reflects LV contractility only when the changes are sufficiently gross and may not be able to detect small changes in cardiac contractility, which is required in HF monitoring.

5.7.2. Multipolar impedance

Several groups and manufacturers have conducted investigations on the optimal electrode arrangement for detecting ventricular volumes. With currents flowing between intracardiac electrodes (RV, LV, and RA) and to the CIED casing, this arrangement will decrease the impedance since more of the heart is encompassed by these impedance vectors. Four intrathoracic and 2 intracardiac vectors were examined in 16 dogs and 5 sheep [63]. Impedance values measured by all vectors decreased with the onset of HF, with the maximum decrease occurring with LV-Can and LV-RV. Importantly, HF-related changes are greater for LV-Can impedance than vectors involving the right heart electrodes (RA-Can, RV-Can, and RV Coil-Can), while those for RV-LV and LV-RA are intermediate. LA pressure showed greater correlation with LV-Can impedance ($r^2 = 0.73$) than RV-Can ($r^2 = 0.43$) and RV Coil-Can ($r^2 = 0.52$) impedance. Circadian variation in impedance also decreased in HF (5 ± 2% to 2 ± 1%). Thus, in these animal models, the incorporation of a LV vector significantly improves the detection of LV volume increase occurring in HF.

Biventricular impedance has been measured using a quadripolar electrode arrangement [64,65]. In 9 mini-pigs with pacing-induced HF, biphasic pulses (15 μs, pulse width: 600 μA, constant current amplitude) were applied between the RV ring and tip electrode, and impedance was sourced using the LV ring and tip electrode. “Stroke impedance” was calculated as the difference between impedance values during systole and diastole. Systolic impedance was defined as the highest impedance 50–500 ms after the R-wave, whereas diastolic impedance was measured during a 20-ms window within the R-wave. After 20 days of HF induction by rapid pacing in these animals, the increase in LV end-diastolic pressure was found to be significantly correlated with the end-diastolic impedance, which decreased by 30% ($r = -0.81, p < 0.001$). End-diastolic volume also trended in the same direction as the impedance value, which decreased by 20%. The corresponding intrathoracic impedance decreased by 8%, which had a poorer correlation with the end-diastolic pressure.

These animal experiments suggest that biventricular impedance can be used to monitor LV size and pressure changes that occur with HF. Theoretically, the advantages of using biventricular impedance over transthoracic impedance are that there will not be significant time lag for lead/pocket maturation and the measurement will not be affected by pulmonary conditions, such as pleural effusion and pneumothorax. Because the elevation of LV end-diastolic pressure occurs earlier than pulmonary edema, this sensor can be used to detect deterioration of early HF, where significant pulmonary fluid accumulation has not occurred and for monitoring LV function. The limitations include the need of a LV lead (which restricts its use in a CRT device), dependence on the relative position of RV-LV leads (only relative changes rather than absolute value can be detected), and significant diurnal (and possible postural) changes that need to be accounted for in an implantable system.

5.7.3. Clinical studies

An acute study was conducted on biventricularly measured impedance in 14 HF patients during implantation...
of CRT devices [66]. The authors also tested the effect of different LV lead locations on biventricular impedance measurements, and changes in stroke volume were induced with overdrive pacing. Pooled data obtained from a study of 20 overdrive pacing episodes and 6 different lead locations showed good correlation between stroke impedance measured with stroke volume ($r=0.82 \pm 0.10$) and pulse pressure ($r=0.81 \pm 0.16$). The authors reported no significant effect of LV lead positions, but the accuracy and signal sizes tend to be better in the mid-ventricular region than in the basal and apical regions (Fig. 7).

Currently, data on long-term implants is scarce. The relative merits and limitations of intrathoracic and intracardiac impedance are summarized in Table 4. In patients with a suitable device (i.e., with an LV lead), it is very likely that a combined transthoracic and biventricular impedance can be used.

### 5.7.4. Minute ventilation and respiration rate

Dual sensor pacemakers that encompass activity and minute ventilation (MV) have been developed for rate-adaptive pacing. HF leads to compensatory hyperventilation, especially in the resting state. An algorithm [67] published that includes mean daily resting and MV during activity and mean daily activity level. A stable MV and activity level will suggest stable clinical HF, whereas an increase in MV, especially at rest and combined with a decrease in activity, suggests deterioration of HF. Conversely, a stable MV level with an increase in activity indicates recovery from HF. Nineteen patients who had no history of HF and underwent Talent™ (Sorin-ELA, Italy) implantation were compared with 48 HF patients implanted with Talent CRT. Wide inter- and intraindividual variability was noted, and fast Fourier transformed data allowed for 7-day periodicity. While mean activity was similar in the 2 groups, the resting and activity MV levels were higher in the CRT group. Overall, it was reported that the algorithm has a sensitivity of 88%, specificity of 94.7%, positive predictive value of 71%, and negative predictive value of 98.2% for HF.

Unlike MV, which can only be measured in relative terms, respiratory rate can be easily assessed. It is anticipated that respiratory rate will increase during ADHF, although investigations regarding this aspect are minimal. The Boston Scientific has introduced an ICD (Energen™) capable of monitoring the respiratory rate. Further investigation, especially in relation to interference and accuracy in prediction of ADHF, will be required to verify its effectiveness.

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**Fig. 7.** Biventricular impedance derived raw data recording (ECG, surface electrocardiogram; AortaP, aortic blood pressure; Z, intracardiac impedance. Vertical lines 100 ms in front of the QRS complex). The respiratory influence is clearly visible in the pressure and impedance traces. Reproduced with permission [66].

**Table 4**

<table>
<thead>
<tr>
<th>Heart failure parameters</th>
<th>Intrathoracic impedance</th>
<th>Intracardiac biventricular impedance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary edema</td>
<td>LV volume and contractivity</td>
<td></td>
</tr>
<tr>
<td>RV lead or coil to casing (tripolar)</td>
<td>RV–LV bipoles (quadripolar)</td>
<td></td>
</tr>
<tr>
<td>Takes up to 1 month</td>
<td>Less</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Less</td>
<td></td>
</tr>
<tr>
<td>Significat</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>~70% (depends on threshold)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Pacemakers and ICD</td>
<td>CRT-P or CRT-D</td>
<td></td>
</tr>
<tr>
<td>Relatively extensive</td>
<td>Limited</td>
<td></td>
</tr>
</tbody>
</table>
5.8. ST-segment shift

ST segment deviation heralds either ischemia or myocardial injury. Myocardial ischemia requires medical therapy or revascularization, especially in symptomatic individuals. Myocardial injury, on the other hand, is a medical emergency that calls for emergency reperfusion. Prompt treatment of myocardial infarction will significantly reduce mortality. Delay in the recognition of chest pain due to infarction (and in some instances, silent infarction) is a significant contribution to the appearance of the delayed presentation of myocardial infarction. Since long-term external ambulatory ECG recording may not be practical, intracardiac electrograms have been tested and thought to reflect infarction and ischemia in an animal model [68]. When incorporated into a CIED with patient alert and remote monitoring, ST segment monitoring becomes a possibility.

The Angel Med Guardian (now under St Jude Medical) is a single-chamber device with an RV apical lead. An intracardiac electrogram (ICEG) was derived from the RV apex to the device casing. The device records a 10-s ICEG once every 90 s for normal sinus beat within 50–90 bpm. Data are amplified with a gain of 62.5–625 times and band passed between 0.25 to 45 Hz, followed by A/D conversion at 200 Hz. ST segment level is compared to the corresponding PQ segment level, and a baseline ST segment level is calculated as a rolling 24-h average, which is determined hourly. The extent of the deviation is normalized by the average R wave voltage, including the effect of heart rate tested during an exercise. A rate-adjusted spontaneous ST deviation can then be considered as an ischemic event, and an alert will be triggered.

A limited number of devices have been implanted in humans [69]. During angioplasty with temporary coronary artery occlusions, ST segment deviations occur, with a negative shift in the presence of occlusion of the left anterior descending artery and a positive shift in that of other arteries. In this study, 10 abnormal alerts occurred in 6 patients, necessitating coronary artery interventions.

In addition to its usefulness in the detection of ischemia, ST deviation may shed light on the ischemic cause of arrhythmia, by virtue of its association with the occurrence of arrhythmias, such as ventricular tachycardia. Apart from its logistic implications, ST segment monitoring (which sometimes may require urgent intervention) will be possible only for patients not dependent on pacemakers. The influence of medications, electrolytes, and heart rate on ST segment needs further evaluation.

5.9. Peak endocardial acceleration

Peak endocardial acceleration (PEA) sensor has been used for rate adaptation. The PEA signal measures the closure sound of the mitral valve and reflects cardiac contractility. A minimal PEA signal occurs during the optimal AV interval in DDD devices [70] and reflects the optimal AV interval in most patients. A new CRT-P (The New Living™ CHF, Sorin-Elia, Italy) is now available to monitor heart function and program the AV interval in the CRT device. The PEA is contributed by both the contractility and LV filling, and an index known as the PEA area is derived by measuring the PEA values at different AV interval scanning at each VV interval. The maximum PEA area will define the optimal VV and AV interval for the patient.

In 15 patients implanted with a CRT device with PEA sensor, cardiac catheterization was performed and the LV dp/dr and the PEA area were determined [71]. AV interval was scanned between 60 and 220 ms. The authors noted response to CRT (defined by 10% increase in dp/dr) in 75% of the patients. Concordance of PEA area versus the dp/dr methods was noted in 8/12 patients. These data are interesting, although the role of AV interval programming over a long period is uncertain, and the ability of the sensor to monitor LV function remains to be tested.

6. Combined heart failure diagnostics

The Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients with HF (PARTNERS HF) is an observational study on the use of diagnostics to predict HF [72]. Hundred sites in the US prospectively recruited 694 patients implanted with CRT-D and followed them for 11.7 ± 2 months. Table 5 shows the diagnostic data considered important in an algorithm to predict ADHF.

Ninety patients had 141 adjudicated HF events, occurring after 60 days of implantation. A positive combined diagnostic set predicts a 5.5-fold risk of hospitalization in

<table>
<thead>
<tr>
<th>HF device diagnostic parameter</th>
<th>Algorithm</th>
</tr>
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<tbody>
<tr>
<td>AF duration</td>
<td>AF for ≥ 6 h on at least 1 day in patients without persistent AF (7 consecutive days with ≥ 23 h AF)</td>
</tr>
<tr>
<td>Ventricular rate during AF</td>
<td>AF for 24 h and the average ventricular rate during AF being ≥ 90 beats/min on at least 1 day</td>
</tr>
<tr>
<td>Fluid index (OptVol)</td>
<td>High fluid index on at least 1 day; thresholds included, ≥ 60, ≥ 80, and ≥ 100</td>
</tr>
<tr>
<td>Patient activity</td>
<td>Average patient activity &lt; 1 h over 1 week (nonoverlapping weekly windows)</td>
</tr>
<tr>
<td>Night heart rate</td>
<td>Average night heart rate of &gt; 85 beats/min for 7 consecutive days (nonoverlapping weekly windows)</td>
</tr>
<tr>
<td>HRV</td>
<td>HRV of &lt; 60 ms everyday for 1 week (minimum 5 measured days; nonoverlapping weekly windows)</td>
</tr>
<tr>
<td>Percent of pacing CRT</td>
<td>Ventricular pacing ≤ 90% for 5 of 7 days (nonoverlapping weekly windows)</td>
</tr>
<tr>
<td>ICD shock for potentially lethal VT/VF</td>
<td>≥ 1 Shocks during the evaluation period</td>
</tr>
</tbody>
</table>

AF=atrial fibrillation; AT/AF=atrial tachycardia/atrial fibrillation; CRT=cardiac resynchronization therapy; HF=heart failure; HRV=heart rate variability; ICD=implantable cardioverter-defibrillator; VT/VF=ventricular tachycardia/ventricular fibrillation.
the next month, even after adjusting for the clinical variables. The main diagnostic parameters are OptiVol $\geq 60$ Ω day, low activity, and low HRV. When additional OptiVol was $\geq 100$ (28% of patients), it was also predictive of ADHF (Fig. 8). Further sub-group analysis suggested that the specificity of ADHF is improved with setting a higher level of fluid index, and using more non-fluid related indices (at the expense of some loss of specificity.) There is an improvement in the diagnostic accuracy if sampling is performed every 15 days versus less frequently. Further tests are required to verify whether closer monitoring, such as with the use of remote web-based system, can further reduce ADHF.

The PARTNERS HF is an important study that highlights the role of combined HF diagnostics in predicting ADHF. While the sensitivity and specificity of the algorithm needs to be tested in prospective randomized trials, the occurrence of positive diagnostic criteria are predictive of a group of high-risk HF patients. Conversely, the absence of diagnostic alerts predicts a stable HF. This risk stratification is over and above that achieved with the conventional clinical risk factors.

7. Conclusion

Sensors have been introduced to optimize the pacing rate in patients with chronotropic incompetence. With the increasing use of devices to treat and monitor HF, sensors have now metamorphosed from their role in optimizing HF management to preventing the worsening of HF.

Conflict of interest

All authors have no conflicts of interest to declare.

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