Heart failure represents a major public health concern, associated with high rates of morbidity and mortality. A particular focus of contemporary heart failure management is reduction of hospital admission and readmission rates. While optimal medical therapy favourably impacts the natural history of the disease, devices such as cardiac resynchronization therapy devices and implantable cardioverter defibrillators have added incremental value in improving heart failure outcomes. These devices also enable remote patient monitoring via device-based diagnostics. Device-based measurement of physiological parameters, such as intrathoracic impedance and heart rate variability, provide a means to assess risk of worsening heart failure and the possibility of future hospitalization. Beyond this capability, implantable haemodynamic monitors have the potential to direct day-to-day management of heart failure patients to significantly reduce hospitalization rates. The use of a pulmonary artery pressure measurement system has been shown to significantly reduce the risk of heart failure hospitalization in a large randomized controlled study, the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial. Observations from a pilot study also support the potential use of a left atrial pressure monitoring system and physician-directed patient self-management paradigm; these observations are under further investigation in the ongoing LAPTOP-HF trial. All these devices depend upon high-intensity remote monitoring for successful detection of parameter deviations and for directing and following therapy.

Introduction

Heart failure disease management to prevent worsening symptoms and/or hospital admission in ambulatory heart failure patients remains a challenge. Despite current evidence-based, guideline-recommended drug therapies, hospitalization rates remain unacceptably high. The number of yearly hospitalizations for heart failure as a primary discharge diagnosis was unchanged from 1997 to 2007 at almost 1 million (Medicare). Approximately 25% of discharged patients were readmitted within 30 days. More over, the outpatient burden of heart failure care is an estimated 3 434 000 ambulatory medical encounters annually. Improvements in outpatient management of heart failure are needed to address this substantial burden of inpatient and outpatient care.

An increasing number of heart failure patients are living with implanted cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillator (ICD) devices. In addition to their direct therapeutic benefits and ability to remotely monitor device function and arrhythmias, these can also monitor physiological parameters of interest to heart failure management. Investigational implantable haemodynamic monitors, whether used alone or in combination with CRT and ICD devices, may provide information useful for further improvement of heart failure disease management. These device-based diagnostics and haemodynamic monitors could allow for more frequent or continuous assessment of a patient’s heart failure status and thereby inform preventive measures to mitigate further deterioration and hospitalization. This article will contrast non-invasive remote patient monitoring vs. device-based physiological and haemodynamic information in heart failure disease management.

Limitations of non-invasive remote patient monitoring

Non-invasive remote heart failure patient monitoring generally involves regularly scheduled structured telephone contact
between patients and healthcare providers and/or the electronic transfer of physiological data using remote access technology via electronic devices. This approach allows for assessment of symptoms, weight changes, blood pressure, heart rate, and activity logs. The efficacy of such non-invasive monitoring methods remains unclear. A recent large meta-analysis of randomized control trials and observational cohort studies suggested that remote telemonitoring may be beneficial for reducing death, hospitalizations, and hospitalizations for heart failure, with a 17 and 47% reduction in the risk of death for randomized controlled trial and cohort studies, respectively.\(^1\) However, two recent large prospective randomized controlled trials contradicted these findings. In a National Institutes of Health sponsored study (Telemonitoring to Improve Heart Failure Outcomes [TELE-HF]), 1653 patients, recently hospitalized heart failure patients, were randomized to undergo either telemonitoring or usual care.\(^4\) Telemonitoring was accomplished by means of a telephone-based interactive voice-response system that collected daily information about symptoms and weight that was reviewed by the subjects’ clinicians. There were no significant differences in the primary endpoint of readmissions or death for any cause at 180 days. Likewise, hospitalizations for heart failure, the number of days in hospital, and the total number of hospitalizations were not significantly reduced by telemonitoring. Similarly, the Telemedical Interventional Monitoring in Heart Failure trial in Europe randomized New York Heart association (NYHA) class II or III heart failure patients with left ventricular dysfunction (left ventricular ejection fraction \(\leq 35\%\)) to daily remote telemonitoring (including an electrocardiogram, blood pressure measurement, and assessment of body weight) coupled with medical telephone support or to usual care led by the subjects’ local physician.\(^3\) After 2 years, there was no significant difference in all-cause mortality (the primary endpoint) or in the composite of cardiovascular death or heart failure hospitalization (a major secondary endpoint) between the two groups. At present, the role on non-invasive remote patient monitoring remains unclear and may be inadequate for improving outcomes. Thus, alternatives to non-invasive remote patient monitoring systems are needed. These are discussed below.

An increasing number of patients with a history of heart failure or at-risk for future heart failure receive ICD and CRT devices, which impart survival benefit. For example, \(> 8500\) subjects have been evaluated in randomized controlled trials of CRT and combined CRT–ICD devices since the first large prospective double-blind study of CRT in patients with moderate-to-severe heart failure and a prolonged QRS interval (MIRACLE) was completed in 2001.\(^6\)–\(^13\) In NYHA class I–IV subjects, CRT alone or in combination with an ICD, has consistently been shown to improve cardiac structure and function and to reduce heart failure as well as all-cause morbidity and mortality. In NYHA class III and IV patients, CRT also improves quality of life, functional status, and exercise capacity. The recent guideline update for CRT advocates the use of remote monitoring in this high-risk group of patients.\(^14\) It may be possible to improve prognosis, beyond their directly therapeutic effect, by following existing or novel diagnostic parameters (shared by many ICD devices) to guide therapy. For example, during arrhythmia monitoring the burden of atrial fibrillation may be a predictor of worsening heart failure per se and also by reducing the percent of biventricular pacing.\(^15\) Among the most potentially useful device-based physiological parameters are intrathoracic impedance, heart rate variability (HRV), and patient activity level. When coupled to internet-based patient-specific information systems and non-invasive sensors, device-based diagnostics may be combined with other parameters (including daily weights and blood pressure changes) to provide a better picture of clinical status.

### Intrathoracic impedance monitoring

Accumulation of lung water decreases electrical impedance across the lung. Using the right ventricular (RV) lead to send an electrical current to an implanted pulse generator permits measurement of intrathoracic impedance. This yields a relative measure of lung ‘wetness’ that may be useful in heart failure patients. Intrathoracic impedance inversely correlated with pulmonary capillary wedge pressure and net fluid loss during hospitalization in one small observational study.\(^16\) Moreover, a decrease in impedance was noted before the onset of symptoms and hospital admission for pulmonary fluid volume overload, suggesting utility to predict heart failure hospitalizations. Impedance index increase greater than a pre-defined level may trigger an audible alarm in the device (only enabled outside of the US presently) or the measure can be monitored using proprietary remote web-based information systems.

Studies to date assessing different thresholds of impedance change have proven to be highly sensitive but with low positive predictive value for heart failure hospitalization.\(^17\),\(^18\) In the Fluid Accumulation Status Trial (FAST), intrathoracic impedance monitoring was much more sensitive than daily weight monitoring for predicting a heart failure hospitalization (sensitivities of 76.4 and 22.5%, respectively) for the commonly used (and pre-specified) cutoffs of 60 ohm-days and 3 lbs in 1 day or 5 lbs in 3 days.\(^19\) The unexplained detection or threshold-crossing rate was substantially higher for weight monitoring (4.3 per year) compared with intrathoracic impedance monitoring (1.9 per year). Thus, intrathoracic impedance monitoring appears more sensitive and is associated with fewer ‘false alarms’, when compared with standard of care daily weight monitoring.

Despite this apparent diagnostic superiority of intrathoracic impedance monitoring, to date no randomized controlled trial has demonstrated a reduction in heart failure hospitalization on the basis of this technology. One attempt to do so, the Diagnostic Outcome Trial in Heart Failure (DOT-HF), demonstrated an ‘expected’ increase in outpatient heart failure clinic visits and an ‘unexpected’ increase in heart failure hospitalizations.\(^19\)

### Heart rate variability

Continuous HRV can be derived from implanted devices and remote patient monitoring systems. Heart rate variability is a physiological marker of cardiac autonomic control, describing the balance between sympathetic and parasympathetic activity. Increased sympathetic and decreased parasympathetic activity in heart failure is associated with worse outcomes. Heart rate variability can be defined as the standard deviation of 5 min median atrial-to-atrial intervals (SDAAM). In one study, SDAAM \(< 50\) ms when averaged over 4 weeks was associated with a greater than three-fold mortality
Moreover, SDAAM decreased a median of 16 days before hospitalization and returned to baseline after treatment, suggesting a role for HRV monitoring in heart failure. However, automated detection of SDAAM decreases was 70% sensitive in predicting heart failure hospitalization, but with 2.4 false-positives per patient-year of follow-up.

Combining intrathoracic impedance, heart rate variability, and other device-based diagnostics

The Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure (PARTNERS-HF) trial was a prospective, multicentre observational study in patients receiving CRT. The devices used assessed patient activity level, atrial fibrillation duration, ventricular rate during atrial fibrillation, intrathoracic impedance, night heart rate, HRV, the percentage of time of pacing in CRT, and appropriate ICD shocks. Of these parameters, the three most commonly triggering the algorithm were reduced patient activity level, reduced intrathoracic impedance, and reduced HRV. Patients with a positive combined heart failure device diagnostics score had a 5.5-fold increased risk of heart failure hospitalization with pulmonary signs or symptoms within the next month. Thus, it appears that changes in device-based heart failure diagnostic parameters, using an algorithm based on combined parameters, can stratify patients into high-risk and low-risk subgroups. While the PARTNERS-HF trial required monthly in person evaluations for downloading of device-based diagnostic data, remote monitoring of these data may provide a more clinically sustainable model for care.

Figure 1 Pulmonary artery pressure monitor system. (A) The PAP MEMS-based sensor; see the text for description of the device. (B) An antenna embedded in a pillow simultaneously powers and interrogates the sensor using radiofrequency. (C) Pressure data are uploaded to a secure website for clinician assessment of discrete data and pressure trends.
These device-based physiological parameters, while useful in risk stratification, may not be precise enough to enable day-to-day heart failure disease management. Since the proximate cause of worsening heart failure symptoms, pulmonary congestion, and the need for heart failure hospitalization is related to increases in intracardiac and pulmonary artery pressures (PAPs), direct measurement of such pressures in ambulatory patients using implantable haemodynamic monitors is under investigation.

**Implantable haemodynamic monitoring**

Assessment of ventricular filling pressures with investigational devices in an ambulatory setting include RV, pulmonary artery (PA), and left atrial pressure (LAP) monitors.

**Right ventricular pressure monitors**

The ability to estimate pulmonary artery end-diastolic pressure (ePAD) from within the RV was established in 1995.22 Based on the notion that RV pressure at the time of pulmonary valve opening is equal to PA diastolic pressure, RV pressure at the time of RV maximum change in pressure over time (dP/dt) was considered the ePAD and this correlated with directly measured PA diastolic pressures at baseline, during isometric work, and during the Valsalva manoeuvre. This was incorporated into an implantable leaded RV pressure monitoring system (similar to a single-lead permanent pacemaker) to continuously measure RV systolic and diastolic pressures (RVSP and RVDP), ePAD, RV dP/dt, heart rate, patient activity level, and temperature.23 Using this device in a pilot study in 32 patients with NYHA class II/III heart failure showed RVSP increases occurred on average 4 ± 2 days before the exacerbations requiring hospitalization. In a prospective, multicentre trial [Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF)] NYHA class III/IV heart failure patients were randomized to usual care alone vs. usual care plus care guided by knowledge from the RV sensor system.24 The study demonstrated a non-significant 21% reduction in the RV sensor group compared with the control in the primary efficacy endpoint of reduction in heart failure events (hospitalizations, emergency or urgent care visits requiring intravenous therapy). The COMPASS-HF trial was underpowered for its primary endpoint, and clinicians generally failed to adequately lower ePAD without target values or an algorithm to guide therapy. Thus, the hypothesis that lower pressures result in reduced rates of heart failure events was not adequately tested in this study.

**Pulmonary artery pressure monitors**

A novel wireless PAP monitoring system has recently been evaluated in the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial.25,26 The PAP sensor is a coil- and a pressure-sensitive capacitor encased in a capsule (Figure 1A) without leads or batteries. It is implanted into the PA during right heart catheterization, i.e. is less invasive than the RV and LAP sensors. Pressure applied to the sensor causes deflections of the pressure-sensitive surface, resulting in a characteristic shift in the resonant frequency. Electromagnetic coupling is achieved by an external antenna, which is held against the patient’s body or embedded in a pillow (Figure 1B). The antenna provides power to the device, continuously measuring its resonant frequency, which is then converted to a pressure waveform. Pressure data are then transmitted wirelessly to a secure website, where

![Figure 2](https://academic.oup.com/europace/article-abstract/15/suppl_1/i40/526579/1445557678) Primary (6-month) and extended results of the CHAMPION trial for the primary endpoint of heart failure hospitalization rate.
The CHAMPION trial randomized 550 patients to two groups, where the clinicians used daily measurement of PAPs in addition to standard of care (treatment group; \(N = 270\)) vs. standard of care alone (control group; \(N = 280\)). The CHAMPION trial differed from prior studies of implantable haemodynamic monitors in that specific pressure targets and treatment algorithms were mandated by protocol to assure adequate testing of the hypothesis. The protocol-specified pressure goals were PA systolic pressure 15–35 mmHg, PA diastolic pressure 8–20 mmHg, and PA mean pressure 10–25 mmHg. Patients were considered hypervolaemic and at-risk for heart failure hospitalization, if their pressures were above these ranges. Protocol recommended responses to hypervolaemia included initiation or intensification of diuretics (including increasing, adding, or changing diuretics or the use of intravenous diuretics), initiation or intensification long-acting nitrates, and initiation or intensification of education regarding dietary salt and fluid restrictions, as well as other treatment options described in detail elsewhere. The trial was adequately powered to its primary endpoint of heart failure hospitalization rate over 6 months.

Over 6 months, significantly fewer heart failure hospitalizations occurred in the treatment group compared with the control group (83 in the treatment group vs. 120 in the control group). During the entire single-blinded follow-up averaging 15 months, the treatment group had a 37% relative risk reduction in heart failure hospitalizations compared with the control group (Figure 2). The majority of pressure-based medication changes (about 75%) involved, as expected, diuretics and long-acting nitrates. All four pre-specified and statistically powered secondary endpoints were met favouring the treatment group, including PAP reduction, proportion of patients hospitalized for heart failure, days alive and out of the hospital for heart failure, and quality of life score. Freedom from device-related or system-related complications was 98.6%, and overall freedom from pressure-sensor failures was 100%. This is the first positive randomized controlled trial of implantable haemodynamic monitoring in patients with moderately symptomatic heart failure.
Left atrial pressure monitors

Direct measurement of LAP has been accomplished in ambulatory heart failure patients with an investigational monitoring system.27,28 The system consists of an implantable sensor lead coupled to a subcutaneous antenna coil, a patient advisory module (PAM), and remote clinician access via secure computer-based data management. The tip of the sensor system lead is implanted transvenously into the atrial septum oriented to the left atrium (Figure 3A), measuring and communicating LAP, temperature, and intracardiac electrogram. The implant is powered and interrogated through the skin by 125 kHz radiofrequency wireless transmissions from the PAM, when high-fidelity physiological waveforms are captured for periods of up to 20 s and stored in the PAM. Left atrial pressure measurements were within ±5 mmHg of simultaneous pulmonary capillary wedge pressure readings via right heart catheterization.29 A prospective, observational, first-in-human study of this LAP monitoring system, utilizing a physician-directed patient self-management paradigm (Figure 3B), suggested potential to improve haemodynamics, symptoms, and outcomes in advanced (NYHA class III/IV) heart failure.25 Following a 3-month blinded period, LAP and individualized therapy instructions guided by these pressures were disclosed to the patient. The mean daily LAP fell from 17.6 mmHg in the first 3 months to 14.8 mmHg (P < 0.003) during pressure-guided therapy. The frequency of readings >25 mmHg was reduced by 67% (P < 0.001). Left ventricular ejection fraction and NYHA class improved. Compared with the year prior to LAP monitor implantation and to the 3-month period of observation post-implantation, the annualized rate of heart failure hospitalization was significantly reduced following initiation of the physician-directed patient self-management algorithm. These preliminary findings are being evaluated further in a large prospective randomized controlled outcomes study.

Summary

The incidence and prevalence of heart failure will likely continue to increase, as the population ages and lives longer. Optimal medical therapy alone is not always sufficient to treat these patients, who continue to have unacceptably high rates of morbidity and mortality. Devices, such as CRT, have entered our routine armamentarium for the treatment of heart failure. While CRT is therapeutic in and of itself, improving patient well-being, morbidity, and mortality, it also permits remote patient monitoring via device-based diagnostics. For those without a CRT (or ICD) indication, stand-alone implantable monitors may provide sufficient value to warrant their implantation. While data are lacking to support the use of device-based diagnostics such as intrathoracic impedance and HRV as day-to-day heart failure disease management tools, implantable haemodynamic monitors, in particular the PAP sensor, have shown this potential. This ushered in a new era of physician-directed patient self-management based on direct measurement of intracardiac pressure, enabled by remote monitoring.

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References


