Telemonitoring and Contemporary Outpatient Management of Patients with Heart Failure: Is it Time?

Tamas Alexy, Gary S. Francis

Department of Medicine, Division of Cardiology, University of Minnesota, Minneapolis, MN 55455, USA

Correspondence:
Tamas Alexy, MD, PhD, Assistant Professor of Medicine, University of Minnesota, Division of Cardiology
420 Delaware St SE, Minneapolis, MN 55455, USA, E-mail: alexy001@umn.edu, tel.: 1 (612) 626 1370

Chronic heart failure is not going away, but continues to expand globally. This is largely driven by new cases of heart failure with preserved ejection fraction. Patients receive chronic disease management complicated by frequent hospitalizations to treat episodes of exacerbation that not only affect quality of life but is also associated with a significant financial burden to the society. With a better understanding of heart failure pathophysiology, our management strategy has shifted progressively from reactive to preventive, such as daily weight monitoring and interaction with specialized nurses. With the advent of new technology, non-invasive remote monitoring is now more available with regular, automatic data transmission to the health care center, including heart rate, blood pressure, weight and daily activity. The widespread use of implanted cardioverter defibrillators and cardiac resynchronization therapy in patients with heart failure has enabled the expansion of these devices with various indwelling sensors aimed at monitoring volume status and predicting need for hospitalization. As the success of this approach was noted to be limited, implantable hemodynamic sensors have been subsequently developed in an attempt to reduce heart failure hospitalizations and mortality. This manuscript provides a brief review and clinical utility of the available remote monitoring approaches and devices for patients with heart failure.

Keywords: heart failure, remote monitoring, hemodynamic sensors, mortality

Újabb lehetőségek a telemonitorozás és a krónikus szívelégtelenség ambuláns kezelésében

A krónikus szívelégtelenség incidenciája világszerte emelkedik elsődlegesen az újonnan diagnosztizált megtartott ejekciós frakciójú szívelégtelenségben szenvedő betegek magas számának köszönhetően. A szívelégtelen betegek krónikus ellátást és gyakori kórházi kezelést igényelnek, amely nemcsak az életminőségre van negatív hatással, de a társadalomra is jelentős anyagi terhet ró. A szívelégtelenség patofiziológiájának megismerésével párhuzamosan terápiás stratégiánk egyre inkább a reaktív felől a preventív felé tolódott, mint például a testsúly napi követése és a szívelégtelenség ellátásában jártas nővérekkel való rendszeres kapcsolattartás. A technológia fejlődésével noninvaziv telemonitorozás is lehetővé vált, amely rendszeresen és automatikusan továbbít bizonyos paramétereket az egészségügyi centrumba, mint például szívfrekvencia, vérnyomás, testsúly és napi aktivitás. A defibrillátorok és reszinkronizációs terápia elterjedése lehetővé tette különböző szenzorok integrálását, amelyek alkalmasak lehetnek a folyadékfelesleg monitorozására és emiatti kórházi felvétel szükségességének előre történő megjóslására. Mivel ezen módszerek sikere limitáltnak bizonyult, implantálható hemodinamikai monitorok kerültek kifejlesztésre, melyek használata a szívelégtelenség miatti halálozás és kórházi felvételek számának csökkenéséhez vezetett. Ezen közlemény a szívelégtelenségben szenvedő betegpopuláció számára rendelkezésre álló invazív és noninvazív telemonitorozási lehetőségeket, valamint az ezekkel elért eredményeket foglalja össze.

Kulcsszavak: szívelégtelenség, telemonitorozás, hemodinamikai monitorok, halálozás

Epidemiology and pathophysiology of heart failure

Chronic heart failure (HF) is currently estimated to affect over 38 million adults worldwide (1), a prominent surge from 23 million in the 1990s (2). Despite improved preventive and therapeutic strategies, it's prevalence is projected to increase by an additional 46% by 2030 (3). In the United States (U.S.) alone, 5.7 million adults suffer from symptomatic disease currently (3) and over 500,000 new patients are diagnosed with HF annually. Based on studies performed in the U.S. and f the leading diagnoses for hospitalizations and re-hospitalizations; more than 20% of patients are re admitted within 30 days of discharge and 50% by 6 months (7, 8). Frequent HF hospitalizations not only affect the patient's quality of life but also represent a major financial burden to the society with the total cost estimated to exceed $70 billion in the U.S. by 2030 (9). While not all HF-related healthcare expenditures are preventable, multiple strategies and novel medical devices have been developed aiming to reduce hospital admissions and emergency room/office visits without compromising patient safety. This has required an improved understanding of HF pathophysiology and the identification of milestones whereby early intervention could reduce the risk of further decompensation.

The most common reason for acute HF exacerbation is congestion rather than a rapid, unexpected decline in cardiac output. Despite the significant structural and functional differences between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), rising filling pressures play a pivotal role in the pathophysiology of decompensation in both syndromes (10). Using implantable pressure monitors, subtle but persistent changes can be detected up to 4 weeks prior to hospitalization (11). Within 7 days there is a prominent shift in the balance of the autonomic nervous system with sympathetic activation and reduced parasympathetic tone. These initial compensatory mechanisms lead to increased inotropy, chronotropy, vasoconstriction, activation of the renin-angiotensin system and further fluid retention. The increased intravascular hydrostatic pressure commonly leads to interstitial fluid accumulation in the lungs as well as the periphery overwhelming the lymphatic system (12). In some cases, there is simply a translocation of splanchnic fluid to the thorax without increase in weight. These changes are usually documented 1-2 weeks prior to admission and are accompanied by a decrease in thoracic impedance. Without a change in diuretic regimen, ongoing fluid retention can often, but not always, lead to a detectable increase in body weight. Clinical signs and symptoms of decompensated HF develop within approximately 7 days, ultimately prompting patients to seek medical attention.

As we gain a better understating of the pathophysiology of HF, non-invasive methods as well as invasive sensors have been developed aiming to recognize and block the progression of HF exacerbation at an increasingly earlier stage. Our approach has shifted from being reactive to a more preventive posture by detecting the earliest electronic signals of decompensation via implanted instrumentation. The following sections provide a brief overview of the utility, benefits and disadvantages of various interventions and devices that are currently at our disposal.

Remote monitoring approaches and devices

Non-invasive remote monitoring

Initial attempts to reduce HF hospitalizations were directed at home based, non-invasive telemonitoring. These efforts included symptomatic evaluation using structured telephone support (STS) and the use of electronic devices with digital transmission of simple physiological variables such as weight, heart rate, blood pressure and ECG to the health care team on a regular basis. The clinical, economical and behavioral benefits of non-invasive telemonitoring has been evaluated in numerous single center and large case multicenter trials with their findings summarized in multiple meta-analyses. While some studies described a benefit from these approaches in reducing HF-hospitalizations and mortality (13), other studies failed to confirm a positive impact. 2 kg increase in body weight over a period of 48 hours, for example, had a sensitivity of merely 9% and showed no close correlation with intracardiac filling pressures (14). This is not unexpected as fluid sometimes simply translocates from the splanchnic vascular bed to the thoracic veins. Selected trials focusing on different physiological metrics with positive and negative outcomes are listed in *Table 1.*

Device-based monitoring

Based on guideline recommendations for patients with HFrEF, the use of implanted cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT) has increased dramatically in recent years. This opened up the opportunity to build in thoracic volume sensors into these devices in an attempt to predict impending HF decompensation. Monitored parameters commonly include heart rate variability, incidence of arrhythmias, daily physical activity level, sleep patterns and thoracic impedance, each of which demonstrates an inverse relationship with pulmonary capillary wedge pressure (15). Multiple randomized trials and meta-analyses were published in the field with variable results regarding the clinical utility of these implanted devices. Selected papers with negative and positive findings are listed in *Table 2.*

Given the variable success with the approaches detailed above, a new device algorithm was recently devel-

TABLE 1. Selected trials evaluating the efficacy of non-invasive telemonitoring. Green square indicates positive results red square marks studies with negative results BP: blood pressure; ECG: electrocardiogram; QOL: quality of life

Trial	Parameters monitored	Findings
WISH (37)	Weight	No effect on cardiac re-hospitalization, mortality
TEHAF (38)	Symptoms, health behaviors	No effect on mortality, HF-hospitalizations
TEMA-HF1 (39)	Weight, BP, heart rate	Reduced mortality, hospitalizations
SPAN-CHF II (40)	BP, heart rate, weight, symptoms, adherence	Reduced 90-days hospitalizations
DIAL (41)	Weight, symptoms, adherence, activity	Reduced HF-admissions
TEN-HMS (42)	Weight, BP, heart rate and rhythm	No effect on admission, reduced mortality
TIM-HF (43)	ECG, BP, weight	No effect on HF-hospitalization or mortality
INH (44)	Signs and symptoms, nurse coordinated management	No effect on mortality and re-hospitalization
TELE-HF (45)	Symptoms, weight	No effect on 180-days re-admissions, mortality
BEAT-HF (46)	BP, heart rate, weight, symptoms	No effect on 180-days re-admissions
IN TOUCH (47)	Weight, BP, blood pressure, symptoms	No effect on HF-hospitalization, mortality QOL
Kingston-upon-Hull (48)	Weight and diastolic BP	Predicted HF-admissions (Measured over 8 days)

oped combining input from multiple sensors monitoring various aspects of HF pathophysiology. The hypothesis was tested in the international, multicenter, non-randomized MultiSENSE study (16). Collected data included respiratory rate, relative tidal volume, heart rate, heart sounds focusing on S3, patient activity and thoracic impedance. The HeartLogic algorithm was able to detect HF decompensation with a median lead time of 34 days, a sensitivity of 70% and an unexplained alert rate of only 1.47 per patient year. Further studies are underway to establish if widespread use of this novel algorithm would reduce HF-related hospitalizations, healthcare costs, mortality and its impact on quality of life.

Implantable hemodynamic monitors
Better understanding of HF pathophysiology has also led to the development of implantable hemodynamic sensors to monitor filling pressures. The Chronicle device (Medtronic Inc, Minneapolis, MN) was designed to measure systolic and diastolic right ventricular (RV) pressure and to estimate pulmonary artery (PA) diastolic pressure using a lead secured in the RV outflow tract (17). The COMPASS-HF was a multicenter, single-blinded, randomized, parallel-controlled study designed to evaluate if hemodynamic monitoring with the Chronicle device would reduce the composite endpoint of HF-related hospitalizations and the need for IV diuretic therapy (18). Hemodynamic data were downloaded and transmitted weekly but the heart failure team could only review these for the treatment group. Compared to the controls, there was a 21% reduction in the total event rate with monitoring. Yet, the difference did not reach statistical significance. This may be explained by the lack of pre-specified pressure targets and that

TABLE 2. Selected trials evaluating the utility of device-based therapies in reducing HF outcomes. Green square indicates positive results, red square marks studies with negative results HRV: Heart Rate Variability; OptiVolTM: Proprietary algorhythm to measure electrical impedance between the device can and RV electrode (Medtronic, Inc.)

Trial	Parameters monitored	Findings
IN-TIME (49)	Reduced activity, arrhythmias	Reduced mortality, no effect on HF-hospitalizations
PARTNERS-HF (50)	Arrhythmias, activity, OptiVolTM, HRV	Predicted HF-hospitalizations
SENSE-HF (51)	OptiVolTM	Low sensitivity and predictive value for HF-hospitalization
MORE-CARE (52)	OptiVolTM and arrhythmias	No effect on mortality or HF-hospitalizations but reduced in-office visits
REM-HF (53)	Multiple parameters	No effect on mortality or HF-hospitalizations
EVOLVO (54)	Multiple parameters	Reduced heart care utilization
DOT-HF (55)	Multiple parameters	No effect on outcomes and increased HF-hospitalizations
COMPAS (56)	HRV, arrhythmias	Reduced ambulatory clinic visits
TRUST (57)	Arrhythmias	Reduced health care utilization
OPTILINK (58)	Volume status	No effect on outcomes

medical therapy was not adjusted in response to the PA diastolic pressures. However, there was a significant 36% reduction in the relative risk of HF-associated hospitalizations and the treatment effect was more pronounced in patients with NYHA Class III symptoms. Due to the overall negative study results, the Food and Drug Administration voted against the approval of the Chronicle device.

Given the limited but encouraging success of Chronicle, a new, implantable, battery-free, wireless hemodynamic monitoring system (CardioMems™, Abbott, Minneapolis, MN) was developed. The sensor is implanted during a minimally invasive right heart catheterization with the aim to detect early, subtle changes in intracardiac and PA pressures. Sensor data were shown to correlate well with hemodynamic measurements obtained during simultaneous Swan-Ganz catheterization as well as Doppler echocardiographic assessments (19). CHAMPION, a prospective, single-blind, multicenter trial enrolled 550 patients with NYHA Class III HF symptoms with at least one hospitalization in the previous year, regardless of etiology or EF and randomly assigned them to guideline-directed optimal medical therapy with or without CardioMems ™ monitoring (20). In addition to frequent clinic visits, PA pressures were monitored daily. Diuretic regimen and vasodilator therapy were adjusted based on the hemodynamic data, following a strict, pre-defined study protocol. While the trial was not powered to detect direct impact on mortality, the group managed using CardioMems ™ data had a significant 28% reduction in HF hospitalizations at 6 months and 37% at 15 months. A post-hoc analysis of the patient subgroup with HFrEF (EF<40%, 445 patients) and on maximal medical therapy revealed a significant reduction in mortality after initiating PA pressure-guided HF management (21). In addition, there was a significant drop in 30-day all cause readmission rates as well as an improvement in quality of life (22). Utilizing the CardioMems ™ system was shown to be cost effective to the U.S. healthcare system in the "real-world" setting with the benefits sustained at 1 year (23, 24). It gained FDA approval in 2014 with the indication to reduce HF hospitalizations. These devices are costly, but so are frequent hospitalizations that they may prevent. It is too early to know if more wide-spread use of implanted pressure sensing devices will ensue.

OnTrack patient self-management system
A new, innovative iPad-based application, called OnTrack to Health, goes beyond remote monitoring. It was developed based on the observation that self-management is of critical importance for patients with chronic HF. Serving as major drivers for decompensation, the rates of dietary indiscretion and medication non adherence may reach, or even surpass, 50% in this patient population (25–28). The system is designed to promote patient engagement, active decision making and compliance by providing individualized daily reminders and teaching materials. At the same time, it allows for secure, real-time, two-way communication with the healthcare team. This feature is particularly important for patients living in remote areas with no easy access to medical care. Full integration with electronic medical record systems and remote monitoring equipment is ongoing. Based on initial experience, the OnTrack Health system improves patient satisfaction with health care delivery, quality of life and reduces HF-related hospitalizations.

Innovative outpatient volume management strategies

Once congestion is detected by one of the remote monitoring strategies, patient contact and rapid intervention are of critical importance. As intestinal edema progresses with rising filing pressures, the absorption and efficacy of oral medications often decline, despite dosing escalation. Developing novel outpatient approaches and strategies to deliver adequate doses of diuretics are essential in order to reduce the risk of hospital admission. While several ideas have been proposed and tested, we will review the utility of outpatient diuretic infusion clinics and subcutaneous furosemide administration.

Outpatient diuretic infusion clinics
The mainstay of HF therapy continues to be intravenous loop diuretic administration with no significant difference between the efficacy of continuous infusion and bolus dosing (29, 30). In response to financial incentives to reduce the expenditures associated with chronic HF management, driven primarily by expensive emergency room visits and hospitalizations, many healthcare systems have established outpatient clinics specialized in intravenous (IV) loop diuretic administration. Using standardized protocols, this approach has been shown to represent a safe and effective alternative to hospital admissions in selected, hemodynamically stable patients with mild to moderate heart failure exacerbation across a wide spectrum of EF (31). Reported side effects, including hypokalemia and worsening renal failure were transient and rare (31). While approximately one third of the population may eventually require admission and intensified HF management (32), 30-day readmission rates were shown to decrease by 10% (33) and patients spend 3 fewer days on average in the hospital per every 6 months, leading to an estimated annular saving of $12,000 (34). Overall these findings suggest that outpatient IV diuretic administration to a selected group of HF patients is safe and improves quality of life while reducing health care expenses. More of these clinics are now appearing in the U.S. with increasingly favorable results.

Subcutaneous furosemide therapy

Aiming to further reduce healthcare utilization and to improve quality of life, a novel, pH-neutral subcutaneous formulation of furosemide has recently been developed. In a small, phase II, proof of concept study, a total of 80 mg furosemide was injected under the skin over 5 hours using an automated infusion pump (35). Upon direct comparison to a dose adjusted, single traditional IV furosemide injection, the new formulation provided comparable urine output with a more sustained diuretic effect. Subcutaneous furosemide was well tolerated with no evidence for worsening renal function or skin irritation. Importantly, thirty-day hospitalization rates for acute HF exacerbation was similar between the two treatment arms. Further studies with the novel furosemide formulation and the delivery pump are ongoing. It is conceivable that selected patients may eventually use this strategy at home, with guidance from the medical team, to reduce HF symptoms to the point that emergency room visit and hospital admission will not be necessary (36).

Conclusions

Management of patients with HF remains a major challenge to providers worldwide. Advances in technology enabled remote monitoring of a wide range of physiological variables by multidisciplinary health care teams. However, telemonitoring alone did not improve outcomes or reduce expenditures as described by several studies. It is the combination of monitoring, timely data interpretation and protocol-driven therapeutic interventions that prevent decompensation and may lead to a decline in HF admissions, mortality as well as health care expenses. The importance of self-management, with continuous assistance from the HF team, is increasingly recognized and improves outcomes. Novel management strategies, such as outpatient diuretic clinics and home subcutaneous furosemide infusion, may also reduce hospitalizations. Further studies and innovative management strategies are needed to reduce the burden of HF over the next decade.

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