CHANGING THE COURSE OF HEART FAILURE DISEASE MANAGEMENT USING MEMS – A CARDIOMEMS STORY

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ABSTRACT

Heart failure (HF) poses a significant global health challenge, characterized by inadequate heart function leading to fluid buildup and debilitating symptoms. Recurrent HF hospitalizations (HFH) contribute to the disease burden, with staggering economic costs and mortality rates. Traditional diagnostics like right heart catheterization (RHC) are too invasive for frequent measurements that are needed for effective and personalized HF management. Innovations like the CardioMEMS wireless MEMS pressure sensor offer a paradigm shift. Implanted entirely within the vasculature, this device wirelessly transmits pulmonary artery pressures, enabling real-time monitoring and personalized therapy adjustments. MEMS technology can enable improved remote medical care.

KEYWORDS

MEMS, CardioMEMS, Heart Failure, Implantable devices, Telemonitoring, Hemodynamics, Wireless Pressure, Pulmonary Artery, Passive Resonant Circuits, Personalized Medicine.

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome and global public health problem that occurs when the heart cannot pump enough blood and oxygen to support the organs or body and can lead to congestive HF. Congestion, the main reason for HF hospitalizations (HFH), is the fluid accumulation in the vascular system or in the interstitium from increased cardiac pressures [1]. Common symptoms are shortness of breath, difficulty laying down, weight gain with swelling in the feet, legs, ankles or abdomen, and generally feeling tired or weak. Patients alter between compensated and decompensated states, where the latter often requires a trip to the hospital to decongest the patient before discharge. The mortality (cardiovascular and all-cause) increases six-fold with four or more recurrent HF hospitalizations [2]. The US prevalence from 2017 to 2020 exceeded 6.7 million and accounted for over 85,000 deaths in 2020 [3]. The overall US cost of HF is around $30 billion, continues to rise, and is estimated to exceed $69.8 billion by 2030 [3].

Avoiding decompensation leading to HFH is challenging and has been the focus of many pharmaceutical drug therapies. The gold standard for HF diagnosis and assessment of congestion has historically been to assess cardiac filling pressures using minimally invasive procedures in the hospital by performing a right heart catheterization (RHC). Pulmonary artery pressures from RHC correlate to left-sided cardiac pressures, where left ventricular filling pressures are key parameters for guiding clinical therapy [4, 5]. A limitation that quickly becomes obvious is that an invasive RHC cannot provide frequent pressure data to effectively manage HF, as collecting daily to weekly pressures is not practical. For the management of HF, the most common classification systems is the New York Heart Association (NYHA) functional classification, where patients are classified by symptoms into four classes, with class I being the least severe and typically described as not noticeable by the patient, and class IV the most severe with discomfort at rest and for any level of physical activity. Class IV patients have progressed to a stage where guideline-directed medical therapy (GDMT) alone is inadequate and would require either mechanical support from a left ventricular assist device (LVAD) or heart transplantation.

With rising recurrent HFH, this growing clinical and economic burden led to the development of several efforts over the past thirty years to better manage HF, many of which failed to achieve primary endpoints and FDA approval. A study in 1995 demonstrated benefit (> 50% reduction in HFH in elderly) when multidisciplinary clinical teams cared for the patients post discharge [6]. Since then, examples of types of monitoring, representing a meta-analysis of over 10,000 patients and 29 trials (2006 - 2023), include telemonitoring using traditional gold standard metrics (patient weight, vital signs, reported symptoms, & rhythm strips), lung congestion (lung fluid) using thoracic impedance, hemodynamic pressure monitoring, ICD/CRTD score-based rhythm devices, and more recently multiparameter wearables [6]. In 2009, Adamson introduced a simplified understanding of the HF pathophysiology from a device perspective that outlined the timing of clinical biomarkers leading up to a HFH, where up to thirty days prior to the HFH event, hemodynamic pressures are the earliest leading indicators and have a strong predictive value [7]. All other biomarkers known at this time come later and possibly too late to intervene.

The race for HF management using ambulatory pressure measurement began with an ICD-based device from Medtronic, the Chronicle implantable hemodynamic monitor (IHM) designed to measure right ventricular (RV) pressure [4]. The Chronicle included a housing implanted subcutaneously with a transvenous wired lead into the RV, very similar to ICD/CRTD devices of the time. The device was tested in a randomized control trial (COMPASS-HF) enrolling class III and class IV HF patients, which started in 2003, enrolled 274 patients (134 treatment, 140 control) [8]. The Medtronic Chronicle did not meet the primary endpoint as the 21% reduction of HFH was not statistically significant ($p = 0.33$) [8]. A key finding of the study was the difference between functional class III vs. class IV management, where subgroup analysis showed with high significance that the treatment benefit to the class III group was positive (35% reduction, $p = 0.03$) and a negative result (more HFH events) for the class IV subgroup [Abraham]. Another device being developed around the same time was the HeartPOD (from St. Jude Medical/Savacor), which measured left atrial pressure by implanting the electronics and antenna subcutaneously and a transvenous lead into the right atrium with the pressure tip transeptally inserted into the left atrium [9]. A prospective randomized control trial study (LAPTOP-HF) evaluated the safety and efficacy in NYHA class III patients. Enrollment was suspended due to perceived excess implant complications [9]. Both the Chronicle and HeartPOD implemented transvenous leads wired to a housing, where the housing was implanted subcutaneously. The innovation that would gain first FDA approval, miniaturize the sensor and electronics into a package small enough to reside entirely within the vasculature, and to wirelessly transmit pressure was a MEMS-based system developed by CardioMEMS [10].

A WIRELESS MEMS PRESSURE SENSOR

CardioMEMS, as the name implies, was the union between cardiology and MEMS. The company was co-founded in 2001 by Jay Yadav (cardiologist and director at the Cleveland Clinic at the

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time) and Mark Allen (professor in Georgia Tech's School of Electrical and Computer Engineering and director of the school's MEMS research group at the time). The company would take advantage of passive inductive (*L*) and capacitive (*C*) resonant MEMS designs originally developed for high temperature application for turbine engines to endovascularly-implant wireless pressure sensors to monitor patients with chronic disease. A key advantage of this approach was that unlike the Chronicle or HeartPOD, the sensor would be entirely implanted within the vasculature and all other electronics would reside external to the patient, negating the need for transvenous leads or transseptal punctures that only exacerbate clinical risks and complications. CardioMEMS first received FDA 510(k) clearance for a wireless pressure sensor for abdominal aortic aneurysms (AAA) in 2005 named EndoSure. The device was used to monitor Intra-aneurysm sac pressure post endovascular repair. Ideally the repair would exclude and depressurize the aneurysm sac and prevent ruptures that are frequently fatal. The EndoSure sensor was used to observe sac pressures (pre and post exclusion without concern of impacting the vascular seal that traditional catheter might present) and could guide physicians intraoperatively as well as postoperatively [11]. The second system CardioMEMS received FDA PMA approval for was for HF management in 2014 and is the focus of this paper.

Figure 1: CardioMEMS heart failure pressure sensor for pulmonary artery pressure measurement.

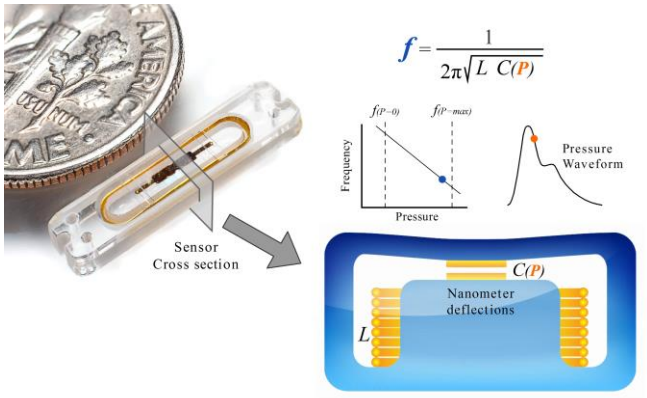

Figure 2: CardioMEMS sensor cross-sectional view illustrating how the MEMS fabricated parallel plate capacitance is pressure variable [14].

The use of passive resonant circuits to measure physiologic parameters dates back to at least 1957 in an article titled "Endoradiosonde" [12]. In 1967, Collins reported a miniature "Transensor" ranging in size from 2-6 mm in diameter designed for ocular pressure [13]. These transesors used two oppositely wound planar spirals connected peripherally to form an *LC* circuit with distributed inductance and capacitance. In the case of CardioMEMS, several iterative designs were explored, from planar spiral inductors on flexible substrates, to flexible inductors overlayered onto ridged ceramic structures, to oppositely wound planar spirals on fused silica substrates. The search for the optimal design required the balancing of several key factors: a high-Q resonance, a small size, low self-resonance frequency, and pressure measurement stability over at least 5 to 10 years. What emerged was the concept commercialized in 2014, acquired by St. Jude Medical (subsequently acquired by Abbott), illustrated in Figure 1 & Figure 2 [14].

The MEMS sensor design is a resonant circuit consisting of a capacitor (C_s) and an inductor (L_s). The capacitance of the sensor is a function of the sensor's pressure environment and thereby the resonance frequency is a function of pressure. The sensor circuit model was reported in previous work for passive *LC* resonant circuits and can be described by a lumped *LCR* circuit illustrated in Figure 3 [15, 16, 17].

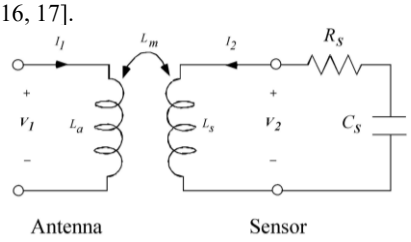

Figure 3: Equivalent circuit of electrical model for a sensor coupled with a loop antenna.

Analysis of the circuit results in the input impedance referenced to the terminals of the coupling antenna. Substituting into the input impedance Z_1 for $fo=[2\pi(L_sC_s)^{½}]^{-1}$, $k=Lm(L_aL_s)^{-½}$ and $Q=\omega L_sR_s^{-1}$ results in Eq. (1) below [17].

$$Z_1 = \frac{V_1}{I_1} = j2\pi \mathrm{f} L_a \left[1 + k^2 \frac{\left(\frac{f}{f_o}\right)^2}{1-\left(\frac{f}{f_o}\right)^2 + \frac{1}{Q} j \frac{f}{f_o}}\right] \qquad (1).$$

Wireless measurement of the implanted sensor is achieved through mutual inductance between the sensor inductor and an external loop antenna, thus allowing measurement of the pressure modulated frequency [14]. The electronics converts the frequency into pressure values using predefined sensor calibration information, enabling wireless pressure measurement from within the pulmonary artery.

The implant procedure leverages a RHC (access via the femoral or jugular vein) and a hand injected selective pulmonary angiogram to define the distal pulmonary artery branch anatomy. A 120 cm 0.018" guidewire is inserted through the RHC. After removing the RHC the CardioMEMS delivery system with sensor attached is advanced over the guidewire to the target vessel location. Pulling the tether wires attached to the catheter hub releases the sensor. The delivery system is then removed and the RHC is reinserted to use as a reference pressure to zero the CardioMEMS system [18].

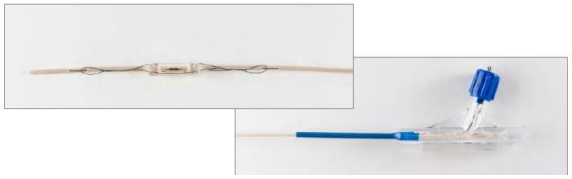

Figure 3: CardioMEMS delivery system with distal side showing the sensor tethered down and the proximal side with the hub and blue cap that secures the tether wires [14].

The CardioMEMS electronics uses an antenna to transmit radiofrequency pulses at or near the sensors self-resonance, energizing the *LC* circuit. A phase-locked-loop in the electronics is used to zero-in on the sensors self-resonance and then tracks the frequency. Software in the electronics uses the sensor calibration

information to convert the frequency to pressure and graphs or collects the data and transmits it to a centralized database [14]. The system includes two types of electronics, one for use in the clinic during the implant procedure or follow-up visits while the other is sent home with the patient for daily home readings. Both systems are illustrated in Figure 3.

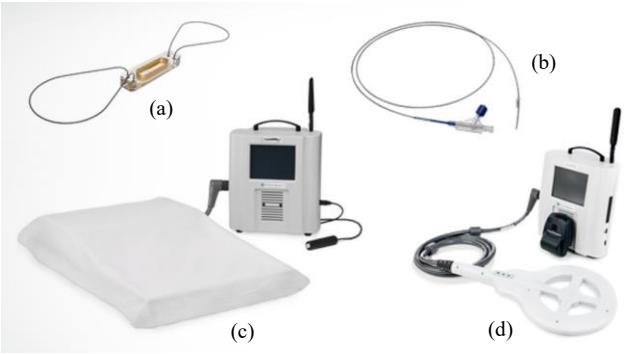

Figure 3: Original CardioMEMS system approved in 2014. Newer versions of the electronics are commercially available today from Abbott. Imaged are (a) sensor, (b) delivery system, (c) patient electronics, (d) hospital electronics.

CLINICAL EVIDANCE

Several factors led to the successful PMA approval of the CardioMEMS system. Some of these were great leadership from the co-founders and executive team, securing funding, a resourceful and relentless engineering and clinical team, and a clinical trial design named CHAMPION (***C**ardioMEMS **H**eart Sensor **A**llows **M**onitoring of **P**ressure to **I**mprove **O**utcomes in **N**YHA Class III Heart Failure Patients*) that learned from previous failed attempts. The path to approval was not straightforward, requiring two FDA panel meetings dating from 2011 to 2013 to resolve concerns of trial bias, leading to an approval letter in May of 2014. The trial included 550 patients (n = 270 Treatment, n = 280 Control), and the key phases of the PMA trail were the Randomized Access and Open Access periods. During the Randomized Access period the control patients received an implant, however physicians did not have access to pressure data and managed patients using the gold standard (weights and symptoms). Treatment patients also received an implant and were managed using pressure data to personalize medication titration and achieve GDMT. Upon completion of the randomized follow-up period, patients transitioned to the Open Access period during which physicians had access to pressures from both groups and provided for a longer trial period to assess safety and efficacy [14].

The study met the two primary safety endpoints: (1) freedom from device/system related complication (DSRC) (98.6%, lower confidence limit of 97.3%, greater than the pre-specified limit of 80%) and (2) freedom from sensor failure (100%, lower confidence limit of 99.3%, greater than the pre-specified limit of 90%) [14]. The primary efficacy endpoint was the rate of HFH for heart failure during the first six months of the Randomized Access period, with a 28% reduction in the rate of HFH in the Treatment group compared to the Control group, illustrated in the cumulative hazard graph in Figure 5 [14]. This reduction represented a clinical and statistically signification reduction, including when accounting for the increase in mortality rate after each HFH (mortality rate 1-year after HFH increased from ~34% to ~58% from the 1st to the 4th hospitalization) [20]. During the entire Randomized Access period with a mean follow-up duration of 17 months per patient (enrollment occurs over several months, therefore early enrolled patients have a longer trial period compared to the last patients enrolled), the rate of HFH was 33% lower in the Treatment group compared to the Control group, an increasing and durable benefit, illustrated in the cumulative hazard graph in Figure 5 [14].

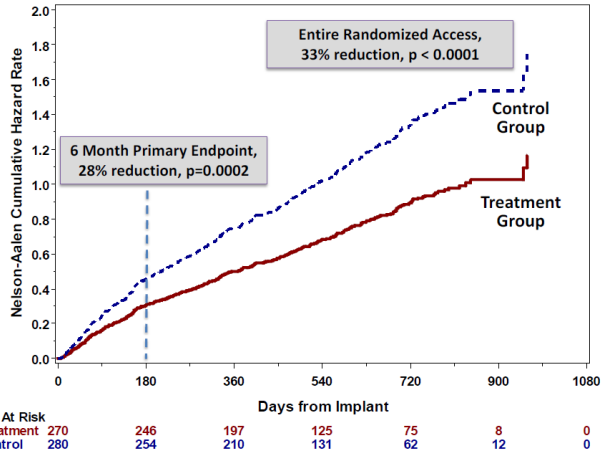

Figure 5: CHAMPION trial results. The cumulative hazard of hospitalization for heart failure during the Randomized Access period [14].

A key finding in CHAMPION, which supports efficacy for hemodynamic management of HF patients, was the benefit shown in the Control group as they transitioned to the Open Access period. Longitudinal analysis showed that the rate of HFH for the Control group dropped 47% when physicians were given access to pressures [14]. The benefits of CardioMEMS were later reinforced with real-world (first 2000 patient implants) and post approval study (1200 patients and statistically powered for women and diversity) data with similar safety and benefit results as CHAMPION [21, 22].

CONCLUSIONS

Chronic cardiovascular diseases, including heart failure, are complex and difficult to manage without the correct signals and feedback mechanisms that enable physicians to customize and personalize medical care, not just in dosage and type but also in time. Hemodynamics and other cardiopulmonary biomarkers are essential for chronic disease management and MEMS technology is uniquely capable and ideally suited to fulfil this unmet need. As we look ahead, new technologies that include both invasive and noninvasive wearables, promise to deliver a new area of personalized remote medical care [23, 24]. One example of exiting MEMS technology is the use micro-gravity accelerometers with out-of-plane sensitivity as noninvasive seismocardiogram (SCG) sensors capable of detecting cardiopulmonary biomarkers. These devices, when coupled with AI/ML algorithms, have demonstrated detection of coexisting valvular heart disease (VHD) or peripheral artery disease with high sensitivity and specificity compared to the gold standards as featured on the cover of *IEEE Biomedical and Health Informatics* and *IEEE Biomedical Engineering*, respectively [25, 26]. Development and implementation of better remote care technologies was spurred in part by the success of CardioMEMS, and only further emphasized during the COVID-19 pandemic. The role of MEMS technology as a vehicle for better patient care is clear, and the era of more effective and personalized medical management is only beginning.

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