The future of implantable hemodynamic monitors

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'A limitation of IHMs as they currently exist includes the lack of a device that can provide a full hemodynamic profile, as one would obtain through pulmonary artery catheterization.'

The syndrome of heart failure (HF) is widely prevalent in North America and Europe, estimated to be 1–2% of the general population in developed countries [1]. Even in patients in whom this common diagnosis is well established, identifying HF decompensation, surprisingly, remains a challenge, even in the hands of experienced clinicians. The reasons for this are many-fold. The usual 'starting point' in the clinician's diagnostic algorithm – the patient's history of present illness – usually includes the nonspecific symptoms of dyspnea, cough and fatigue. The physical examination may be difficult, especially in chronic HF, when recruitment of pulmonary lymphatics may result in the absence of audible rales, even in the setting of an elevated pulmonary capillary wedge pressure. Examination of the jugular venous pressure is poorly performed or not performed at all by many clinicians (at least in the author's experience), and may not always correlate with left-sided filling pressures. The chest x-ray may be nonspecific, and revealing laboratory abnormalities, for example hyponatremia, may not be present until a significant volume overload is observed. More recently, neurohormonal markers such as brain natriuretic peptide (BNP), which are elevated in HF, have been added to the laboratory evaluation [2]. However, BNP may be falsely low, for example in obese individuals [3]. Transthoracic echocardiogram demonstrating depressed left ventricular systolic function may not be helpful as 40% or more of HF is associated with preserved systolic function [4]. It may not be until the patient undergoes invasive evaluation by pulmonary artery catheterization, demonstrating decompensated hemodynamics, that the true clinical picture becomes evident.

Unfortunately, a limitation of hemodynamic evaluation as it is currently performed, at rest in the supine position, is that only a 'snap shot' is provided of the perturbations associated with HF. As patients will relate, symptoms will often worsen or abate with alterations in diet, position, day/night cycle and so on. Although clinicians have some idea of the hemodynamic changes that occur, the dynamic aspects of these changes have likely been underestimated and poorly understood. With better understanding of the hemodynamic fluctuations occurring, it might be possible to detect clinical worsening earlier and intervene quickly, thereby avoiding increased morbidity and mortality.

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These factors ultimately lead to the development of the implantable hemodynamic monitor (IHM). Systems available or under development are variations of two basic configurations. The Chronicle® (Medtronic Inc.) and HeartPOD® (St. Jude Medical) IHMs contain a power source and software housed in a titanium shell, similar to a pacemaker and implanted in the pectoral region of the chest and a transvenous lead with a sensor placed in an intracardiac position. The Chronicle device is positioned in the right ventricular outflow tract, whereas the HeartPOD is fixated to the intra-atrial septum following trans-septal puncture, similar to a patent foramen ovale closure device. By contrast, the CardioMEMS® and RemonCHF® systems are wireless, with a pressure sensor hermetically sealed in a titanium case, implanted in the pulmonary artery and affixed with a self-expanding anchoring system. Data, including hemodynamics, heart rate and temperature, may be collected and stored, allowing either the clinician to access the information or the patient to transmit the information over the telephone. Information may be accessed in a number of ways, for example via a website,

which allows the physician to be able to evaluate the patient remotely. The aforementioned devices each collect a different spectrum of information, and no device is able to measure the full hemodynamic profile obtained from traditional pulmonary artery catheterization. Further detailed information regarding these individual devices, their capabilities and validation are beyond the scope of this article and are reviewed elsewhere [5].

The only IHM to have undergone clinical evaluation and been presented to the US FDA Advisory Panel has been the Chronicle IHM, produced by Medtronic. The clinical trial used as the basis for the application, the Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) study, randomized 274 New York Health Association class III and IV HF patients followed by experienced HF physicians, on optimal medical therapy for at least 3 months, who had at least one HF-related hospitalization or emergency room visit for intravenous diuretics in the 6 months preceding enrollment, to a treatment group, where Chronicle hemodynamics were utilized to apply IHM-directed treatment strategies or a control group where the treating clinician was blinded to the IHM parameters. Patients were blinded to their study group and were observed for 6 months. In both groups, optimal HF care was prescribed, including daily weights, aggressive medication titration and frequent patient contact via telephone or clinic visits. The study event rate was lower than expected, possibly due to the intense baseline HF care provided, resulting in insufficient power to detect a change in the primary end point – cumulative HF-related hospitalization, emergency department visit or urgent clinic visit requiring intravenous HF therapy (relative risk reduction of 21%, $p = 0.33$). Over the 6-month randomized period, the IHM-guided care strategy was associated with a 36% decrease in risk of first HF-related hospitalization ($p = 0.03$). The complete analysis of the COMPASS-HF study is submitted for publication [6].

Based on these results, the FDA advisory group rejected the application by Medtronic for the Chronicle device. In comments made to the committee, it was apparent that this purely diagnostic device was unable to overcome the hurdles that are typically associated with approval of an investigational therapy, rather than a standard reasonable for a diagnostic tool

which is used to guide treatment. In one particularly revealing quote, a panelist commented, “continual hemodynamic monitoring over many months in a heart-failure population like this one has never been available before”. He expressed admiration for Chronicle as “ingenious and innovative” and “a great research tool,” and said, “Ultimately I think it’s going to be a step forward. However, I’d suggest that a diagnostic test is appropriate for application only if we know how to use it. And I don’t think we know yet how to use this one” [101].

Regulatory bodies are charged with the difficult mission of protecting the safety of the general public whilst balancing the need for ongoing scientific innovation. However, the viewpoint summarized above fails to recognize that often the full potential of new technologies cannot be realized until placed in the hands of expert clinicians, who through everyday use, gain better insight into the optimal application of the tool. It is difficult to know how to treat a condition such as acute decompensation of chronic HF effectively, when the hemodynamic derangements that are occurring, and their fluid nature, are not well understood and appreciated. Once this type of understanding is gained, then new therapeutic strategies will be developed. This type of insight can only be attained through the use of the technology, in the clinical setting.

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Given this rationale, it would be unlikely that many of the diagnostic modalities used today, including the Swan-Ganz catheter, would gain approval by current regulatory bodies. In fact, the Swan-Ganz catheter, which is commonly used in intensive care units around the world, has never been demonstrated in a randomized trial to improve mortality, including the recent Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, which specifically studied a HF population [7]. In this study, 433 HF patients with mean left ventricular ejection fraction of 19% were randomized to therapy guided by pulmonary artery catheterization versus clinical assessment alone. The primary end point of days alive and out of the hospital for 6 months was not met, and no

subgroup that benefited for pulmonary artery catheter-guided therapy could be identified. The results of the ESCAPE and COMPASS-HF trials highlight the significant challenges in evaluating a diagnostic tool when consistent strategies for treatment of decompensated HF do not exist. Only a few therapies attain a class I level of recommendation in published guidelines for the treatment of acutely decompensated HF, and even those have only level B or C evidence to support them [8].

Generally, clinical research has focused on end points such as mortality and hospitalization. More recently, the importance of patient-based outcome measures has been recognized. The ESCAPE study demonstrated that patients treated with pulmonary artery catheter-guided therapy had better scores using a time-trade-off instrument, suggesting patients assigned increased value to their lives after having therapy to lower filling pressure [6]. In the future, quality-of-life end points may be weighted equally or perhaps more importantly than other clinical outcomes in trials of new therapies, as clinicians recognize that many patients consider some fates to be ‘worse than death’, and would not choose to live at all costs.

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A limitation of IHMs as they currently exist includes the lack of a device that can provide a full hemodynamic profile, as one would obtain through pulmonary artery catheterization. However, as new technologies and algorithms are developed, this will be addressed. In order to increase the odds of succeeding, implantable hemodynamic monitoring technology will have to be combined with other applications in order to justify the expense and risk to the patient and, as a whole, the cost to the health-care systems. Currently available technologies, such as implantable cardiac defibrillators, are grossly underutilized in appropriate candidates, even though they have been clearly shown to prolong life [9]. The economic burden of this one therapy alone would be tremendous if

every appropriate individual were to be implanted. The additional cost and risks of IHMs could be justified if it were to be implanted along with a defibrillator, ideally without additional leads being placed. Such a device is currently being tested in a randomized study. A ‘super device’ could conceivably consist of a biventricular pacer, defibrillator and hemodynamic monitor, all in one system. Devices that are completely wireless and implanted in the pulmonary artery may be more challenging to combine with other currently existing therapeutic technologies, however, if they are associated with lower complication rates, their implantation as a stand-alone device may be justified.

To summarize, IHMs may be valuable diagnostic tools, however, they remain limited in their application because of a failure to gain regulatory approval related to their inability to demonstrate improvements in clinical end points. It will only be with changes in the philosophical approach to these devices that approval can occur. Studies to determine the most favorable therapy for acutely decompensated HF need to be separated from studies demonstrating safety of these monitoring devices; both need to occur in parallel. These two aims cannot be accomplished by faulting implantable hemodynamic-monitoring technology for the failure of the HF community to find standardized, evidence-based approaches to treatment of acutely decompensated HF. Approval of IHMs needs to occur, albeit with strict implantation criteria to target patients who will likely gain the most benefit and, furthermore, to understand this prevalent disease that is associated with high morbidity and mortality.

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