Pathophysiology of the Transition From Chronic Compensated and Acute Decompensated Heart Failure: New Insights From Continuous Monitoring Devices

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Studies of cardiovascular signals continuously sensed by implantable devices provide unique insight into detailed pathophysiology as patients progress from stable to congested states. These data suggest that volume expansion, autonomic adaptation, and pulmonary interstitial edema begin several weeks before patients develop symptoms or demonstrate changes in daily weight. Monitoring physiologic signals from implanted devices may provide earlier warning of impending decompensation, thereby allowing changes in medical therapy to prevent worsening heart failure.

Introduction

Effective disease management offered to patients with chronic heart failure initially focuses on establishing tolerable doses of disease-modifying medications, which often leads to significant left ventricular recovery [1]. In patients whose ejection fraction remains low despite months of maximal medical therapy, further disease-modifying and lifesaving device therapies are available that effectively reduce the morbidity and mortality of chronic heart failure [1–6]. The months required for establishing lifesaving medical and device therapies are necessary to ensure that the highest quality care is provided to this high-risk patient population.

Nevertheless, data from recently reported registries demonstrate that consensus recommendations for medication therapies are offered to far fewer than all patients who qualify. Device therapies are offered, amazingly, to less than 40% of patients who have a class 1 level of evidence A indication [7]. Such data suggest why mortality in heart failure patients has not declined as significantly as anticipated in the past decade and why heart failure hospitalizations still rise despite clinical trials predicting declines due to appropriate treatment [8]. Therefore, the initial establishment of care in the first months after a heart failure diagnosis is critical to providing the highest quality care to modify costly morbidity and mortality.

Once initial therapies are established, the next phase of disease management for patients with chronic heart failure involves close monitoring for congestion development. Neurohormonal intervention with β-blockers, angiotensin intervention, and aldosterone antagonism effectively inhibits pathophysiologic responses to persistently low cardiac output by attenuating mechanisms responsible for maladaptive tissue changes that promote myocardial fibrosis, cell death, and arrhythmia [1]. In addition to these effects, neurohormonal antagonists help control persistent maladaptive signals that stimulate volume retention. Renin–angiotensin system, adrenergic, and aldosterone activations are all reflexively activated in response to decreased cardiac output and attempt to maintain mean arterial pressure [9].

The afferent signals responsible for neural and hormonal activation rely only on an assessment of volume in the arterial circulation, which is more profoundly affected by a reduction in cardiac output. The central control system's "error" in interpreting afferent information about a reduction in mean arterial pressure is to assume that the drop is caused by volume depletion or hemorrhage. The response to this "error" is to activate mechanisms intended to expand blood volume, even when central venous pressure is high. The resulting increase in cardiac filling pressures, if persistent, leads to congestive symptoms, such as dyspnea with minimal exertion, paroxysmal nocturnal dyspnea, and orthopnea, which most

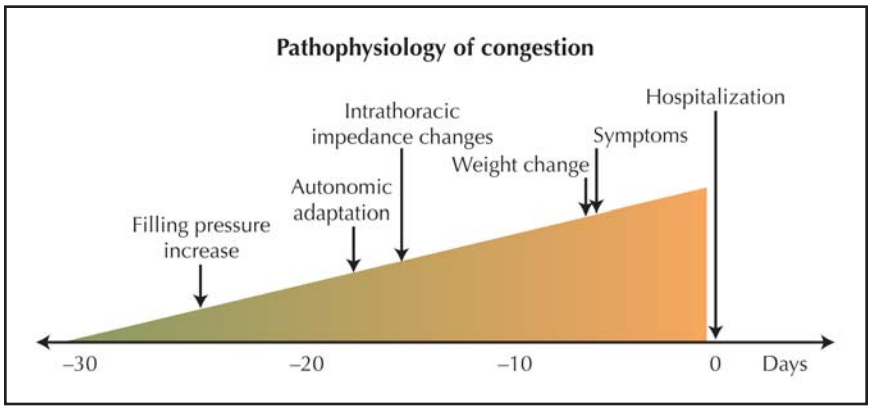

Figure 1. A simplified understanding of heart failure pathophysiology from a device perspective including changes in filling pressures using hemodynamic monitoring devices, autonomic adaptation measuring heart rate variability, and alterations in intrathoracic fluid content using intrathoracic impedance.

commonly results in the need to use in-hospital care plans to restore normal volume and functional status [10].

Heart failure hospitalizations are at the core of the high cost of heart failure care, as well as a strong influence on the progression of left ventricular dysfunction, representing a target to reduce individual morbidity, mortality, and the global economic impact of the disease. Many lessons have recently been learned about heart failure pathophysiology as patients progress from stable, euvolemic, minimally symptomatic status to an acutely decompensated, volume overloaded state with severe symptoms. Most lessons are derived by analyzing changes in physiologic signals obtained using approved and experimental implantable devices. A clearer understanding of the "progression to congestion" may help health care providers deliver higher quality care by allowing a glimpse into the body's own control systems, which seem to respond much earlier to dangerous changes in volume compared with traditional tools, such as symptoms, measurement of daily weights, and physical examination.

It is clear that volume overloaded heart failure exacerbations do not start when the patient's weight changes or when symptoms develop. If practitioners can reliably discover the point at which the system is initially challenged by volume changes, then only subtle medication changes may be needed to maintain homeostasis, compared with dramatic interventions required when patients are hospitalized for volume exacerbation. In fact, based on experimental trial evidence and the community's standard practice of monitoring weight daily, it seems that volume management requires frequent assessment to successfully avoid accumulations [11–13]. The most promising approaches to frequent monitoring of patient status is to automatically provide patients with robust data that may guide appropriate dosing of diuretics on a daily basis. Eventually, new systems may eliminate the need for health care provider involvement in daily assessment. Such systems will undoubtedly reduce the intensity of work required to maximize outcomes in heart failure populations.

This article reviews novel understanding of the pathophysiology of congestion in patients with chronic heart failure from the perspective of physiologic signals sensed by an implantable device (Fig. 1). Because uncontrolled congestion is responsible for more than 90% of hospitalizations for heart failure in the United States and other parts of the world, improvement in detection and treatment guidance may impact the high cost of heart failure care by reducing the need for heart failure hospitalization [10].

Progression to Congestion: The Critical Role of Volume and Filling Pressures

The most important data to understand about how patients progress from stable euvolemic heart failure to decompensation is derived from experimental implantable hemodynamic monitoring systems [14–20]. These systems are in various stages of development and continue to be evaluated in clinical trials to determine if a heart failure management strategy based on frequent assessment of cardiac filling pressures is better at reducing heart failure hospitalizations compared with tools traditionally used in clinical practice [21]. Compulsive testing has clearly proven that systems in place accurately and precisely measure filling pressures over long periods [14,15,17–20]. Therefore, even if a clinical trial cannot be designed to appropriately test the hypothesis that such an approach can reduce hospitalizations in this group, data from these studies clarify how pressures influence patient well being and how changes in filling pressure lead to hospitalization.

The earliest change in a physiologic parameter when patients begin the process of decompensation is a change in filling pressures, which can be detected weeks before hospitalization (Fig. 1) [22••]. Interestingly, the magnitude of pressure increase is typically small, but persistent and is similar between those with systolic and diastolic heart failure [22••,23]. Persistent increases in filling pressures usually result in heart failure decompensation and hospitalization. The exact mechanisms of how increased filling pressures lead to the decompensated state are not clear, but small persistent changes in pulmonary capillary hydrostatic pressures may overwhelm the normal capacity to handle extravasated fluid in the pulmonary interstitial space [23]. Additionally, the pressure–volume relationship present in patients with left ventricular systolic or diastolic heart failure dysfunction predicts that only very small amounts of volume are required to result in larger

changes in pressures. These observations may explain why most patients do not gain substantial amounts of weight as they move toward hospitalization. The small amount of volume required to develop the magnitude of pressure changes seen in hemodynamic studies as patients decompensate are probably lost in the measurement of total body weight.

Traditional use of daily weight measurements usually relies on 2 to 4 pounds of weight change in a 24- to 36-hour timeframe before changes in medical therapy are suggested. This is known to occur during the 7 days before hospitalization, with a sensitivity of 9% [24]. Specificity is very high (97%) because if weight actually does change 2 to 4 pounds in 24 to 36 hours, the patient is very likely to require hospitalization. However, most patients do not experience a change in weights before hospitalization is required [24,25]. Therefore, daily measurement of body weight is a very insensitive means to identify changes in the small changes in body volume required to move patients into an exacerbation.

It is important to consider if pressure changes in anticipation of heart failure hospitalization are mechanistically tied to the decompensated state. In fact, when patients are stable, their pressures remain very stable over time [14,22••]. When patients decompensate, pressures increase, leading to the exacerbation and return to baseline when the exacerbation is treated and volume returns to normal [14,22••]. This provides convincing evidence that pressures reflect the underlying volume state in patients with heart failure and strongly supports the hypothesis that measuring those pressures frequently or continuously using implantable devices may be a superior management strategy to quantifying daily weights [21]. This hypothesis is the focus of several ongoing prospective clinical trials [21].

In conclusion, small increases in cardiac filling pressures caused by increased intravascular volume occur very early in the decompensation process, and, if unattended, eventually overwhelm compensative mechanisms, leading to the congested state. Daily weight measurements are too insensitive to discover such small changes in volume and, therefore, have very little value in predicting an impending hospitalization for most patients. Shortly after persistent volume increases are detected by pressure measurements, alterations in cardiac autonomic control can be detected, presumably as a marker of one of the body's mechanisms to adapt to volume changes.

Autonomic Adaptations to Volume Accumulation

Sympathetic activation and vagal withdrawal characterize cardiac autonomic control in patients with chronic heart failure [26]. The clear mechanistic role of sympathetic activation in the genesis of lethal arrhythmias leading to sudden death and progressive cardiac remodeling leading to pump failure is supported by multiple clinical trials in which adrenergic antagonism with β-blocker therapy significantly reduced morbidity and mortality [27]. Improvement in left ventricular systolic function is also known to occur with β-blocker therapy [1].

Two clinical studies tested the hypothesis that cardiac autonomic control may change as patients favorably respond to cardiac resynchronization therapy or decompensate, requiring hospitalization [26,28]. The indirect autonomic marker heart rate variability was calculated from an implanted device using continuous assessment of the atrial-to-atrial depolarization intervals. Heart rate variability directly relates to parasympathetic control of the heart, with increased variability reflecting more parasympathetic control and decreased variability reflecting less parasympathetic and more sympathetic input to the heart [29]. Device-based heart rate variability, based on atrial-to-atrial depolarization intervals, was calculated as the median SD of 5-minute heart rate epochs and averaged during the 24-hour period [26,28]. This expression of heart rate variability, termed the SD of the atrial-to-atrial median (SDAAM), was used as a marker of cardiac autonomic control. Continuous measurement of heart rate variability by an implanted device allowed the opportunity to observe autonomic activity as patients were stable or as they progressed with time to an exacerbated state.

The first study of continuous device-based heart rate variability suggested that cardiac resynchronization therapy improved overall heart failure status as reflected by an increase in heart rate variability, indicative of a shift in autonomic control from sympathetic dominance [26]. Improved heart rate variability was seen independently of β-blocker use. The correlate to those findings was the observation that heart rate variability was lower in unstable patients at risk for hospitalization and further decreases were seen as those patients became unstable and required hospitalization [28].

An automatic detection algorithm was used to monitor heart rate variability and found significant changes in the SDAAM about 16 to 20 days before patients presented with symptoms of worsening heart failure [28]. This parameter is associated with a sensitivity of 70% and a false positive of 2.4 per patient year of follow-up. Night heart rates tend to be higher as patients progress toward hospitalization, but the sensitivity of this marker is less and the false-positive rate is higher [28]. When this information is integrated into information about filling pressures, it would appear that vagal withdrawal and sympathetic activation occurs in response to persistently increased volume and filling pressures. Further decline in heart rate variability is seen when patients progress toward hospitalization, which returns to baseline levels once the exacerbation and hospitalization are resolved. Therefore, autonomic activation in response to persistent elevation in filling pressures is likely an attempt to increase cardiac output to deal with the volume challenge. Autonomic adaptation is unsuccessful if volume and pressure increases persist over time.

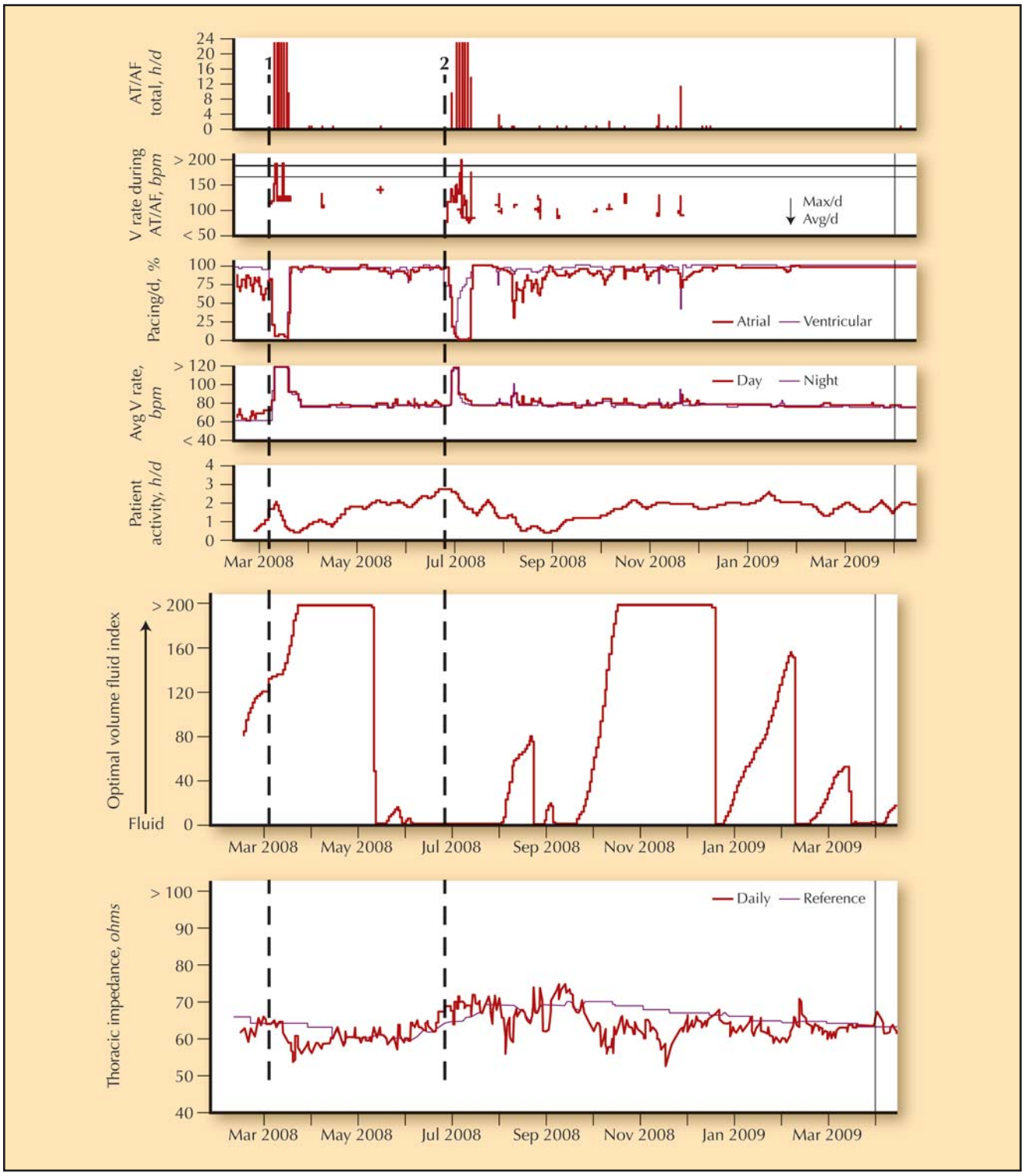

Figure 2. Remotely obtained information from an implanted device demonstrating new onset atrial fibrillation (AF) with loss of biventricular pacing leading to decreased intrathoracic impedance at a time of acutely decompensated heart failure (*dashed line 1*). A second paroxysm of AF, however, still inhibited biventricular pacing, but the patient did not decompensate and intrathoracic impedance did not change (*dashed line 2*). AT—atrial tachyarrhythmia; bpm—beats per minute; V—variability.

Intrathoracic Impedance as a Marker of Pulmonary Fluid Accumulation

Pulmonary venous and arterial capacitance is at some point overwhelmed during progression from stable to unstable congestive heart failure. Before this, however, pulmonary circulation engorgement, which can be sensed by intrathoracic impedance measurements, occurs. Implanted devices, such as cardiac resynchronization therapy pacemakers or implantable cardioverter-defibril-

lators, can emit a subthreshold impulse from the right ventricular lead and measure the time for the impulse to traverse the thorax and reach the pulse generator [30]. This measurement can be made daily and accumulated to determine changes over time [30].

In current devices with this feature, a cumulative summation of the differences between a daily impedance measurement and a running average impedance accumulate until a threshold is crossed suggesting the occurrence of significant increases in lung volume [30]. Multiple threshold crossings are associated with higher risk of hospitalization in the subsequent 4 to 6 months [31]. Further study demonstrated that intrathoracic impedance measurements decrease as the pulmonary capillary wedge pressure increases, again linking changes in intrathoracic impedance to changes in lung water. Changes in intrathoracic impedance appear about 14 days before patients present to the hospital with severe heart failure symptoms [30].

Integrative Physiology

Integration of intrathoracic impedance measurement data into our understanding of the pathophysiology of heart failure exacerbation from other device-based parameters imply that the first effect of accumulating volume as an exacerbation progresses is a slight, persistent increase in filling pressures, which are first sensed by implantable hemodynamic monitoring systems. Within a week, the autonomic nervous system senses this problem and changes cardiac control with an activation of the sympathetic nervous system and withdrawal from the parasympathetic limb. This finding can be sensed by an implanted device with an atrial or ventricular lead and a software system to quantify heart rate variability. Subsequently, if autonomic adaptation is unsuccessful in resolving the problem, other compensatory mechanisms are overwhelmed and intravascular pressure exceeds tissue pressure, resulting in increased intrathoracic fluid volume. Daily intrathoracic impedance monitoring can detect this event, with changes seen about 2 weeks before patients present with symptoms.

Eventually, in some patients, volume accumulation causes an increase in total body volume and weight changes can be detected using daily weight measurements in the 7 days before hospitalization. Finally, symptoms variably develop within the week of hospitalization, although this variability is difficult to quantify. No evidence from clinical trials is available to determine exactly when symptoms typically develop, likely because this parameter is highly dependent on individual factors. All device-based parameters return to baseline values when an exacerbation is appropriately treated. Other exacerbating factors, such as atrial or ventricular arrhythmias, loss of ventricular pacing with a cardiac resynchronization device, or increases in right ventricular apical pacing can be sensed by implantable device diagnostics (Fig. 2).

Conclusions

Health care providers responsible for longitudinal care of patients with heart failure now have remote access to insights into heart failure pathophysiology as patients progress from stable to unstable symptoms. More than 90% of patients hospitalized for heart failure in the United States have excess intravascular volume, leading to unstable symptoms and further hospitalization [10]. Device-based data provide a means to become aware of changes in hospitalization risk status and can be used to alert providers of patients that need more urgent, possibly unscheduled, attention. Future devices with hemodynamic monitoring systems represent the next generation of disease management possibilities with implanted devices.

Disclosure

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- •• Of major importance

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