Device therapy for the management of cardiac arrhythmias has evolved from asynchronous pacing in postsurgical heart block and Stokes-Adams attacks\(^1\) to the use of implantable cardioverter defibrillator (ICDs)\(^2\) and cardiac resynchronization therapy for the prevention of sudden cardiac death and the treatment of heart failure.\(^3\) Algorithms have been developed to optimize pacemaker response during arrhythmias and minimize pacing if indicated by cardiac physiology. Over the last several decades, technological advances and a better understanding of cardiac physiology allowed the development and miniaturization of devices that not only monitor and react to the electric signals from intracardiac electrograms but also use physiological signals to optimize pacing function and monitor disease state. It has become a reality to store this information in modern devices and transmit it to a clinical center, even on a daily basis if needed, by use of a transtelephonic or Internet-based route. As current and emerging indications for device therapy have targeted increasingly larger patient populations,\(^4\) we are now able to use implantable devices to monitor patients at risk of adverse cardiac events.

Emerging technologies aim to provide continuous hemodynamic information to aid the management of chronic heart failure. Technologies under clinical investigation include impedance-based monitoring of fluid status, hemodynamic assessment based on pulmonary artery pressure and its derivatives, or direct left atrial pressure monitoring. A promising possibility is that the information obtained from monitors may be used to predict and avoid adverse clinical outcomes earlier than changes in clinical parameters would otherwise indicate, which would allow physicians an opportunity for earlier intervention. In the present review, we will discuss currently used sensors in cardiac devices and draw attention to some of the future applications of device sensors.

### Sensors for Rate Modulation

#### Rate Modulation

Studies in the 1970s demonstrated that adequate cardiac output during exercise predominantly relies on increases in heart rate,\(^5\) especially if cardiac dysfunction is present. This notion resulted in increased efforts to develop pacing systems that mimic sinus node function and allow rate modulation in patients with sinus node disease or chronotropic incompetence. Normal cardiovascular response to exercise is very complex. The normal well-concerted response is the result of a prompt change in heart rate caused by the interplay between neural, humoral, and hemodynamic inputs to the heart. A detailed discussion of exercise physiology is beyond the scope of the present review, but it is important to understand some basic principles to appreciate the difficulties in simulating normal chronotropy and to understand the limitations of individual sensors.

Aerobic metabolism requires an adequate supply of oxygen transported from the lungs to the tissues by means of the circulation. Thus, both cardiovascular and pulmonary systems play a key role in meeting the demands of increased metabolism. The product of heart rate and stroke volume determines the overall cardiac output, and in healthy individuals, there is a direct, proportional relationship of change in heart rate and oxygen consumption. At the moment of initiation of exercise, vagal tone declines instantaneously, and the relative increase in adrenergic tone causes an immediate increase in heart rate and cardiac output in anticipation of an expected increase in metabolic demand. In fact, cardiac output may increase by 50\% within a few seconds after the start of vigorous exercise, and the heart rate plateau may be reached within 60 to 90 seconds. During graded exercise, the rate of rise in heart rate and cardiac output is proportional to workload.\(^6\) During the initial aerobic part of exercise, there is a steady increase in serum catecholamine level proportionate to oxygen consumption.\(^7\) Increasing sympathetic tone shifts the blood flow to the heart and muscles, increases chronotropy and inotropy, and augments blood return to the heart. There is also interdependence between the cardiac and pulmonary systems. At the beginning of exercise, minute ventilation (the product of tidal volume and respiratory rate) but not respiratory rate increases proportionately to the workload and oxygen consumption. At some point, a level may be reached at which the oxygen demand cannot be matched by oxygen delivery, and the anaerobic threshold is
reached as anaerobic metabolism is begun.\textsuperscript{8} Lactic acid production is increased as anaerobic metabolism persists. Lactic acid in turn dissociates to lactate and H\textsuperscript{+}. The latter (H\textsuperscript{+}) is buffered by bicarbonate and results in an abrupt increase of V\textsubscript{CO\textsubscript{2}} level, which is the main driver of respiration. Thus, once the anaerobic threshold is reached, the heart rate and minute ventilation curves dissociate, and ventilatory efforts increase out of proportion to heart rate and oxygen consumption. At the end of exercise, sympathetic drive is overtaken by the parasympathetic nervous system, and heart rate declines gradually. Heart rate recovery depends on several factors, such as age, physical condition, and duration of exercise.\textsuperscript{9}

An ideal sensor for rate modulation would replicate the function of the sinus node under various degrees of exercise and other metabolic needs, such as anxiety, mental stress, or fever. Given the complexity of sinus node regulation, it is not surprising that no sensor has been able to fulfill this challenge completely. Extensive work has been done since the 1960s to achieve this goal, and many different sensors have been developed to target most physiological parameters that are correlated with exercise. Of the large number of physiological parameters that had been tested for feasibility as a sensor (including pH, temperature, oxygen saturation, respiratory rate, minute ventilation, QT-interval change, and contractility\textsuperscript{10–13}), only a few remain as targets of current technology, and these are discussed in more detail below.

Activity Sensors
Vibration or acceleration is a relatively sensitive early marker of the start of exercise, and activity sensors have become the most widely used sensors for rate adaptation in cardiac devices. The main advantages of these systems are their simplicity, small size, compatibility with standard pacemakers and leads, and minimal energy requirement. Modern cardiac devices almost exclusively use piezoelectric or piezoresistive accelerometers. Accelerometers consist of a coupling mass that is in communication only with piezoelectric material. As the body moves or accelerates, the coupling mass moves, and it applies mechanical stress to the surrounding piezoelectric material. These materials produce an electric charge proportionate to the pressure or mechanical stress. Change in voltage is transformed to estimation of physical activity, which is based on specific algorithms that are programmed in the device.\textsuperscript{14}

Impedance Sensing and Minute Ventilation Sensors
Impedance is a measure of opposition to the flow of electric current through a circuit. Impedance depends on the properties of the tissues between the electrodes. If biphasic current is introduced between a pacemaker lead and pulse generator, variations in impedance may be measured. During the respiratory cycle, the thoracic cavity size and air content change. These changes correlate with impedance changes if correct filtering is applied. With this method, respiratory rate or relative changes in minute ventilation may be measured accurately.\textsuperscript{15} On the basis of these principles, several manufacturers have developed thoracic impedance-based minute ventilation sensors for rate modulation. These sensors may be used with atrial leads.\textsuperscript{16}

Evoked QT-Interval–Based Sensors
The influence of heart rate on QT interval was well established more than a century ago. As elegantly demonstrated by Rickards et al.\textsuperscript{11} QT interval may be shortened not only by an increase in heart rate (by atrial pacing) but also by increased adrenergic tone without a change in heart rate (studied in pacemaker-dependent patients). These sensors measure the evoked QT interval, which is the duration from the ventricular pacing stimulus to the peak of the evoked T wave. The premise of QT-interval–based sensors is that by measuring a surrogate of the adrenergic tone, proportional heart rate response may be predicted.\textsuperscript{7}

Measurement of Myocardial Function
Although heart rate may not respond to circulating catecholamines in states of chronotropic incompetence, contractility will increase if there is inotropic reserve. Measurement of changes in contractility would therefore reflect the sympathetic tone and ambient catecholamine level and may be a useful measure for pacing even during non–exercise-related metabolic demand.

Measurement of unipolar ventricular impedance between a right ventricular (RV) pacemaker lead and a pectoral pulse generator has been shown to be a surrogate for RV contractility. Impedance changes from an adequately designed and filtered electric impulse by use of the small electrode surface of a unipolar lead will predominantly be influenced by local (within 1 cm) tissue changes rather than by changes in the rest of the thorax. Impedance changes during the isovolumic contraction period accurately predict sympathetic influence on the heart, with excellent correlation to changes in contractility.\textsuperscript{17} During periodic changes in the cardiac cycle, the lead-tissue interface changes from higher impedance (systole: contracted, smaller RV; more myocardium and less blood around the lead tip) to lower impedance (diastole: dilated, larger RV; more blood and less myocardium around the lead tip). The impedance-based contractility parameter (ventricular inotropic parameter; CLS sensor, Biotronik Inc, Berlin, Germany) has been shown to correlate well with different metabolic challenges, including mental stress.\textsuperscript{18–20}

The maximal rate of rise in ventricular pressure has been estimated by an acceleration sensor built into an RV lead. The sensor, hermetically sealed within the lead, consists of a micromass that is attached to a force transducer. Acceleration signals undergo preprocessing and are transmitted via the pacing electrode to the pulse generator. The voltage signal related to acceleration is linear. The signal appears to represent global ventricular events and has been shown to be consistently recorded from both an RV and a right atrial lead (Micro-Best ACT sonR sensor, Sorin Group, Milan, Italy).\textsuperscript{21,22} The main signal (also known as peak endocardial acceleration) appears during isovolumic contraction, and it is the equivalent of the first heart sound (S\textsubscript{1}). Invasive studies have confirmed a strong correlation with measures of left ventricular function (such as dP/dt\textsubscript{max}) during both dobutamine infusion and pacing. This sensor has been used successfully to modulate heart rate response during exercise, and it has been proposed to be useful for optimization of atrioventricular delay or cardiac resynchronization therapy\textsuperscript{23} (Figure 1). Advantages and disad-
vantages of currently used rate-modulation sensors are summarized in Table 1.

**Clinical Outcomes**

Several acute hemodynamic and small clinical studies have shown benefits of rate-modulated pacing;24–27 however, controversy remains relative to the clinical usefulness of dual-rate sensors, and even the benefits of rate-modulated pacing have been questioned recently.28–30 Dual sensors (combination of an activity sensor with either a minute ventilation, QT, or peak endocardial acceleration sensor) are thought to complement the deficiencies of the individual sensors and allow for a quick and proportional rate response to exercise.31–33 In a study by Lamas et al,29 pacemaker recipients with chronotropic incompetence (n=872) were randomized to dual-chamber (DDD mode) or dual-chamber, dual-sensor (activity and minute ventilation sensor) rate-adaptive pacing. Over a 12-month study period, neither quality of life nor peak exercise time differed between the 2 groups. Similar conclusions were drawn from a Dutch multicenter, prospective crossover study that assessed the benefits of single (activity) or dual (activity plus minute ventilation) sensors. An algorithm automatically calibrated the sensors for optimal results. In that study, rate-modulated pacing provided no incremental benefit over what was seen with dual-chamber pacing alone. Even in carefully selected patients with chronotropic incompetence, the achievement of better chronotropic response may not result in improved quality of life (summarized in Table 2).

Do we need rate modulation at all? It is clear that some individual patients have a remarkable response to rate-adaptive pacing. One of the challenges is to accurately assess the appropriate heart rate requirement during activity in a diverse group of patients. Optimal heart rate as assessed by invasive hemodynamic studies has significant interindividual variability. Programming a suboptimal (either slower or faster) pacing rate may result in a worse hemodynamic response and may be responsible for the lack of or even a worsened clinical response. Deleterious effects of long-term ventricular pacing are now well recognized. Thus, it is conceivable that the benefits of heart rate optimization are hampered by increased rates of ventricular pacing. Lastly, because most pacemakers are implanted primarily in elderly patients, the presence of other comorbidities may limit or negate the benefits of rate-adaptive pacing.

It is therefore conceivable that meticulous individual programming would be required to show meaningful benefit in a clinical trial, which would have to include relatively active patients with chronotropic incompetence. Because this latter approach is not feasible for everyday clinical management, the ultimate goal is to develop automated, so-called closed-loop systems, which are able to modify device behavior on the basis of changes in real-time cardiovascular physiological parameters.
Sensors Used to Monitor Heart Failure

Heart failure is one of the most important and rapidly growing health problems in the United States and Western world. Management of patients is challenging owing to the diverse causes of the disease, imperfect therapeutic options, and frequent symptomatic disease exacerbations that require hospitalization. Maintenance of adequate fluid status is key in heart failure management, because symptoms are commonly related to increased filling pressures and pulmonary congestion. There are, however, significant challenges to detecting subtle changes in clinical status, either by means of symptoms, physical examination, or other noninvasive measures.36 In a recent study, weight gain had only a 17% sensitivity to predict heart failure exacerbation.37 Close outpatient monitoring and early intervention have been shown to prevent hospitalization and improve long-term outcomes.38,39 Implantable cardiac devices provide an opportunity to gain access to circulatory parameters and promise an even quicker realization of changing cardiac status. Once easy transfer of information is available, rapid adjustment in medical therapy becomes a reality.

Impedance-Based Monitoring

Impedance is constantly changing when measured across the chest between a pacing lead and pulse generator. Rapid changes in impedance are related to the cardiac and respiratory cycles as more or less blood or air fills the tissue between the monitoring electrodes. Less dynamic changes are seen when fluid accumulates in lung tissue. As pulmonary edema develops, conductance improves, which causes a decline in impedance. Temporal changes and adequate filtering of the impedance signal thus not only allow the assessment of cardiac contractility or minute ventilation (as discussed previously) but may also serve as a measure of changing fluid status. This theory has been applied in clinical practice, and an impedance sensor is included in many ICDs (Medtronic Inc, Minneapolis, Minn). In the original study using an ICD lead implanted in the RV apex, impedance was measured periodically between the RV ICD coil and left pectoral pulse generator with the minute ventilation sensor.40 Constant current was applied between the electrodes with a measurement frequency of 16 Hz. Measurements were averaged over a 2-minute period, and multiple samples were acquired during the day. A special algorithm was designed that plotted a slow-moving average of daily impedance values. Daily impedances were then compared against the moving average, and the difference was expressed as a fluid index. As pulmonary edema develops, daily impedance values decline and move away from the average values. Once the cumulative difference between the daily measurement and reference value reaches a programmable threshold, the detection criterion is met (Figure 2).

This algorithm was applied in a prospective study of 34 patients with New York Heart Association class III or IV heart failure symptoms who were followed up for 2 years for heart failure hospitalization.40 During heart failure hospitalization, most patients underwent invasive right-sided heart catheterization that enabled correlation of acute hemodynamic and impedance changes. Once treatment of heart failure was initiated, impedance increased and correlated well with decreases in pulmonary capillary wedge pressure and net fluid loss ($r=-0.61$ and $r=-0.71$, respectively; $P<0.001$). With a threshold value of 60 Ω-days, sensitivity to predict heart failure hospitalization was 76.9%, with 1.5 false-positive readings per patient-year. Early warning criteria were met 13.4±6.2 days (5 to 22 days) before hospitalization. In a larger prospective study, the algorithm was used in patients who underwent biventricular ICD implantation. The end

### Table 1. Commonly Used Sensors for Heart Rate Modulation

<table>
<thead>
<tr>
<th>Technology</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity sensor</td>
<td>Measures mechanical stress to piezoelectric material as a result of motion or acceleration</td>
<td>Simple; compatible with any device or lead; small energy requirement</td>
</tr>
<tr>
<td>Minute ventilation sensor</td>
<td>Measures transthoracic impedance change between pacemaker lead and pulse generator</td>
<td>Compatible with any lead; measures physiological changes related to exercise; proportional response to exercise</td>
</tr>
<tr>
<td>QT-interval–based sensors</td>
<td>Measures evoked QT interval changes as estimate of adrenergic tone</td>
<td>Measures physiological changes related to exercise; responds to mental stress</td>
</tr>
<tr>
<td>Contractility sensors, impedance-based</td>
<td>Measures intracardiac impedance change during early ejection period as estimate of local contractility</td>
<td>Measures physiological changes related to exercise; proportional response to exercise; responds to mental stress</td>
</tr>
<tr>
<td>Contractility sensors, activity sensor–based</td>
<td>Measures peak endocardial acceleration as estimate of contractility and global LV function</td>
<td>Measures physiological changes related to exercise</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; LV, left ventricular.
Table 2. Randomized Multicenter Studies to Assess the Role of Rate Modulation in Quality of Life in Pacemaker Recipients

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>n</th>
<th>Follow-Up</th>
<th>Patient Population</th>
<th>Device Programming</th>
<th>End Point</th>
<th>QOL Measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SQL study28</td>
<td>Prospective, randomized, multicenter, 2-month crossover</td>
<td>64</td>
<td>6 mo</td>
<td>SSS or AVB</td>
<td>DDD for 3 mo, then DDDR MV DDDR MV + ACT</td>
<td>Difference in QOL</td>
<td>SF-36 Aquarel instrument</td>
<td>No additional benefits with rate modulation. SF-36 physical functioning: DDDR MV 64±29, DDDR MV + ACT 65±26 (P=0.59)</td>
</tr>
<tr>
<td>ADEPT29</td>
<td>Prospective, randomized, multicenter</td>
<td>872</td>
<td>12 mo</td>
<td>Chronotropic incompetence</td>
<td>DDD DDDR MV + ACT</td>
<td>Difference in QOL by SAS</td>
<td>SAS, SF-36</td>
<td>No additional benefits with rate modulation. SAS at 1 year: DDD 1.6±0.9, DDDR 1.5±0.8 (P=0.96)</td>
</tr>
<tr>
<td>LIFE34</td>
<td>Prospective, randomized, multicenter</td>
<td>547</td>
<td>6 mo</td>
<td>Standard pacemaker indication</td>
<td>DDDR ACT DDDR MV + ACT</td>
<td>QOL</td>
<td>SF-36</td>
<td>No difference in QOL at 6 mo between single- or dual-sensor groups. Change in SF-36 physical component: ACT sensor: 2.3±8.3 (95% CI −0.46 to 5.10) MV + ACT sensor: −0.3±7.6 (95% CI −2.69 to 2.35; P=0.09)</td>
</tr>
<tr>
<td>DUSISLOG35</td>
<td>Prospective, randomized, multicenter</td>
<td>105</td>
<td>6 mo</td>
<td>SSS</td>
<td>DDDR MV DDDR ACT DDDR MV + ACT</td>
<td>QOL</td>
<td>SF-36</td>
<td>Improved QOL (7±8%; P&lt;0.05) and 6-MWT (12±5%; P&lt;0.01) with single sensor; no additional benefits with dual sensor</td>
</tr>
</tbody>
</table>

QOL indicates quality of life; SQL, Sensor and health-related Quality of Life Study; SSS, Sick sinus syndrome; AVB, atrioventricular block; DDD, dual-chamber pacing and sensing with inhibition and tracking; DDDR, DDD pacing with rate modulation; MV, rate modulation with minute ventilation sensor; MV + ACT, rate modulation with combined minute ventilation and activity sensor; SF-36, 36-Item Medical Outcomes Study Short Form General Health Survey; Aquarel instrument, Assessment of Quality of life and RELATED events; ADEPT, Advanced Elements of Pacing Trial; SAS, Specific Activity Scale; LIFE, Limiting chronotropic incompetence for pacemaker recipients study; ACT, rate modulation with activity sensor; DUSISLOG, Dual-sensor vs Single-Sensor comparison using patient activity LOGbook; CI, confidence interval; and 6-MWT, 6-minute walk test.

The point of that study was deterioration of heart failure on the basis of clinical assessment. Patients were notified by an audible alert when the fluid index threshold was crossed and were examined in an outpatient clinic for further evaluation. Data from 373 subjects were analyzed and showed that the algorithm had a 60% sensitivity (95% confidence interval 46% to 73%) and a positive predictive value of 60% (95% confidence interval 46% to 73%) to predict heart failure events within at least 2 weeks. Another prospective single-center study with 115 consecutive heart failure patients showed that 67% of alerts were false-positive if the fluid index threshold (OptiVol; Medtronic Inc) level was left at nominal settings (60 Ω-days). Analysis of the data suggested that perhaps a higher fluid index threshold (OptiVol) level should be used (100 to 120 Ω-days) to enhance specificity and maintain reasonable sensitivity (60% and 73%, respectively). Thus, limitations of this system remain its relatively low sensitivity and specificity. On the other hand, interpretation of “false-positive” alerts is not straightforward, because these alerts may identify subclinical heart failure exacerbation or other clinically important problems, including pneumonia or exacerbation of chronic obstructive pulmonary disease. The question of whether clinical outcome can be improved by early intervention based on changes in thoracic impedance is currently being investigated in large multicenter trials (http://www.clinicaltrials.gov; unique identifier: NCT00480077). It is also conceivable that impedance measurements from other leads or a combination of leads may yield improved results. There are promising experimental data to suggest that the addition of a left ventricular lead to the measurement vector could enhance specificity. It has been proposed that longitudinal information, collected from a minute ventilation sensor and activity sensor, may be used to better detect heart failure events (Sorin Group, Milan, Italy). Changes in minute ventilation are cross-checked with the activity sensor to assess whether the information was obtained during the resting state or during activity. Data are stored in the device memory and analyzed to express minute ventilation trend at rest and during activity. A workload that corresponds to periods of activity is also
expressed. An algorithm was designed to identify heart failure exacerbation within 30 days (Figure 3). With the use of dual-chamber pacemakers and cardiac resynchronization devices in 67 patients over 195 individual 1-month follow-up periods, the overall sensitivity, specificity, and positive predictive value to predict heart failure events were 88%, 94%, and 71%, respectively. A clinical trial using these sensors to predict heart failure exacerbation is in progress (http://www.clinicaltrials.gov; unique identifier: NCT00957541).

**RV Pressure Monitoring**

Absolute pressure measurement became possible with the design of specialized leads that have pressure sensors incorporated into the lead tip. These leads initially were implanted in the pulmonary artery, but stable lead position could not be achieved easily. Measurement of RV pressure has become feasible with incorporation of the pressure sensor into an RV pacing lead. RV contractility may be derived from the pressure signal by means of the first derivative of the RV pressure signal (dP/dt\text{max}). Because contractility is sensitive to changes in adrenergic tone, these sensors may also aid physiological heart rate regulation. More importantly, RV hemodynamic data may be used to monitor cardiac status and predict adverse cardiac events related to heart failure exacerbation. Although RV pressure may be monitored, interest has increased in obtaining information about left ventricular hemodynamic parameters. The maximal rate of rise in RV pressure occurs at the time of isovolumic contraction, which is followed immediately by the opening of the pulmonary valve. At that time, there is equalization in RV and pulmonary artery (diastolic) pressure. In the absence of a significant transpulmonary gradient, pulmonary artery diastolic pressure correlates well with pulmonary capillary wedge pressure. Thus, estimated pulmonary artery diastolic pressure, derived from the RV pressure curve, may be used to estimate left atrial pressure. The pressure sensor is built into an RV pacing lead that is positioned in the outflow tract and provides stable pressure measurements that remain accurate over time.

A large, single-blind, parallel controlled trial was designed to evaluate the role of continuous hemodynamic monitoring in heart failure (COMPASS-HF [Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure] study). Measurements of heart rate, body temperature, RV pressure, and derived parameters (dP/dt, estimated pulmonary artery diastolic pressure, RV prejection) were obtained from a lead implanted in the RV outflow tract.
tract and connected to a programmable device in the prepectoral region. Intracardiac pressure was corrected for atmospheric pressure by an external pressure sensor device, carried by the patient. A total of 274 patients with New York Heart Association class III or IV heart failure symptoms were successfully implanted with the device and randomized to either standard medical care (n/H11005/134) or medical care assisted by continuous hemodynamic monitoring (n/H11005/140). Over a 6-month study period, there was a nonsignificant 21% reduction in heart failure–related events (P/H11005/0.33) with hemodynamic monitoring. Device-related adverse effects were small, the complication-free rate was 91.5% (95% lower confidence boundary 88.7%), and the few complications were mostly due to lead dislodgement. Surprisingly, a reduced heart failure rate in the control group was seen compared with prior studies, and this was attributed to a beneficial effect of intensive clinical follow-up by a research nurse. Because event rates were lower than expected, the study was likely underpowered to detect a significant reduction in the primary end point. Further development of this technology was not pursued, and this sensor is not currently available for clinical use.

Measurement of Pulmonary Artery Pressure
More recently, the feasibility of using implantable leadless sensors has been demonstrated in smaller trials. A wireless pressure sensor (CardioMEMS Heart Failure Sensor, CardioMEMS Inc, Atlanta, Ga) consists of a sealed, pressure-sensitive capsule and 3-dimensional coil. The device (15 × 3 mm in size) is delivered through a 12F sheath placed in the pulmonary artery and fixed in place passively by 2 nitinol wire loops. The coil and capacitor resonate at a specific frequency. A characteristic shift occurs in the resonant frequency as pressure is applied to the capsule. The coil allows electromagnetic coupling to an external antenna for data transfer. This device does not have an internal battery, but instead, the external antenna is used to power the device. The external device also includes a pressure sensor to enable adjustment of real-time measurements to changes in atmospheric pressure. Twelve heart failure patients (already receiving warfarin) had this device implanted and were followed up for 90 days. Patients underwent Swan-Ganz catheterization at the time of implantation and after 60 days, and serial echocardiography was performed for assessment of RV systolic pressure. Data from the heart failure sensor correlated with invasive assessment of systolic and diastolic pulmonary artery pressure at implantation (r²=0.90 and r²=0.88, respectively; P<0.01) and at 60 days (r²=0.94 and r²=0.48, respectively; P<0.01) and also correlated with echocardiography measurements (r²=0.75, P<0.01). A larger study is now under way to further evaluate this concept (ClinicalTrials.gov, identifier: NCT00531661).

Another pressure-monitoring system (developed by Remon Medical Technologies, now Boston Scientific, Natick, Mass)
consists of a pressure sensor, a transducer, a control chip, and a battery. These are built into a titanium case (15×3×2.4 mm), and the system has the capability to communicate with an external handheld unit. The sensor is attached to a self-expandable stentlike nitinol mesh to stabilize the unit in the pulmonary artery, and a 10F introducer is required for delivery. A pulmonary arteriogram is required to assess the anatomy and ensure suitability for device delivery. When the device is interrogated with an external unit, it downloads a 10-second full pulmonary artery pressure waveform. In a 6-month prospective, multicenter observational study, 40 patients with New York Heart Association class III or IV heart failure symptoms were enrolled to assess medium-term (6-month) device safety and accuracy of pressure measurement by the device (PAPIRUS II study [Pulmonary Artery Pressure by Implantable device Responding to Ultrasonic Signal II]).

Patients received aspirin, clopidogrel, and heparin during the procedure. Aspirin (100 mg) and clopidogrel (75 mg) were maintained for at least 30 days. Overall, 31 patients completed the 6-month study period without any device-related complications. Device implantation was not performed in 7 patients for anatomic reasons (only a single stent size was available during the study), and early device extraction was required in 2 patients. Accuracy of the device measurements was confirmed until the end of the 6-month study period when directly compared with invasive measurements with a high-fidelity pressure catheter (PMS Instruments, Maidenhead, United Kingdom). The current design allows home- or office-based monitoring and displays long-term hemodynamic data.

Measurement of Left Atrial Pressure

Another sensor (HeartPOD, Savacor Inc, subsidiary of St. Jude Medical Inc, Minneapolis, Minn) has been developed to monitor left atrial pressure. The device consists of a lead with a hermetically sealed sensor unit (sized 3×7 mm) with a titanium pressure-sensing membrane implanted in the left atrium and its electric circuitry. The lead is connected to a coil antenna placed in the pacemaker pocket. An external unit (called a Patient Advisory Module, or PAM) has a barometer to allow adjustment for atmospheric pressure. The external unit is used to communicate with the device via radiofrequency wireless communication. During interrogation, up to a 20-second recording of atrial electrograms and left atrial pressure is transmitted to the Patient Advisory Module. Memory in the Patient Advisory Module allows data storage for several months. The HOMEOSTASIS I (Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients) study tested the safety and reliability of this system in 8 patients with New York Heart Association class III or IV heart failure. The lead was implanted by a femoral approach, and after transseptal puncture, the sensor was implanted in the left atrium with an 11F sheath and fixed to the interatrial septum with the sensor facing the left atrium. The lead was fixed in place by use of anchors at the tip of the lead. The lead and device were then secured in the abdominal subcutaneous layer. Currently, a transseptal access system that allows safe puncture of the interatrial septum via subclavian access is being developed. The initial experience with this device in a small single-center cohort confirmed stable measurement of high-fidelity left atrial pressure signal over a 12-week observation period. No device-related complications were seen. At follow-up, there was strong correlation (r=0.95, P<0.001) between pulmonary capillary wedge pressure (measured with a Swan-Ganz catheter) and left atrial pressure (measured with the device). An example from a patient is shown in Figure 4. A large multicenter study is currently evaluating the clinical utility and safety of this sensor (http://www.clinicaltrials.gov; unique identifier: NCT00632372)

Although the most recently developed true hemodynamic sensors bear great promise, one should remember that there are few human data available, and short- and long-term safety and efficacy have not been established. There is concern about thrombogenesis, device migration, erosion, and possible difficulty of device extraction in case of complication or infection. As with all emerging medical technology, carefully conducted safety and outcome studies are needed to address these issues. Clinical studies to evaluate sensors for heart failure monitoring are summarized in Table 3.

Current Challenges in Device-Based Heart Failure Monitoring

The increasing prevalence of heart failure poses a significant burden to caregivers and challenges to the stretched healthcare budget. A large part of the cost is related to heart failure rehospitalization and inpatient management. These costs may be reduced significantly and outcomes improved with an integrated multidisciplinary approach to therapy in specialized heart failure centers. Specific interventions include patient education, physical therapy, and frequent office and telephone follow-ups for symptom and fluid management. The burden for providers is not insignificant. According to a prospective study in which the majority of patients had prior heart failure admissions, experienced outpatient heart failure providers spent more than 300 hours in a 3-month period to manage 130 patients; 38% of that time was spent over the telephone. The most common reason for any encounter was diuretic and fluid status management. Continuous hemodynamic monitoring may help to objectively assess fluid status and allow a more tailored approach in therapy. Wireless, Internet-based technology augments data exchange between centers and the patient. One may envision that some patients may be allowed to access the hemodynamic data and adjust the diuretic dose themselves via instructions from the heart failure clinic under close supervision. In other patients, predefined alerts would apprise providers of a possible change in status.

This new, immense data flow to the clinician needs to be managed in a meaningful way; without appropriate clinical trial data and guidelines, excess information will do nothing more than flood an already overstretched clinical service without adding any clinical value. Moreover, the existence of readily available, up-to-the-minute hemodynamic data raises important medicolegal questions about timely processing of this information. Whether outpatient treatment could be managed more efficiently or outcomes improved with continuous hemodynamic monitoring is yet to be answered by large multicenter studies. Currently available data on sensors
fall short on several fronts. Impedance-based monitoring at this time is limited by low overall sensitivity or specificity, clinical data with emerging sensor technology are limited, and safety is not yet established. It would be important to show in future studies that any added procedures, devices, and costs would substantially improve outcomes or resource utilization compared with the current state-of-the-art integrated heart failure treatment approach. This is an important issue in the current era of skyrocketing healthcare costs and exponential expansion of new therapies and technologies. This problem may be highlighted by looking back at the history of rate-modulated pacing. As detailed in previous sections, rate-modulated pacing was shown in small studies to provide hemodynamic benefits, and the technology proliferated to be included in virtually all pacemakers and ICDs. Although the addition of sensors to implanted devices does not substantially complicate device manufacturing and is easily implemented, implantation and follow-up costs are increased. In contrast, large randomized trials were disappointing in that they failed to show a significant improvement in symptoms beyond what was seen with bradycardia pacing alone (Table 2). Although some individual patients surely benefit from rate-adaptive pacing, often the additional cost of this feature in clinical care is not justified. It is therefore very important that cost implications be studied carefully with the introduction and approval of any new technology before recommendations are made for widespread use. In the case of heart failure monitoring, additional new technology must show that clinically important “hard” outcomes (mortality, a decrease in heart failure hospitalization) are improved or healthcare use and costs are reduced significantly compared with the current state-of-the-art cardiovascular care.

**Monitoring of Other Parameters**

**Sleep-Disordered Breathing**

Sleep-disordered breathing is broadly divided into obstructive sleep apnea and central sleep apnea (CSA) and increasingly has been recognized as an important factor in the development of several cardiovascular conditions. Obstructive sleep apnea, the most common form in the general population, is characterized by collapse of the upper airways. CSA is thought to be the result of intermittent alteration of the respiratory drive and hyperventilation (Cheyne-Stokes respiration) and is frequently seen in heart failure patients, perhaps as a result of pulmonary edema. The prevalence of sleep-disordered breathing may reach up to 50% in advanced heart failure patients, and it may be responsible for worsening heart failure. Although treatment of obstructive sleep apnea has been well established, management of CSA is less well defined. CSA has been linked to worse prognosis in heart failure, but it is still debated whether this finding is a reflection of underlying

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**Figure 4.** Direct left atrial pressure measurement (HeartPOD device, St Jude Medical). Recordings are from an implantable left atrial pressure sensor (HeartPOD) device in a patient with heart failure. The left atrial pressure waveforms were acquired from a patient performing a variety of physiological maneuvers. LAP indicates left atrial pressure (mean); Handgrip, isometric hand grip for 3 minutes; End Valsalva, end of Valsalva maneuver; and pNTG, after 0.6 mg of nitroglycerin administered sublingually. A large V wave reflected the development of ischemic mitral regurgitation. After sublingual nitroglycerin administration, left atrial pressure fell and the V wave disappeared. Figure courtesy of Drs Richard Troughton and Iain C. Melton, Christchurch, New Zealand.
cardiac pathology or whether the diagnosis carries independent adverse prognostic implications. Optimal specific treatment for CSA is being debated, but it is well established that treatment of heart failure (by medical therapy, diuresis, or biventricular pacing\textsuperscript{57}) improves CSA, and worsened heart failure is associated with increased CSA. Thus, diagnosis and monitoring may help to assess future treatments and allow identification of worsening heart failure.

Sleep-disordered breathing remains underdiagnosed in part because the availability of a standard diagnostic modality

### Table 3. Clinical Investigations to Evaluate Sensors for Management of Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Follow-Up</th>
<th>Patient Population</th>
<th>Sensor</th>
<th>Measured Parameter</th>
<th>Technical Details</th>
<th>Results</th>
<th>Technical Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohlsson et al\textsuperscript{45}</td>
<td>5</td>
<td>11 mo</td>
<td>NYHA class III heart failure</td>
<td>Oxygen sensor (2 light-emitting diodes)</td>
<td>Oxygen saturation; cardiac output is estimated by the Fick principle</td>
<td>Sensor is incorporated in RV lead and connected to an implanted pectoral monitor</td>
<td>Stable sensor function (correlation with blood samples: $r^2=0.89$, $P&lt;0.001$)</td>
<td>Drifting of baseline; fibrin coating of sensors; not in clinical use</td>
</tr>
<tr>
<td>HOMEOSTASIS I\textsuperscript{40}</td>
<td>8</td>
<td>12 wk</td>
<td>NYHA class III–IV heart failure</td>
<td>Pressure-sensing membrane</td>
<td>Direct left atrial pressure</td>
<td>Sensor is incorporated in the lead tip, and lead is connected to an implanted abdominal coil antenna. Sensor is placed in the left atrial septum after transseptal puncture</td>
<td>87% of LAP measurements=PCWP ± 5 mm Hg</td>
<td>Femoral implantation\textsuperscript{*}; transseptal access</td>
</tr>
<tr>
<td>Verdejo et al\textsuperscript{48}</td>
<td>12</td>
<td>3 mo</td>
<td>NYHA class III–IV heart failure</td>
<td>Pressure-sensitive capacitor (CardioMEMS Heart Failure Sensor)</td>
<td>Direct PA pressure</td>
<td>Capsule (3 mm×15 mm) is delivered by catheter and fixed in the PA with 2 wire loops</td>
<td>Stable and accurate sensor function PASP: $r^2=0.94$ PADP: $r^2=0.48$</td>
<td>Device migration</td>
</tr>
<tr>
<td>PAPIRUS II\textsuperscript{49}</td>
<td>31</td>
<td>6 mo</td>
<td>NYHA class III–IV heart failure</td>
<td>Pressure sensor</td>
<td>Direct PA pressure</td>
<td>Capsule (3 mm×15 mm) is delivered by catheter and fixed in the PA with a stentlike anchor</td>
<td>No device-related SAE</td>
<td>Implantation is not feasible in certain PA anatomy; device migration</td>
</tr>
<tr>
<td>Page et al\textsuperscript{45}</td>
<td>67</td>
<td>12 mo</td>
<td>NYHA class III–IV heart failure</td>
<td>MV and ACT sensor in standard CRT and pacemaker system</td>
<td>Mean daily MV at rest and during activity; mean daily workload</td>
<td>Measured parameters are smoothed over a 7-day period, and clinical events are predicted by an algorithm</td>
<td>Prediction of CHF episodes:PPV 71%; NPV 98%</td>
<td>Indirect information</td>
</tr>
<tr>
<td>COMPASS-HF\textsuperscript{42}</td>
<td>274</td>
<td>6 mo</td>
<td>NYHA class III–IV heart failure</td>
<td>Pressure sensor in intravascular RV lead</td>
<td>RV pressure ePAD</td>
<td>The lead is connected to a pacemaker-like pectoral device; hemodynamic data are only used in the treatment group</td>
<td>21% Reduction in CHF-related events vs controls ($P&lt;0.33$)</td>
<td>Specialized ventricular lead is required; not in clinical use</td>
</tr>
<tr>
<td>Yu et al\textsuperscript{46}</td>
<td>34</td>
<td>24 mo</td>
<td>NYHA class III–IV heart failure</td>
<td>MV sensor</td>
<td>Intrathoracic impedance</td>
<td>Impedance is measured between standard ICD lead coil and pectoral pacemaker-like device. Actual impedance is compared with long-term impedance trend, and difference is summed</td>
<td>Prediction of CHF episodes: sensitivity 77%</td>
<td>Indirect information; high rate of false-positive warnings (1.5 per patient-year)</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; HOMEOSTASIS I, Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients; LAP, left atrial pressure; PCWP, pulmonary capillary wedge pressure; PA, pulmonary artery; PASP, pulmonary artery systolic pressure; PADP, pulmonary artery diastolic pressure; PAPIRUS II, Pulmonary Artery Pressure by Implantable device Responding to Ultrasonic Signal II trial; SAE, serious adverse events; CRT, cardiac resynchronization therapy; MV, minute ventilation sensor; ACT, activity sensor; CHF, congestive heart failure; PPV, positive predictive value; NPV, negative predictive value; COMPASS-HF, Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure study; and ePAD, estimated PADP.

*Transseptal access kit for subclavian access is under development.
(clinical polysomnography) remains suboptimal. Recent work with impedance-based minute ventilation sensors in cardiac devices has shown promise in the diagnosis of moderate to severe sleep apnea. This method has been validated with simultaneous polysomnography (correlation of apnea/hypopnea index: Pearson’s $r=0.869$, $P<0.001$).

Early results suggest that automated detection of sleep apnea with a commercially available pacemaker may also be feasible and may be useful for diagnosis or perhaps evaluation of therapy efficacy. Although the preliminary data are very promising, subsequent randomized studies will need to examine the accuracy of the algorithm and assess whether enhanced diagnosis and treatment would change outcomes.

### Arrhythmia Discrimination in Cardiac Devices

Inappropriate ICD shocks remain an important clinical problem. In the 1990s, extensive efforts were made to identify hemodynamic parameters that could reliably discriminate between supraventricular and ventricular arrhythmias. The specificity of hemodynamic data derived from RV leads has been less than ideal, and in the future, integration of strategically positioned miniaturized sensors with wireless communication to the pulse generator may solve some of these shortcomings.

### Future Directions

Principles of cardiac hemodynamics form the basis of many decisions for the management of heart disease. It is therefore logical that developments in cardiac sensors target these parameters to support clinical decision making (for example, RV pressure, pulmonary artery pressure, and left atrial pressure). Although results are promising, there are also significant limitations with current technologies (as detailed in previous sections).

An ideal device-based continuous hemodynamic sensor would allow adequate monitoring of certain conditions (such as heart failure or sleep apnea) and would enhance automatic optimization of device function and therapy. At present, optimization of certain pacing parameters, such as atrioventricular delay or left ventricular–to-RV delay (in biventricular pacemakers), is either determined empirically or the interval is adjusted on the basis of timing of intracardiac electrograms. Precise hemodynamic evaluation requires invasive measurements or resource-intensive echocardiographic studies of surrogate parameters. Once a reliable sensor technology is developed, it may become possible to build completely automated (eg, closed-loop) systems. In these systems, the sensor would provide positive or negative feedback to the algorithm based on real hemodynamic data to optimize a specific parameter (such as atrioventricular delay or pacing rate based on change in cardiac output or atrial pressure).

The ideal sensor should be small, energy efficient, and resistant to the hostile biological environment. Past experience has led us to use surrogate measures such as activity because of the significant challenges in building reliable pacemaker and ICD leads and the concern that the addition of dedicated built-in sensors would likely erode their reliability. Several other promising technologies that are commercially available have been discussed in previous sections (an activity sensor incorporated in the pacemaker lead, or different impedance-based technologies). Further research is needed to optimize sensor function and improve the specificity and sensitivity of sensors for monitoring heart failure status. Approaches include the combination of sensors to enhance specificity and the use of a remote intravascular sensor that communicates with the patient’s device. Short- and long-term risks with the latter approach are currently unknown.

Hemodynamic information may also be gathered by use of photoplethysmography. The technology, which is commonly used in noninvasive pulse oximetry, uses light for noninvasive assessment of microvascular blood volume. In a proof-of-concept canine study, a photoplethysmography sensor was implanted subcutaneously, and waveforms showed an excellent correlation with aortic pressure during rapid ventricular pacing or changes in atrioventricular delay. It was proposed that inclusion of this sensor in a pulse generator may allow measurement of a surrogate marker for acute changes in arterial pressure. Furthermore, appropriately filtered photoplethysmography data may provide information on venous capillary flow and respiration and may be used to aid management of sleep-disordered breathing.

Exciting technological developments have occurred in nanotechnology. Development of carbon nanotubes allows fabrication of sensors that are in the nanometer range, and they offer an excellent interface between biological events and electronic signal transduction. Carbon nanotubes are hexagonal networks of carbon atoms (approximately 1 nm by 1 to 100 $\mu$m) with high strength and electric conductivity. This technology, which is compatible with implantable devices, provides a platform for innovative sensors that could measure hemodynamic parameters. These sensors not only may be used to measure macroscopic changes in patient profile (such as blood pressure or heart rate) but also may allow detection of changes at the cellular level and open completely new avenues to how we approach and treat different cardiac conditions. These systems have little energy requirement and may be built to allow remote communication.

Research has also progressed in the development of technology that scavenges energy from the body (reviewed by Romero et al), which may be key to the successful development of long-term implantable monitors. Although the possibilities with the emerging technology are endless, long-term toxicity and safety are unclear, and further research will be needed to clarify whether biochemical or molecular signaling information would have incremental value to the current sensors.

In summary, technological advances have opened new avenues for device therapy and diagnosis in various cardiovascular conditions. Future efforts must focus on finding the appropriate clinical roles for these new technologies and ensuring that the incremental costs are justified by improvements in outcome and delivery of more (cost) effective care.

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**References**


more favorably than an accelerometer alone in pacemaker patients: the LIFE study results. Pacing Clin Electrophysiol. 2008;31:1433–1442.


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