The initial requirement for implanted ventricular pacing was the provision of a stable, regular, reliably paced ventricular rate and rhythm more rapid than the idioventricular rate. This combination eliminated the potentially lethal episodes of ventricular asystole and escape tachycardias that characterized the unprotected, atrially dissociated idioventricular rate characteristic of complete heart block. It was soon recognized that increased cardiac output resulted from an increase in ventricular rate but that above a rate of 60–80 beats/min, increased physiological need, usually as a result of exercise, was necessary to further increase cardiac output.

Research during the past 5 years has further clarified the central role that ventricular rate plays in cardiac output control. The role of atrial contraction, ventricular preload, and atrioventricular (AV) synchrony remain controversial, as they have for many years. Atrial synchrony may be more important at the lower end of the “normal” rate range (i.e., between 50 and 90–100 beats/min), whereas at more rapid ventricular rates (i.e., 120–180 beats/min), heart rate appears more important and AV synchrony appears less so. The establishment of a rate proportional to need was initially dependent on atrial sensing. However, in the presence of severe sinus node dysfunction and arrhythmias such as atrial fibrillation or flutter with a slow ventricular response or sinus bradycardia, atrial sensing does not provide the rate modulation required to increase cardiac output.

The effect of rate-modulated ventricular pacing differs, depending on the rhythm being paced. In complete antegrade and retrograde heart block, such pacing may provide a satisfactory result, whereas in the presence of sinus bradycardia with retained retrograde conduction, ventricular pacing may produce retrograde atrial contraction and the “pacemaker syndrome.” The consequences of making the right ventricular apex the overriding “pacemaker” of the heart and the potential reversal of the sequence of cardiac contraction remain uncertain in some patients and detrimental in others. Because the incidence of retrograde conduction decreases with ventricular rate increases, patients may be symptomatic at one rate and not at another. This issue can now be resolved with the introduction of dual-chamber, rate-modulated pacing, which of course retains the normal AV sequence. Each pacing circumstance, whether atrial, ventricular, or dual chamber, and each rhythm, whether AV nodal disease, sinoatrial (SA) nodal disease, or a combination in the presence or absence of retrograde conduction, should be judged during pacemaker implantation and when the selection of a pacing mode is being made.

The provision of an AV delay of physiological duration is important, and the avoidance of retrograde conduction is critical in some patients, but a ventricular rate responsive to physiological need is probably the most important factor in allowing increases of cardiac output, particularly in the absence of retrograde atrial activation and in the presence of fixed arrhythmia (Table 1).

The increase in cardiac output follows the formula:

\[
\text{Cardiac output} = \text{rate} \times \text{stroke volume}
\]

In normal subjects, cardiac rate can increase about threefold to fourfold between rest and maximal stress. Stroke volume may increase by 50% (if rate increases), and the arteriovenous oxygen difference (A–V \(O_2\)) widens. Other consequences such as changes in peripheral and central arterial pressures and in blood pH follow. At a fixed ventricular rate, cardiac output could increase because of an increase in stroke volume of more than 50%. Those with congenital complete heart block can achieve relatively normal cardiac output by the ability to increase stroke volume and a modest ventricular rate increase that generally occurs in such patients.

Increase of cardiac output and \(\dot{V}O_2\) by anaerobic metabolism and widening of the A–V \(O_2\) difference causes an oxygen debt that is always symptomatic. When sufficiently severe, breathlessness is produced; at more severe levels, chest pain, lightheadedness, muscle cramps, and ventricular ectopy occur. Like all other times, reduction of anaerobic metabolism during exercise is desirable.

A variety of physiological changes take place during exercise that are potentially useful for sensing the requirement for increased heart rate (Table 2). Sensors of physiological function that measure metabolic effect directly such as central venous pH, temperature, or oxygen saturation or that sense body motion...
TABLE 1. The Effect of Rate Modulation

<table>
<thead>
<tr>
<th>Patients (n)/Reference</th>
<th>Exercise type/protocol</th>
<th>Sensor</th>
<th>Duration (min)</th>
<th>Rate (beats/min)</th>
<th>Peak VO₂ (ml/min)</th>
<th>Cardiac output (l/min)</th>
<th>Maximum work load (W)</th>
<th>Anaerobic threshold (O₂ ml/min)</th>
<th>Duration (min)</th>
<th>Rate modulated (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12^51</td>
<td>Treadmill/Balke</td>
<td>Activity</td>
<td>7.7±2.5</td>
<td>90±28.4</td>
<td>1,325±451</td>
<td>NA</td>
<td>NA</td>
<td>1,064±377</td>
<td>10.2±3.8</td>
<td>128±12</td>
</tr>
<tr>
<td>6^60</td>
<td>Treadmill/Naughton</td>
<td>Activity</td>
<td>4.3±4.2</td>
<td>68±2</td>
<td>11.7±3.7</td>
<td>3.61±0.84</td>
<td>NA</td>
<td>10.8±2.3</td>
<td>4.7±4.1</td>
<td>95±12</td>
</tr>
<tr>
<td>5^70</td>
<td>Treadmill/Bruce</td>
<td>QT interval</td>
<td>NA</td>
<td>70</td>
<td>5.3±1.2</td>
<td>9.3±2.2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>125</td>
</tr>
<tr>
<td>11^48</td>
<td>Supine/bicycle</td>
<td>Respiratory rate</td>
<td>9.4±2.5</td>
<td>70</td>
<td>967±336</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>12±2.8</td>
<td>135–145 approximately</td>
</tr>
<tr>
<td>16^60</td>
<td>Bicycle/ergometer</td>
<td>Atrial rate</td>
<td>NA</td>
<td>76±16</td>
<td>NA</td>
<td>NA</td>
<td>94±26</td>
<td>NA</td>
<td>NA</td>
<td>152±22</td>
</tr>
<tr>
<td>16^63</td>
<td>Bicycle/ergometer</td>
<td>Atrial rate</td>
<td>NA</td>
<td>72±8</td>
<td>NA</td>
<td>11.8±25</td>
<td>88±22</td>
<td>NA</td>
<td>NA</td>
<td>149±21</td>
</tr>
</tbody>
</table>

ED, exercise duration; AT, anaerobic threshold; CO, cardiac output.

can substitute for the normal atrial sensitivity to physiological need,^26 although no available sensor system completely reproduces this atrial function. The pacemaker stimulation rate can be driven by such a sensor without sensing the atrium. The response of the pacemaker to what the sensor detects is referred to as "rate responsive," "rate-modulated," or "adaptive rate" pacing. Conditions for which sensor-driven, single-chamber ventricular pacing is useful include those in which normal atrial activity is absent or inadequate (Table 3).

Despite the more clear-cut indications listed, implantation of a rate-modulated, single-lead, single-chamber ventricular (VVIR)* pacemaker is often performed in the presence of intermittent, partial, or complete AV block and sinus node dysfunction. As an atrial (AAIR)* pacemaker, in the presence of satisfactory AV conduction, both rate modulation and retention of AV conduction may occur. A single-rate DVI or dual-chamber (DDD) pacemaker in a patient with atrial chronotropic incompetence restores the normal AV sequence but not the cardiac rate response. A dual-chamber, rate-modulated (DDDR) pacemaker can do both. The technical ability of a sensing circuit to deal with two incoming signals (atrial and ventricular) simultaneously permitted development of the DDD and the single-chamber, rate-modulated (SSIR) pacemakers. The ability to sense three incoming signals (i.e., atrium, sensor, and ventricle) allowed development of the DDRR pacemaker.

Sensor Requirements

Muscle metabolism emits various byproducts (Table 4) to which the sensor must respond in a physiological or near-physiological manner to mimic the normal cardiac response. Sensor response should parallel the normal response (i.e., not be delayed until well into exercise nor persist after exercise has ceased) (Figure 1). Onset of pacemaker response should be as rapid as the normal atrium,^28 free of idiosyncrasies (i.e., smooth over the entire exercise range), stable for years, and reproducible from one moment to the next. It should be adaptable for a wide range of patients (e.g., young or old, in good cardiovascular health or fragile) and ideally respond to nonphysical demands such as emotion and mental work (most currently implanted rate-modulated pacemakers do not). Finally, the sensor should respond appropriately to rest; mild-to-moderate activity, the usual submaximal activity of normal life; and maximal activity. If response cannot be adequate in all three states, it is most important that the pacemaker respond appropriately to submaximal activity. The pacemaker should not exceed specific upper and lower rates, and should either pacemaker or sensor malfunction, it should fail safely. In effect, the sensor system should be more reliable than the atrium.

Development of a sensor-based, rate-modulated pacing system requires at least four components: 1) a physiological indicator or one that can substitute for physiological effects (i.e., changes of which are associated directly or indirectly with metabolic need,^30 2) a sensor that will detect these changes and respond

^*Pacemaker function terminology is according to NBG code (PACE 1987;10:794–799).
TABLE 1. The Effect of Rate Modulation (Continued)

<table>
<thead>
<tr>
<th>Rate modulated</th>
<th>Cardiac output (l/min)</th>
<th>Maximum work load (w)</th>
<th>Anaerobic threshold (O₂ ml/min)</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO₂ (ml/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,617±656</td>
<td>NA</td>
<td>NA</td>
<td>1,208±343</td>
<td>ED +33%</td>
</tr>
<tr>
<td>13.4±3.4 (ml/min/kg)</td>
<td>4.51±1.3 (l/min/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.4±0.96</td>
<td>13.5±1.9</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,158±443</td>
<td>NA</td>
<td>NA</td>
<td>1,13±33</td>
<td></td>
</tr>
<tr>
<td>15.6±2.2</td>
<td>109±32</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

reliably and reproducibly, 3) a pacemaker algorithm that will translate the changes detected by the sensor into a change in pacemaker stimulation rate and compensate for deviations from a purely physiological response, and 4) a single- or dual-chamber cardiac stimulator.

The algorithm receives the information generated by the sensor and determines the timing and rate of response that will drive the pulse generator for every level of change in sensor input. The physiological indicator may be nonlinear with respect to body need, whereas the desired response is linear and proportional to physiological need. An example of this effect is central venous temperature. Blood warmed by lower-extremity activity is driven into the central venous system but is preceded by cool (unwarmed) blood. The first blood to reach an intracardiac thermistor reduces central venous temperature. The algorithm should not reduce the cardiac rate in response to the flush of cool blood. Instead, in the usual algorithm, this flush causes a step function increase in cardiac pacing rate (i.e., by

TABLE 2. Metabolic Changes During Exercise

| Arteriovenous oxygen difference is broadened. Anaerobic metabolism occurs. Right-sided cardiac pressures are increased. Left-sided cardiac pressures are increased. Myocardial contractility is increased. Stroke volume increases. Body temperature rises. Preejection interval changes. Changes occur in cardiac muscle electrophysiology. |

TABLE 3. Indications for Rate-Modulated Ventricular Pacing

<table>
<thead>
<tr>
<th>Silent atrium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed sinus bradycardia with or without nodal rhythm</td>
</tr>
<tr>
<td>Fixed atrial fibrillation or flutter with atrioventricular block or medication-induced bradycardia</td>
</tr>
<tr>
<td>Postconduction system ablation atrioventricular block with residual atrial arrhythmias</td>
</tr>
<tr>
<td>Chronotropic incompetence, in which the responsiveness of the atrium is not proportional to activity needs</td>
</tr>
</tbody>
</table>

| 15 beats/min, from 70 to 85 beats/min. If warm blood follows, the rate increase will be maintained and become proportional to temperature; otherwise, rate returns to the preset level. Cessation of muscle activity reduces central venous temperature and cardiac rate. The algorithm will determine how long to consider a change physiological or artifactual. Important new terminology involves the open-loop sensor, which does not respond to a specifically physiological function. An example is the activity sensor, which responds to imposed motion of any kind. The closed-loop sensor responds specifically to physiological change and will increase and decrease response as indicated by physiological change. In practice, there may be little difference between the two approaches, and an open-loop system may appear to function as well or better than a closed-loop system. |

Speed of Response and Idiosyncracies

Some responses may be physiological but slow in onset. Central venous temperature, for example, follows muscular activity well, but responsiveness is slow—a brief burst of activity may be completed before temperature increase, and a consequent cardiac rate response occurs. Imposed temperatures such as drinking warm or cold liquids affect the central venous temperature and the pacemaker-imposed cardiac rate.

Other idiosyncrasies include unequal responsiveness to activity needs. Respiratory sensors respond to arm movement as well as breathing. The response of a respiratory sensor is modified by speech (i.e., walking and talking produces one response, and walking silently produces another). The activity sensor responds to motion, not to actual body need. The response, for example, to movement of the arm on

TABLE 4. Byproducts of Muscle Metabolism

| Heat, producing body temperature |
| Electricity, producing the electrocardiogram and electromyogram |
| Carbon dioxide |
| Lactic acid |
| Intracardiac pressure |
| Skeletal muscle movement |
| Reduction of QT interval |
| Change in ventricular depolarization gradient |
| Change in myocardial muscle mechanics |
the side of the implanted activity sensor is greater than that to movement of the contralateral arm. Walking up stairs produces a paradoxical lesser response than descending the same staircase because the "heel strike" rate is greater when descending although the metabolic needs are reversed. Tapping the activity sensor pulse generator promptly increases the pacing rate.

Two functioning sensors in the same device are now being evaluated. The capabilities of both may be complementary, and the inadequacies of each can be ameliorated. For the DDDR pacemaker, the atrial rate and another sensor (e.g., activity, temperature, preejection interval, stroke volume, or contractility) interact to produce a rate determined to be most suitable. A possible combination for a single-chamber pacemaker is activity and temperature; activity provides a rapid rate response, and central venous temperature provides a longer-term proportional response. The ventricular gradient sensor responds rapidly to onset of exercise and to nonexercise needs. Its combination with the slower but more sustained response of the respiratory impedance sensor is being considered.

**Dual-Sensor Interaction**

In the DDDR pacemaker, the atrium is one sensor of physiological need, and the artificial sensor is the other. The selection of a rate that paces the atrium or senses is set in part by the physician and in part by the sensitivity and responsiveness of the sensor. Because the atrium is one of the sensors, the underlying assumption may be that, at many rates, the atrium is a more correct sensor of body need than is the artificial sensor. That may, of course, not be accurate, but in any dual-sensor system it is unlikely that the two will indicate the same rate at the same time. The algorithm must then determine whether the higher or lower rate of the two (at a given activity level) will be taken as correct. In such an atrial sensor system, one rate will be achieved if the atrium is given precedence, and another will be achieved if the sensor is given precedence. During modest activity, whether the atrium- or sensor-driven rate dominates will depend on the degree of atrial chronotropically competitive and the sensor sensitivity and responsiveness. Rate modulation can be set to ameliorate any broad swings of atrial and ventricular rate (i.e., to avoid a precipitous drop in ventricular rate should 2:1 AV block occur at the upper rate limit for atrial sensing).

**Programming**

Programming the rate of a single-chamber, single-rate pacemaker is generally not difficult because the realistic options are few and the indications for the proper rate under all conditions of activity are even fewer. Traditionally, and probably correctly, the rate for pacing fixed or intermittent complete heart block has been set at 70 beats/min, whereas for patients with sinus node dysfunction, another rate may be selected. For the dual-chamber, atrial-sensing pacemaker, the atrium itself sets the pacemaker rate. Programming sets a lower rate limit, below which the heart beat is not allowed, and an upper rate, above which the pacemaker will not stimulate the ventricle (or track the atrium). Between the two limits, the atrium controls the ventricular stimulation rate, the rate of increase or decrease, and the responsiveness to specific activities.

For a rate-modulated pacemaker, the physician must set the lower and upper rates and the sensitivity and responsiveness of the pacing system, including the acceleration with which it increases and decreases rate and the threshold of physiological or imposed change necessary to produce a change in pacing rate. Setting the non-sensor-driven DDD pacemaker is relatively simpler because of the guide
the atrium provides. Setting the sensor-driven, dual-chamber pulse generator may be much more difficult, including programming of two upper rates that may be dissimilar—one for atrial tracking, and the other for sensor drive. Programming the DDD pacemaker may be far less labor-intensive than programming the rate-modulated pacemaker single or dual chamber. It is as yet unclear whether a stress or activity test will be routinely required to achieve optimal programming and, if so, which is the most suitable\textsuperscript{45} (Table 5).

Each device is delivered with a default setting for the rate-modulated mode (i.e., one that is deemed to be safe and effective in producing modulation during activity). That setting may produce modest changes only and be unsuited for the specific patient.

**Sensors for Clinical Pacing**

*Completed Clinical Evaluation in the United States*

**Atrium.** The SA node is usually a reliable sensor of body need, but it may be dissociated from the ventricle by AV nodal disease and may suffer its own disabilities (i.e., sinus node dysfunction). It then becomes unreliable. It is the rate drive for DDD pacemakers.

**Activity.** During the early 1980s, atrial synchronous (VDD) pacemakers were introduced that sensed atrial activity but could not pace the atrium. In one design, the atrial channel input was replaced by input from a piezoelectric crystal bonded to the pulse generator case. This device was programmable, as was the predecessor VDD generator, to three levels of sensitivity that correspond to three programmable levels of atrial electrogram sensitivity and 10 levels of responsiveness that correspond to the programmable AV interval.\textsuperscript{46} In a single-chamber version, it has become the most successful of rate-modulated pacing systems, is used in atrium and ventricle, and is the most popular pacemaker currently implanted (Activitrac, Medtronic, Inc., Minneapolis, Minn.). Another manufacturer now uses a similar approach to rate modulation. Two dual-chamber activity-sensing (DDDR) devices are now commercially available.

The voltage developed by the piezoelectric crystal may be 5–50 mV at rest and as much as 200 mV during running or other vigorous activity. Crystal response results from episodic or continuous pressure. Most sensed events result from body movement, although imposed movement such as riding in a vehicle, sleeping face down, application of pressure, or tapping, can increase its rate. Piezoelectric crystal response is the most rapid of any of the sensors, and movement causes as prompt a response as the normal atrium. Physical activities, which have little vibrational effect, and intellectual and emotional activities produce little pacemaker response. Hand-grip, Valsalva maneuver, and standing produce minimal response; jogging in place produces a prompt maximum response.\textsuperscript{47} These idiosyncratic responses remain relatively modest and have not limited the usefulness of the rate-modulated approach.

### Table 5. Sensor Programming

<table>
<thead>
<tr>
<th>Sensitivity of sensor to physiological (or nonphysiological) event that is to set rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responsiveness of sensor to physiological change</td>
</tr>
<tr>
<td>Rate at which cardiac rate will be increased by sensor response</td>
</tr>
<tr>
<td>Maximum and minimum rates that are to be achieved—one at rest and the other with maximum activity</td>
</tr>
</tbody>
</table>

**Respiration.** An almost linear relation exists between minute ventilation and cardiac rate during exercise.\textsuperscript{48} Oxygen consumption may be the most physiological determinant of metabolic need. Two factors are the respiratory rate and the tidal volume, which together constitute minute ventilation\textsuperscript{49} and can be measured by determining the respiratory rate from impedance variations between the pacemaker case and a second lead implanted subcutaneously in the chest wall.\textsuperscript{50} The interelectrode impedance can be measured by placing current impulses between the electrode tip and the pulse generator. By maintaining a rapid pulse repetition rate (at a 125-msec interval) and a low-intensity stimulus (pulse duration, 0.12 msec; amplitude, 0.2 mA), no adjacent muscle stimulation occurs.\textsuperscript{51}

Another approach, available for general use, calculates minute ventilation by impedance measurements made between an intracardiac bipolar lead and the pulse generator case.\textsuperscript{52} Again, low-amplitude pulses that are well below the stimulation threshold are delivered through the ring of a bipolar electrode and detected by the tip. The impedance of the system increases during inhalation and decreases during exhalation proportionally to the tidal volume and allows calculation of rate\textsuperscript{52} (Figure 2). A dual-chamber pacemaker based on this principal is now in clinical evaluation.

**Body temperature.** Central body temperature rises as a result of the metabolism from increased muscular activity and is a sensitive and reliable indicator of metabolic state.\textsuperscript{53,54} Skeletal muscular contraction is about 20\% efficient; energy not expended in actual movement is converted into heat, which increases the local blood temperature. With maximum activity, it is possible to increase central venous temperature from 37\(^\circ\)C (98.6\(^\circ\)F) to 38.5\(^\circ\)C (101.3\(^\circ\)F). A thermistor on the pacing lead (i.e., in the right ventricle) can detect that change and increase the ventricular rate in response.\textsuperscript{55}

Brief activity, such as a sprint, may not produce a sufficient temperature change to increase the cardiac rate; if it does, activity may have ended before the central temperature rises so that the physiological tachycardia will occur after the end of the activity. Another difficulty is the response to fever. While tachycardia is normally associated with pyrexia, the device is unable to distinguish between a physiological increase in body temperature and pyrexia; therefore, after an interval following the increase in temperature, it returns to the lower rate setting, in effect disregarding the fever. One implantable tempera-
ture-sensitive, single-chamber, rate-modulated device has been useful and is available for general use\(^6\) (Figure 3).

**Undergoing Clinical Evaluation in the United States**

**Endocardial-evoked potential.** An evoked response measurement by a bipolar endocardial electrode is based on the concept of the "ventricular gradient."\(^7\)\(^,\)\(^7\) The pacemaker conventionally senses spontaneous cardiac activity between the tip and ring of its bipolar electrode during its alert period. If no spontaneous cardiac event occurs for the duration of the escape interval, a unipolar stimulus between the pulse generator (+) case and the electrode tip (−) is emitted. Pulse generator output is then temporarily short-circuited (10 msec) to allow recording by the ring electrode of the evoked response of cardiac depolarization after the stimulus. If the endocardial electrographic voltages are integrated over a cardiac cycle, electrophysiological dispersion may be determined. The area of the poststimulus ventricular depolarization gradient depends on the activity status of the myocardium. The pacemaker changes its stimulation rate to achieve a normal gradient; the cardiac rate is then adjusted to need. This measurement depends on instantaneous amplifier recovery from poststimulus polarization. The ventricular gradient decreases with onset of activity at a fixed cardiac rate, increases during rest at an increased cardiac rate, and remains constant during exercise in the presence of a normal rate response. The pacemaker analyzes these changes in an attempt to increase or decrease its stimulation rate to return the ventricular gradient to its normal resting level.\(^5\)\(^8\) Both endocardial-evoked potential techniques (see below) measure a cardiac response to a stimulus and can determine whether depolarization occurs after a stimulus.\(^5\)\(^9\) Stimulus energy can be increased if no depolarization follows a stimulus, producing an automatic threshold determination and correction mechanism.

**Preejection interval.** The interval between the beginning of electrical and mechanical systole in either the right or left ventricle has been referred to as the preejection period or interval.\(^6\)\(^0\) It is mediated by autonomic influences that normally increase

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**Figure 2.** Holter recording of a respiratory-sensing, rate-modulated, single-chamber pacemaker accentuates pacemaker stimuli on its second channel. Upper channel electrocardiographic recording shows small continuous stimuli. Lower channel accentuates both rate modulation and pacemaker stimuli.
cardiac rate and the force and speed of contraction. The preejection interval shortens with each of these stresses.64 Active exercise with movement or isometric exercise such as hand-grip, emotion, and increase in circulating catecholamines and sympathetic tone all abbreviate the preejection interval. In practice, the measured preejection interval during cardiac pacing occurs between the ventricular pacemaker stimulus and the beginning of ventricular systole.62 The interval will be very different when measured from the intrinsic deflection of a spontaneous beat to the beginning of mechanical systole. This system can also evaluate a proportional change in stroke volume (Figure 4).

Not Undergoing Clinical Evaluation in the United States pH. The initial effort to use a sensor other than the atrium was made by Cammilli et al in 1977 when he demonstrated that the pH of the mixed venous blood decreased (became more acidic) by as much as 0.06 units during activity.63 This effect was mediated by the production of lactic acid during even modest anaerobic metabolism. The pacemaker rate was correlated with pH, increasing with reduction in pH and returning to normal as pH rose. The system was never widely evaluated but is now being reassessed.64

Oxygen saturation. At rest, approximately 27% of oxyhemoglobin is reduced to hemoglobin with loss of oxygen to cells. During maximum activity, approximately 80% of oxygen may be lost. Normal arterial oxygen saturation approximates 95–98% and normal mixed venous oxygen saturation approximates 75% while breathing ordinary air. A drop of one third in mixed venous oxygen saturation to about 50% at maximum activity can occur.65 This can be measured with an optical oximeter and correlated with pacemaker rate. A pacemaker is in clinical evaluation.66

Endocardial-evoked potential. Since 1920, it has been recognized that the interval between the onset of the QRS complex and the end of repolarization (i.e., the T wave) varies as a function of cardiac rate.67 QT interval duration and cardiac rate result, at least in part, from the effect of circulating catecholamines and myocardial response to stress and activity. In the presence of complete AV block, the interval between the stimulus beginning ventricular depolarization and the end of repolarization (i.e., the T wave) is abbreviated during activity, even without change in the ventricular rate.68 Measurement requires instantaneous amplifier recovery from post-stimulus polarization. Stimulus-to-T-wave duration can be an indicator of the need for an increased rate and can participate in an algorithm to drive a pulse

Figure 4. Measurement of myocardial mechanics after a pacemaker stimulus (Stv) allows determination of interval between stimulus and beginning ventricular response, preejection interval (PEI), and rate of development of the myocardial contraction [i.e., dV/dt of upstroke velocity and impedance of the system (dZ/dt), all of which change with contractility, which in turn changes with exercise]. This system allows calculation of end-systolic volume (ESV) and end-diastolic volume (EDV) and stroke volume (SV), all of which also change with physiological need.

Figure 5. Stimulus-to-T-wave pacemaker senses the interval after a pacemaker stimulus produced ventricular response. Left: Spontaneous event sensing of which is followed by a conventional 250-msec interval of ventricular refractoriness. Right: Pacemaker-induced contraction followed by 200 msec of absolute refractoriness followed by another 250 msec during which T wave is sensed to set stimulus-to-T-wave interval.
generator. The absence of easily discernible repolarization precludes use in the atrium (Figure 5).

A single unipolar ventricular lead can sense the interval \( \frac{dP}{dt} \) from the stimulus to the end of the resultant T wave. In the absence of a stimulus, the interval cannot be determined; therefore, no rate modulation exists when the pacemaker is inhibited. Thus, the inhibited pacemaker episodically emits a stimulus at a brief interal compared to the existing spontaneous rate, produces a ventricular response, and measures the stimulus-to-T-wave interval. The stimulus-to-T-wave interval had been in a clinical evaluation that has ended without device release in the United States. It is, however, in widespread use outside of the United States.

Right ventricular pressure. The sensor determines the derivative, the rate of change, of right ventricular pressure \( \left( \frac{dP}{dt} \right) \). \( 
\frac{dP}{dt} \) is increased by preload (i.e., myocardial fiber length and venous pressure) and by afterload, the pulmonary artery pressure. Drugs, cardiac rate, and autonomic tone each have a variable effect. The range of \( \frac{dP}{dt} \) may be between 300 and 700 mm Hg/sec, with higher cardiac rates produced by greater rates of change. The sensor is a piezoelectric crystal bonded to a titanium diaphragm, is part of the unipolar right ventricular lead, and is set 3 cm proximal to the electrode. Deflection of the diaphragm produces pressure on the piezoelectric crystal, which in turn yields a proportional voltage monitored by the pulse generator after each paced or sensed ventricular event to determine the escape interval. The lead is unique for this system. This device has been implanted in facilities outside of the United States, and clinical evaluation is not scheduled to begin in the United States.

Rate-Modulated Pacemaker Longevity

In the non-rate-modulated mode, a pulse generator is entirely conventional in operation with programmability in rate, output, sensitivity, and possibly other functions. The battery is drained for sensing cardiac function and operation of the logic and output circuits. Each artificial sensor requires some current drain—some drain little, and others drain much more. If a rate-modulated pulse generator is programmed out of that mode much of the time, its longevity may be the same as that of other similar models. If the sensor is active, longevity will decrease because of the operation of the sensor and microprocessor and the increase in average rate of stimulation.

In some models, programming the sensor to "off" eliminates the battery drain incurred during operation and increases pulse generator longevity. In other models, sensor drain continues even when rate modulation is not operative; therefore, pulse generator longevity is not increased. Contemporary pulse generator design tends toward cessation of sensor drain when rate modulation is turned to "off." In other models, the sensor may be operative even when rate modulation is inoperative so an assessment of the sensor-determined appropriate rate can be teleme-

tered for programming purposes. In these models, there are three sensor positions that have a corresponding battery drain: 1) active with rate modulation, 2) active without rate modulation, and 3) inactive.

Change in stimulation rate drains relatively little. The piezoelectric sensor drains little. The drain for sensing electrocardiographic changes such as that for the stimulus-to-T-wave sensor is also relatively small. The circuit drain for operation of the special sensor should be equal to the atrial sensing circuit in a modern dual-chamber pacemaker. Some sensors emit stimuli (i.e., the impedance sensors) and then sense the modification of those stimuli. The battery drain in measurement of respiratory rate or cardiac mechanics by impedance measurement consumes energy and reduces the longevity of a single-chamber device. Other sensors are likely to fall between the two limits. The operation of the microprocessor required by all of the rate-modulated units is energy intensive and produces a pulse generator with far shorter longevity than non-rate-modulated units of similar electrical output. If a sensor allows automatic threshold assessment, the output circuit may be run at a very low output rather than the customary higher output used as a safety margin. Safety and energy conservation result from the ability to determine threshold and emit a higher stimulus amplitude as needed.

Lead Systems for Rate-Modulated Pacing

Either specialized or conventional leads may be used with rate-modulated systems, depending on whether the sensor is within the pulse generator or the lead and whether the sensor is based on electrographic data.

Conventional Unipolar and Bipolar Leads

Piezoelectric sensors (activity) are within the pulse generator so any lead that can be physically connected is suitable. The stimulus-to-T-wave electrographic sensor requires a normal-to-low impedance unipolar lead. Some older unipolar leads were of very high impedance and attenuated the electrogram sufficiently so satisfactory measurement could not be accomplished.

Bipolar Leads Only

Impedance measurements between two intracardiac electrodes require a conventional bipolar lead. The evoked ventricular gradient mode stimulates via the unipolar tip but senses the response via the ring and requires a bipolar lead. The respiratory impedance sensor requires a bipolar lead.

Specialized Leads

Sensors that require an intracardiac measurement require a specialized lead. Cardiac mechanics, temperature sensing via a thermistor, oxygen tension \( \frac{dP}{dt} \), and \( \text{pH} \) all use an intravascular transducer and require a specialized lead.
Pulse generator interchangeability at the time of replacement may be restricted because of lead incompatibility. The choice of a sensor-driven pacemaker as a replacement on an existing lead will be dictated by its functional connectability to the existing lead.

**Electrocardiography of Rate-Modulated Pacemakers**

**Single Chamber**

Electrocardiography of single-chamber, rate-modulated pacemakers is relatively simple. Any escape interval that is briefer (i.e., more rapid rate) than the lower-rate interval is sensor driven. The interval between one stimulus event and the next may vary. The stimulation rate is a result of these individual variations. A smooth rate of acceleration or deceleration with continuous pacing provides a small variation from one stimulus to the next (Figure 6). If the sensor modifies the escape (lower) rate but spontaneous cardiac events occur, the interval between a sensed spontaneous event and the next pacemaker stimulus will vary depending on the sensor-imposed escape interval. Electrocardiographic interpretation requires recognition of the absence of a fixed pacemaker escape interval during sensor operation.

The action of some sensors is electrocardiographically invisible except for changes in the escape interval; others produce an electrocardiographic mark. The respiratory impedance sensor continually emits rapid small-amplitude stimuli that can be seen on the electrocardiogram. In the absence of these stimuli, the pulse generator is in the "sensor off" mode and no modulation of rate or escape interval should be anticipated73 (Figure 2).

The stimulus-to-T-wave and evoked potential sensors can make a rate determination only after a paced
event. During pacemaker inhibition (i.e., with the sensor determining a rate less than the spontaneous rate), the sensor "tests" the cardiac status (i.e., the stimulus-to-T-wave interval or the area under the curve of the evoked potential) by determining the actual rate (i.e., spontaneous QRS coupling interval) and emitting stimuli at a briefer coupling interval, stimulating the ventricle and determining what the pacemaker rate should be. If the appropriate rate is determined to be less than the spontaneous rate, the pacemaker will return to its inhibited state. If the appropriate rate is determined to be more rapid than the spontaneous rate, pacing will continue.\textsuperscript{74} During continuous pacing, each QRS interval will be evaluated (invisibly on the electrocardiogram) to determine an increase or decrease in rate. Thresholds will be tested by the periodic emission of lower-amplitude stimuli. Should a stimulus fail to capture, no ventricular response occurs; 60 msec later, a greater amplitude stimulus is emitted (Figure 7).

**Dual Chamber**

A single timing interval exists in a single-chamber pacemaker; several exist in a dual-chamber device.
The lower rate limit is set by the programmed atrial and ventricular pacing rate. The AV delay is also set and can be fixed or of rate-modulated duration. The fixed AV delay will be of the same duration at the lower rate limit and at the upper rate limit when both atrium and ventricle are driven by artificial sensor or the atrium. The modulated AV delay will be abbreviated at higher rates whether sensor or atrial driven (Figure 8). The upper rate limit of atrial tracking, as in other DDD modes of operation, is determined by the duration of atrial refractoriness. In the rate-modulated (DDDR) unit, a second and independent (i.e., sensor-driven) upper rate limit exists. It may be set to be higher, the same, or lower than the upper limit of atrial tracking. Therefore, there may be three different upper rate limits, and these can be anticipated only by knowledge of the various pacemaker refractory settings and sensor upper rate limits.76,77

The availability of a rate drive independent of the atrium has increased the use of a previously infrequently used dual-chamber mode, DDI. In this mode, the atrium is sensed and paced at the lower rate limit, but sensing of an atrial event does not cause emission of a ventricular stimulus after the programmed AV delay. In the presence of sinus bradycardia (i.e., spontaneous rate below the pacemaker escape rate) DDI, DVI (atrium is not sensed), and DDD pacing are indistinguishable. During an atrial arrhythmia (atrial flutter or fibrillation), the DDD mode is often driven to the upper rate limit. The DVI mode produces atrial and ventricular stimuli at the programmed escape interval; these drive the ventricle, are competitive with the atrium, and may tend to fix the arrhythmia. The DDI mode produces only ventricular stimuli at the escape interval with the atrial channel inhibited by atrial activity.78 The DDI mode is particularly useful in a patient in whom sinus bradycardia (possibly medication induced) alternates with supraventricular arrhythmia. In the past, a rate more rapid than the escape rate (lower rate interval) could not exist. With
dual-chamber rate modulation (DDIR), the cardiac rate is established independently of the atrial rate during sinus bradycardia, with maintenance of the normal AV sequence, with disregard of the atrial arrhythmia, and without atrial competition, although loss of the normal AV sequence occurs. This mode is particularly useful in pacing after AV node ablation for intractable but episodic atrial arrhythmia. It provides rate modulation and the normal AV sequence during pacing of sinus bradycardia and rate modulation during ventricular pacing of atrial arrhythmia (Figure 9).

Because of the importance of variation in ventricular rate as a determinant of cardiac output, the ability of a pacemaker to vary rate has become recognized as one of the basic pacemaker functions, along with sensing the chamber paced and programming output and sensitivity. It is likely that in the near future that all pacemakers will include the ability to modulate the cardiac rate in response to physiological need, in addition to or independent of atrial sensing.

Summary

The primary role of cardiac rate in adapting cardiac output to changing physiological needs has been more clearly recognized in recent years. Previously, the rate of cardiac stimulation had been determined either at pacemaker manufacture, by programming a single rate, or by sensing the atrium. More recently, sensing another physiological or nonphysiological function that changes in response to body need has become possible. Exercise changes blood oxygen saturation, central venous pH, central venous temperature, minute ventilation and respiratory rate, stroke volume, circulating catecholamines, QT interval, evoked endocardial response to a stimulus, and the mechanics of myocardial contraction. Some sensors respond to muscle work but not to intellectual effort or emotion. Pacemaker-based sensors of physiological function or activity allow a change in cardiac stimulation rate in response to need. Whichever sensor is used, increases in ventricular rate during exercise regularly produce a cardiac output response. Single-chamber, rate-modulated pacemakers in atrium or ventricle and dual-chamber devices are now implanted on a widespread basis. These drive the atrium, the ventricle, or both, sensing or pacing the atrium at a rate determined by the sensor.

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