PACEMAKERS

Today, implantable cardiac pacemakers are used with exceptional success as a long-term, safe, and reliable form of therapy for different kinds of cardiac rhythm disturbances. Numerous pioneering, technological developments, such as highly integrated circuits or lithium batteries, are significant milestones in this field. During the short history of the pacemaker, beginning with the first implantation in 1958, a turbulent technical evolution has occurred. The early devices were heavy, simple impulse generators with two transistors and short operating lifetimes. These could pace only the right ventricle asynchronously with impulses of a constant rate and amplitude. Modern, rate-adaptive dual-chamber pacemakers possess highly complex integrated circuits with several hundred thousand transistors. They can pace in the right atrium and the ventricle, monitor the intrinsic cardiac activity, adapt automatically to changing needs of the heart, be programmed through inductive telemetry in a variety of ways, and guarantee an operating lifetime of 8 years or longer. These devices now weigh approximately 25 g and are getting increasingly smaller, given continued advances in electronics and battery technology. Multidisciplinary cooperation between the diverse fields of physiology, physics, electrochemistry, electronics, and materials science have made these impressive developments possible. Consequently, the goal of pacemaker therapy has exceeded that of merely a life-maintaining function. It has instead become more adept at the reestablishment of a high quality of life for the patient.

Through different pacing functions, modern, rate-adaptive, dual-chamber pacemakers can adjust to an optimal mode of pacing and pacing rate at any time. Thus, interference between the pacemaker stimulus and the cardiac intrinsic rate is prevented through continuous intracardiac electrogram (IEGM) monitoring. If the intrinsic activity is absent for a certain anticipated interval, the pacemaker commences pacing to prevent a sinking heart rate or cardiac arrest. Today, all single- and dual-chamber pacemakers are designed to pace on demand. The ever increasingly used, rate-adaptive pacemakers can control the stimulation rate with a physiological sensor if a sufficient sinus rhythm is no longer present. A rate increase is additionally accompanied by a dynamic shortening of the atrioventricular (AV) delay to guarantee atrial and ventricular synchrony. This allows for the best possible pumping performance at any time. In addition, modern pacemakers record large quantities of diagnostic information in an internal memory over long periods of time. At follow-up, the physician can use the programmer to analyze data that greatly contribute to therapy optimization. Rhythm disturbances requiring treatment and the basic, technical solutions in a modern cardiac pacemaker will be described to augment understanding of the versatile functions of the pacemaker.

THE HEART RHYTHM

The autonomic nervous system (ANS) mainly controls the adaptation processes and innervates different regions of the heart via the parasympathetic and sympathetic branches. Both branches have an opposite effect on the pumping efficiency. The sympathetic branch increases the cardiac output, and the parasympathetic branch inhibits it. Under resting conditions, the volume pumped per heartbeat, or the stroke volume, is about 70 mL on average. At a resting heart rate of 70 beats per minute (bpm), the cardiac output is about 5 L/min. Under heavy exercise, this value can rise up to 25 L/min in trained athletes. To increase the cardiac output, both factors are increased simultaneously, but to different degrees. Even though the stroke volume can increase only moderately, by 50% at the most, the heart rate rises under heavy load conditions to 180 bpm or higher. A simple way to estimate the maximum heart rate (in beats per minute) for an individual is done by subtracting the age in years from 220. For example, the maximum heart rate for a 40 year old woman would be 180 bpm. The following four, qualitatively different effects influence heart rhythm:

1. Chronotropy—pertains to the heart rate. Heightened sympathetic activity increases the heart rate; this is termed a positive chronotropic effect. A heightened parasympathetic tone can reduce the heart rate, even lowering it to a cardiac arrest. This is referred to as a negative chronotropic effect.
2. Inotropy—pertains to contractility. The sympathetic transmitter substances that ligate to specific receptors in the myocardial cells effect different changes in the cellular ion balance, especially in increasing the amount of released calcium. Called positive inotropy, this intensifies the electromechanical coupling, which is the conversion of ionic balance equilibria to muscle contraction. With the release of more calcium, the contraction velocity increases, leading to a higher pressure rise velocity in both ventricles and to the maximum contractile force attainable. Although the parasympathetic innervation of the ventricular myocardium is physiologically less developed, a negative inotropic effect can nevertheless be detected. This acts both through an increase in parasympathetic and a decrease in sympathetic activity (1).
3. Dromotropy—pertains to the AV conduction time. Through sympathetic influence, the excitation conduction in the AV node is increased (i.e., the time between the atrial and ventricular contractions is shortened), this being a positive dromotropic effect. Parasympathetic activation slows conduction, a negative dromotropic effect. In extreme cases, this can lead to a temporary total AV block. The AV conduction time is shortened with an increase in heart rate. Normally, the interval at 70 bpm is 190 ms and at 130 bpm is 120 ms. Because the rate increase is largely attained by shortening the diastolic interval, shortening the AV delay is key to maintaining synchrony between the atria and the ventricles. The delay is important for an optimum ventricular filling, also at higher rates.
4. Bathmotropy—pertains to the excitability. Through sympathetic activation, the pacing threshold of the

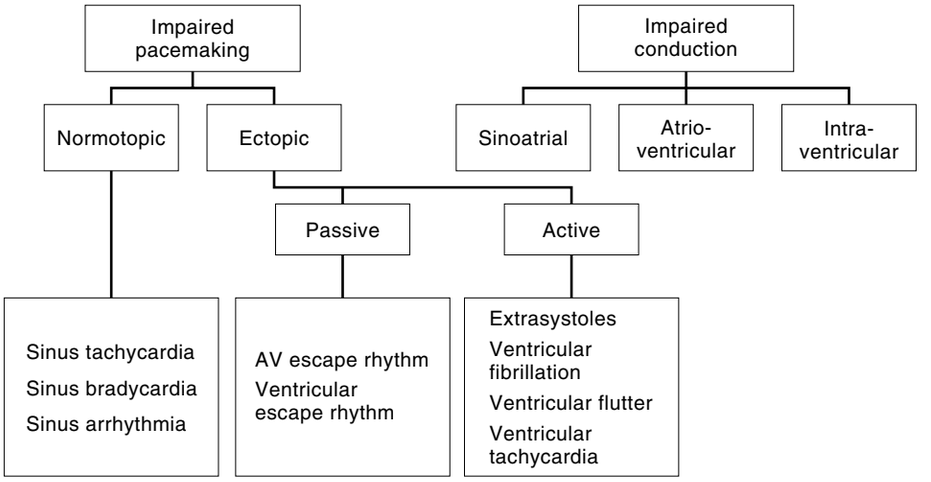

Figure 1. Schematic classification of heart rhythm disturbances, which can result either from pacemaking or conduction disorders. For each of the depicted rhythm disturbance subclasses, specialized forms of electrotherapy have been developed.

myocardial cells is lowered, so the cells become more excitable. This is a positive bathmotropic effect. Parasympathetic influence has an opposite effect by raising the threshold potential for the cells and reducing excitability. This is called a negative bathmotropic effect. However, bathmotropy plays only a minor role in cardiac pumping.

Rhythm Disturbances

The prerequisite for maintaining homeostasis, which applies to keeping all bodily functions constant, is the coordinated interaction of all local autonomic and neural regulation mechanisms of the heart and circulation. Through illness or congenital anomalies, the natural cardiac pacing and conduction mechanisms can be disturbed in different ways or be completely absent (Fig. 1). Without treatment, these disturbances can lead to either death or to a permanent or temporary blood flow insufficiency.

A pacemaking disturbance is present, for example, when excitation still exits the sinus node (normotopic pacemaker), but the sinus rate is too low (bradycardia), too high (tachycardia), or irregular, as with an arrhythmia. Ectopic rhythms also belong in this category. This applies to a condition with sinus node failure or a conduction disturbance (e.g., AV block), where the remaining parts of the conduction system are capable of spontaneously pacing but have lower intrinsic rates the farther away they are from the sinus node. This phenomena is referred to as ectopic pacing, because excitation originates from an abnormal site. Especially dangerous members of this group are the actively occurring rhythms, such as those independent of the sinus node function. These include ventricular flutter and ventricular fibrillation, which ensues at an even higher rate. In the latter case, coordinated filling and emptying of the heart are no longer possible. Ventricular fibrillation is the most common cause of death in electrical accidents and is responsible for some fraction of cardiac infarctions. These states can be interrupted only by electrical defibrillation.

A conduction disturbance can occur between the sinus node and the sections following it (SA Block), in the region of the AV node (AV block), or even within the ventricle. To further subdivide these, a medical differentiation is made between conduction disturbances of the first degree (delayed conduction), the second degree (occasional interruption), and the third degree (total interruption). A first-degree AV block is diagnosed if the AV conduction time, the PQ interval on the ECG, is greater than 210 ms. For second-degree AV block, two types exist. In type I (Wenckebach or Mobitz I block), the PQ interval is extended with each heartbeat, until a ventricular contraction is missing. In type II (Mobitz II block), the PQ interval is constant as a rule, whereby individual atrial activity is either irregularly or regularly not continued on to the ventricle (e.g., in a 2 : 1, 3 : 1, 4 : 1 rhythm). A total block of conduction is called third-degree AV block. Here, a ventricular substitute rhythm is normally formed within a few seconds below the block that has a much lower rate, but it secures patient survival. The situation referred to as an Adams–Stokes attack occurs when there is a temporarily diminished, cerebral circulation resulting from an acutely occurring rhythm disturbance, as a corollary to some of the conditions described previously. Depending on the type and length of the rhythm disturbance, symptoms of failure include intermittent dizziness, loss of consciousness, cramps, and arrested breathing. If no substitute rhythm has formed after a 3 to 4 min arrest, even death can occur. Because of the high level of technology attained in modern pacemakers, an artificial cardiac pacemaker can treat practically every kind of bradycardic rhythm disturbance today. Also, in another category of electronic therapeutic devices, the implantable defibrillators are increasingly able to treat tachycardic rhythm disturbances. Thus, rectifying a slow and a fast heart rate is now achievable with state-of-the-art electronic technology.

THE DEVELOPMENT OF PACEMAKER THERAPY

The roots of contemporary pacemaker therapy can be traced back to the eighteenth century. In 1791, Luigi Galvani documented, for the first time, experiments in which the heart and muscle tissue were electrically stimulated. In the nineteenth century, additional experiments, conducted by Bichat in 1800, electrically stimulated animal hearts or decapitated humans. The syndrome of bradycardia and syncope, which would be

later named after its discoverers, was described by Adams in 1827 and by Stokes in 1846.

Hyman, who coined the term pacemaker, constructed the first transportable, artificial pacemaker in 1932. The device consisted of an electromechanical construction that had to be carried on the patient's back. It contained a mechanical clockwork as its energy source. In 1952, Zoll treated Adams–Stokes attacks with external stimulation through plate electrodes. The treatment could be performed only in emergency situations in the clinic because of numerous difficulties (burns, pain, skeletal muscle stimulation). Furman and Robinson were able to solve these problems later with an endocardiac electrode that still had to be attached to an external pacemaker. Only the availability of semiconductor components made the construction of the first implantable pacemaker possible. Developed by Elmqvist and implanted by Senning in 1958, this "grandfather" of all contemporary, implantable pacemakers possessed an externally rechargeable battery and consisted of a simple impulse generator with two transistors, delivering impulses at a constant rate of 70 bpm. The pulse rate was determined solely by the time constant in the RC network. Detecting intrinsic cardiac activity was not yet possible. The asynchronous ventricular pacing provided by these devices, however, could not rule out the interference between the pacemaker and the intrinsic rhythm.

The next logical step was taken in the 1960s through the introduction of R-wave synchronizing or inhibiting. Introduced by Castellano in 1964, the demand pacemaker had an additional input amplifier and could then detect cardiac intrinsic events with the ECG measured by the electrode. If intrinsic activity was detected, it was possible to inhibit impulses. Delivering pacemaker impulses during the vulnerable phase was avoided, and pacemaker-induced arrhythmias were largely eliminated. This generation was constructed with discrete transistors, thus attaining only limited functionality. Programmable pacemakers were only possible in the early 1970s with the advent of integrated circuits, which had significantly expanded functions. These systems allowed different stimulation parameters to be adjusted postoperatively, greatly improving the individual patient treatment throughout the operation time of the device. At about the same time, it was possible to extend the pacemaker operating lifetime with lithium batteries to such an extent that it lasted as long as the life expectancy of most patients.

Physiological pacemakers were developed in parallel with the continued development of single-chamber pacemakers. Ventricular pacing through the depolarization signal of the atrium was a decisive step in improving electrotherapy. With this, in addition to eradicating bradycardic symptoms, atrial and ventricular contractions could be synchronized. For patients with AV block and intact sinus node function, adapting the cardiac output under physical stress was possible. This was a decisive step in increasing the quality of life. The dual-chamber pacemaker with atrial and ventricular demand pacing and P-wave synchronous ventricular pacing characterized the next breakthrough in re-creating the coordinated course of contractions between the atrium and ventricle.

Rate-adaptive pacemakers are increasingly gaining significance in bradycardic rhythm disturbance therapy, in addition to re-creating the natural course of contraction. With measurement of appropriate physiological values, these adaptive devices allow load-dependent adaptation of the pacing rate in cases of sinoatrial excitation formation disturbances. This enables cardiac output to be adaptable over a greater range. In 1974, Camilli described the first experimental, rate-adaptive pacemaker based on pH-levels in the blood. However, the first rate-adaptive pacemakers were not commercially available until 1983. The most commonly used principle in the past, the motion sensor, is integrated in the pacemaker (e.g., as a piezoelectric crystal) and is known for its simple implementation and easy-to-comprehend functioning principles. The pacing rate determined in this fashion correlates however rather imprecisely with actual metabolic demands. For this reason, researchers are currently focusing their efforts on perfecting pacemaker technology in rate-adaptive systems. These perfected models will determine metabolic needs with higher specificity and ideally re-create the natural feedback control loop for heart rate adaptation.

OPERATING MODES AND PACEMAKER CODES

To clearly mark different operating modes, an international, uniform system of nomenclature was established (2). Table 1 shows this generic pacemaker code. It consists of letters symbolizing: the paced chamber (the first letter), the sensed chamber (the second letter), the type of reaction to the sensed signal (triggering or inhibiting, the third letter), programmable and rate-adaptive functions (the fourth letter), and antitachycardic functions (the fifth letter). The code is an extension of the three-letter code from 1974. Consequently, it is still common to refer only to the first three letters of the basic pacing principle. The earlier described single-chamber pacemaker that paces and senses in the ventricle only, is called VVI. And if it includes rate-adaptive impulse delivery, it is termed VVIR. The dual-chamber pacemaker that senses atri-

Table 1. The NASPE/BPEG Generic (NBG) Pacemaker Code (2)

Position				
I Chamber(s) Paced	II Chamber(s) Sensed	III Response to Sensing	IV Programmability, Rate Modulation	V Antitachyarrhythmia Function(s)
0 = None	0 = None	0 = None	0 = None	0 = None
A = Atrium	A = Atrium	T = Triggered	P = Simple programmable	P = Pacing (antitachyarrhythmia)
V = Ventricle	V = Ventricle	I = Inhibited	M = Multiprogrammable	S = Shock
D = Dual (A + V)	D = Dual (A + V)	D = Dual (T + I)	C = Communicating	D = Dual (P + S)
	S = Single (A or V)	S = Single (A or V)	R = Rate modulation	

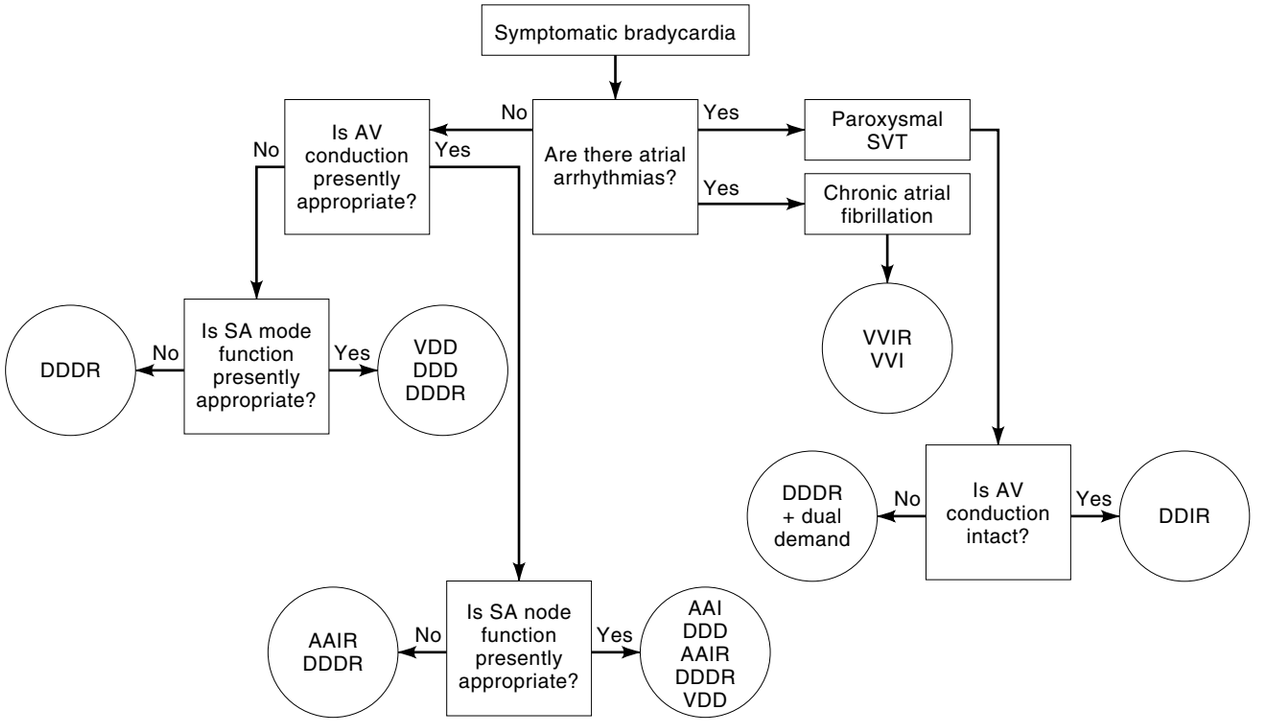

Figure 2. Flow chart of pacing mode selection and its dependence on the rhythm disturbance. Ventricular single-chamber pacing (VVI) should be applied only for chronic atrial fibrillation. Otherwise, DDD(R) or—if AV-conduction is still present—AAI(R) modes are indicated.

ally and uses the natural intrinsic activity to pace the ventricle, functions in the VAT mode. However, it is often necessary to pace and sense in both chambers (DDD, DDDR). A flow chart in Fig. 2 illustrates the selection of the most important pacing modes given the profile of the disease. With the exception of chronic atrial fibrillation, which today still requires implantation of single-chamber systems (VVI, VVIR), rate-adaptive dual-chamber pacemakers are becoming more and more the standard for providing therapy.

ELECTRODES

Equally important progress has been made in electrode technology in parallel with semiconductor technology. Through new electrode technologies and coating methods, decisive progress was achievable for better electrode-tissue interfacing. Improved ingrowth characteristics and a drastic reduction of the pacing threshold, and thus the energy consumption, are examples of these innovations. The pacemaker impulse is conducted through a special electrode (or in the case of a dual-chamber pacemaker, through two separate electrodes) to the atrial and/or ventricular myocardium to trigger depolarization. To this end, principally only the chambers on the right side are considered (right atrium or right ventricle). Introducing the pacemaker electrode(s) is feasible only with a low-pressure system approach. One such case would be a transvenous entry, through the right half of the heart. Excitation of the tissue is done through the electrically conductive tip of the electrode, which is formed or surface-treated for optimal charge transmission (3). The geometric (macroscopic) electrode surface is designed to attain the highest current density possible with limited impulse energy and reduced contact resistance of the fibrotic tissue that builds up immediately after the in-growth process around the electrode. Even though the macroscopic surface is kept relatively small (typically 4 to 20 mm^2), an attempt is made to increase the electrically active (microscopic) surface by depositing a porous structure so that losses through dynamic resistance and electrode polarization are reduced. The different methods that have been applied are sintering, deposition of gridlike structures, sputter coating, and physical vapor deposition (PVD) coating. Under controlled process conditions, it is possible to create surfaces possessing a fractal structure through PVD coating with TiN or IrN. These surfaces are larger than the geometric surface by a factor of more than a 1000 (4).

For passive fixation, either a conical formed "collar" or small tines made of silicone rubber, polyurethane, or another lead-insulating material are located directly behind the electrode tip (Fig. 3). Because of the requirements for flexibility and stability, the lead is principally constructed with a coil design. At the other end of the electrode is a standardized axial pin connector IS-1, which connects and mechanically fixates the electrode to the pacemaker by a screw-in contact. In addition to unipolar designs, bipolar electrodes exist with an additional ring contact at a distance 15 to 30 mm away from the electrode tip, which has a separate point of contact through a separate lead. Unipolar pacing forms the negative pole through the electrode tip (the stimulating or different electrode) and the positive pole through the pacemaker housing (the indifferent electrode). However, bipolar electrodes

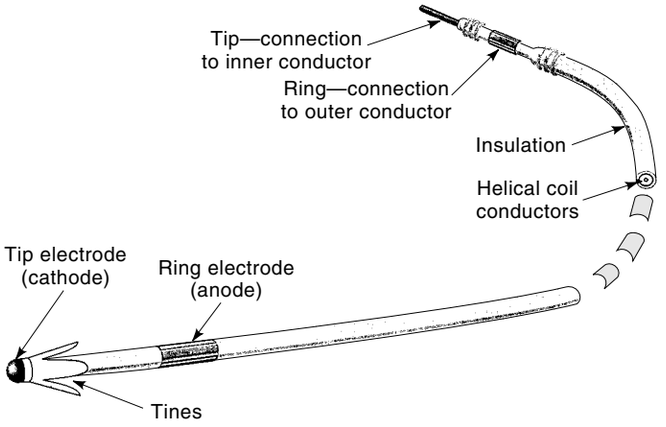

Figure 3. Typical shape of a bipolar pacing electrode. It is connected to the pacemaker by a standardized IS-1 pin connector (upper end); two helical coil conductors (only one for unipolar leads) guarantee sufficient mechanical flexibility. The electrode tip and tines show just one possible shape; several other designs (e.g., screw-in leads for active fixation) are also available.

provide bipolar pacing, in which the ring electrode functions as the indifferent electrode. Both configurations are also used for sensing. A frequently applied configuration is the combination of bipolar sensing and unipolar pacing, which offers the following advantages:

1. Avoids inhibition resulting from muscle potentials,
2. Results in less cross-talk by ventricular activity during atrial sensing,
3. Improves the signal-to-noise ratio of sensing, and
4. Creates clearly visible pacing pulses on the surface ECG.

BATTERY

In estimating the energy consumption of an implantable cardiac pacemaker, the following basic information is to be considered. In most cases, stimulation impulses are 5 to 19 mA with 0.1 to 9.6 V and 0.1 to 2 ms impulse widths at a rate of 30 to 150 bpm. With a typical setting of 10 mA with 5 V and 0.5 ms at 70 bpm, the power consumption is 30 μW (5). The first implanted pacemaker from 1958 was equipped with a rechargeable (secondary) NiCd battery with a 190 mAh capacity with 1.25 V. Charging was done inductively and took an hour per week (6). This battery type was used only five times in implantable pacemakers worldwide because the service lifetime was significantly lower than that of primary (nonrechargeable) batteries. In addition, it was too risky to place the responsibility of recharging the battery in the hands of the patient. Instead, the zinc–mercury battery became the standard energy source in implantable pacemakers from 1958 into the early 1970s (7). Normally, three to six cells were connected in series to achieve an operating voltage of 4 to 8 V. The problem of hydrogen evolution from operating these devices was solved by using epoxy encapsulation of the pacemaker, which was gas permeable. Despite continual improvement until 1970, these cells had only a 2 year lifetime. Although the capacity would theoretically suffice for 5 years, high internal losses (10 to 20%) limited the actual service lifetime (5). Various other solution concepts such as biological, piezoelectric, biogalvanic, and even nuclear batteries were researched as well. With the exception of the nuclear battery, none of these methods went beyond the experimental stage.

Since 1972, different types of lithium batteries have been used and in the meantime have come to be the standard solution. Although improved rechargeable generators have been available since the early 1970s, this has not yet had an impact on present pacemaker application. This is because lithium batteries have enabled pacemaker operation for more than 10 years because of their significantly higher energy density and low internal energy dissipation. An additional advantage to the lithium battery is that of no gas evolution. This allows pacemakers to be encapsulated largely by titanium for a hermetic seal. Electronic circuit reliability has therefore been significantly improved because circuit failures caused by released hydrogen have been eliminated. Of the numerous types developed (5), mainly the LiI battery (Fig. 4) is used for pacemakers, which delivers a voltage of 2.8 V with capacities of 0.8 to 3 Ah. The voltage falls gradually through discharging, resulting in a very flat curve the first year. However, increased discharging results in a much steeper curve. Concurrently, internal resistance increases greatly, from approximately 100 Ω with a new battery to approximately 40 kΩ at the end of the service lifetime. This point in time is usually expressed in two stages. If the voltage has attained a value between 2.0 and 2.2 V [internal resistance then being 20 to 30 kΩ (8)], the beginning of the elective replacement interval (ERI) is indicated. ERI is defined as the interval between this stage of battery depletion and the end-of-service (EOS) stage, where the voltage has further dropped down to 1.8 V and the internal resistance has increased to 40 kΩ. This additionally discharged state, where the device no longer functions regularly, is reached about six months after start of ERI, depending on the device and pacing mode. The pacemaker should be replaced during ERI and must be immediately replaced when the EOS criteria are met.

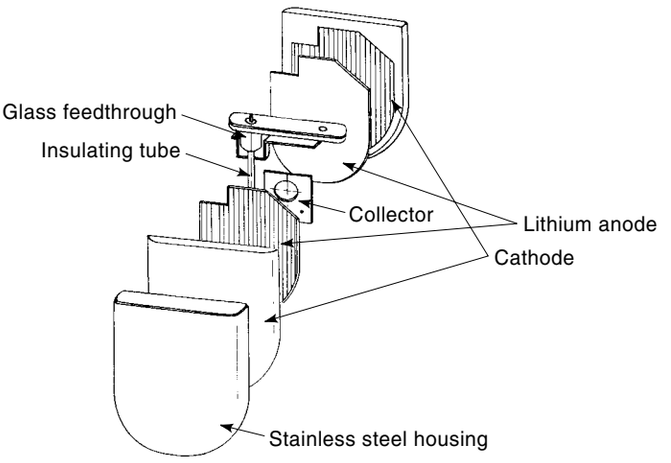

Figure 4. Internal construction of a central lithium anode/case-grounded pacemaker battery. The precoated lithium anode, which is surrounded by the cathode material, is connected to the negative pin by a central collector and a glass feedthrough. The housing itself serves as the cathode current collector.

Depending on the pacemaker model, ERI is shown by a defined decrease in the pacing frequency, (e.g., by 11% as opposed to the programmed rate with the device PHYSIOS TC, Biotronik, Inc). Alternatively, ERI may be indicated by a variation in the magnet placement frequency, the rate at which the pacemaker paces for a certain number of cycles, (e.g., 10), when a magnet that is usually in the programming head is placed over the pacemaker. Aside from this, all important electrical parameters, including battery voltage and the battery internal resistance, can be interrogated in modern pacemakers through telemetry. The respective voltage threshold values are not uniform, and they are determined by each manufacturer.

BASIC FUNCTIONS OF THE DUAL-CHAMBER PACEMAKER

The multiprogrammability of the function and pacing parameters enables an optimized, individual form of electrotherapy through postoperative, noninvasive pacemaker programming for each indication. This function is designated by the M in the pacemaker nomenclature code. Besides the basic rate and pacing mode, other programmable parameters are the stimulation energy (i.e., the impulse amplitude and duration), sensing sensitivity, refractory period, and hysteresis setting. In addition, diagnostic and electrophysiologic examinations can be conducted postoperatively with these implants. The same applies for temporary antitachycardia pacing, which is performed noninvasively with an external programming device using a chosen algorithm.

With the programmability of the stimulus impulse parameter, energy can be effectively conserved with the possibility of extending the operating lifetime. Thus ineffective pacing, resulting for example from changing pacing thresholds, can be controlled. The pacing threshold is the minimum pacing energy needed to trigger the myocardial depolarization. It is measured after pacemaker implantation and during follow-up examinations by both the pacemaker and the programmer. Pacing energy is adjusted via two parameters—impulse amplitude and duration. The adjustment is done to a value above the pacing threshold by a defined safety margin. By adapting sensitivity and choosing between unipolar and bipolar electrode configurations, extensive protection is afforded against external and intrinsic disturbing signals. Rate and refractory period programming optimizes the significant cardiologic parameters of the artificial pacing system according to therapy requirements. It also suppresses depolarization phenomena, crosstalk, and extrasystolic arrhythmias.

Above all, rate programming allows intrinsic heartbeats to ensue in patients who need only occasional pacing. The hysteresis setting avoids pacemaker-mediated syncope resulting from intermittent conduction at nearly identical rates of intrinsic and artificial pacing (9). The pacemaker engages only when the natural sinus rhythm falls below a certain beat rate, but then stimulates at a higher (adjustable) rate. Hysteresis programming also provides the advantages of compensating for missing atrial contribution by pacing at a higher rate (with single-chamber pacing) and limiting pacemaker activity to only when it is absolutely necessary. With an intact sinus node and the presence of conduction disturbances, P-wave-controlled ventricular pacing (VAT) can function like an electronic bridge for the AV interruption. However, abnormal excitation, such as premature supraventricular or retrogradely conducted ventricular extrasystoles, and ectopic ventricular rhythms, limits the wide application of atrial control.

Only through additional control functions for the ventricle can pacemaker-mediated parasystoles be suppressed. The dual-chamber pacemaker with an atrial and ventricular control circuit for pacing (DDD) solely guarantees physiological atrial and ventricular pacing. This is accomplished by recognizing atrial, as well as ventricular, arrhythmias under nearly all conditions of pacemaking and conduction disturbances (10). The case of sick sinus syndrome is an exception, in that no physiologic rate-adaptation is possible under conditions of stress, unless a rate-adaptive pacemaker is implemented.

The technical challenge for re-creating the natural course of excitation is that of synchronizing the ventricles with the atria. The AV delay and the atrial and ventricular refractory periods regulate the course of pacing. Adapting AV delays automatically to the heart rate optimizes the atrial hemodynamic contribution for filling the ventricle, which contributes up to 30% to the cardiac output. By reducing the artificial conduction time with sensed P waves, the latency period between the atrial stimulus and atrial excitation is additionally compensated. Arrhythmias can be eliminated by selecting appropriate control intervals. These rhythmic disturbances may result from ventricular extrasystoles or the abnormal spread of excitation. For the majority of clinically significant rhythm disturbances, this option allows for an automatic adaptation of pacing to the therapy requirements (11). In the event of extreme arrhythmias, programmability offers specific control programs that interrupt supraventricular and ventricular reentry tachycardia by prematurely exciting the myocardium.

TECHNICAL SOLUTION

The block diagram of a multiprogrammable dual-chamber pacemaker in Fig. 5 affords an overview of the basic components. Atrial and ventricular channels each possess separate input and output amplifiers connected to the myocardium through the atrial or the ventricular electrode. The program memory digitally controls the adjustment of the impulse energy through the amplitude and the impulse duration of the stimulus and the sensitivity of the input amplifier. The central, quartz-controlled clock and the counter keep the timing of all control processes, such as pacing rate, refractory period, hysteresis, and program transmission. Programming is performed inductively through a program amplifier with a decoder, a control circuit, and a register that stores the temporary and permanent programs.

Figure 6 shows the construction of an implant, in which the two significant components are the lithium battery, occupying the right two-thirds of the housing, and the hybrid circuit. The pacemaker housing consists of a dual-sectioned titanium capsule, which is reliably sealed by laser welding and has a long-term resistance to corrosion. The electrode connection block consists of a cast epoxy resin head with hermetically sealed feedthrough. The hybrid substrate contains all electronic components, including a coil that enables bidirectional inductive telemetry for postoperative programming through a programmer. Some applications for this programmer are an inductive transmission of pacing and function pa-

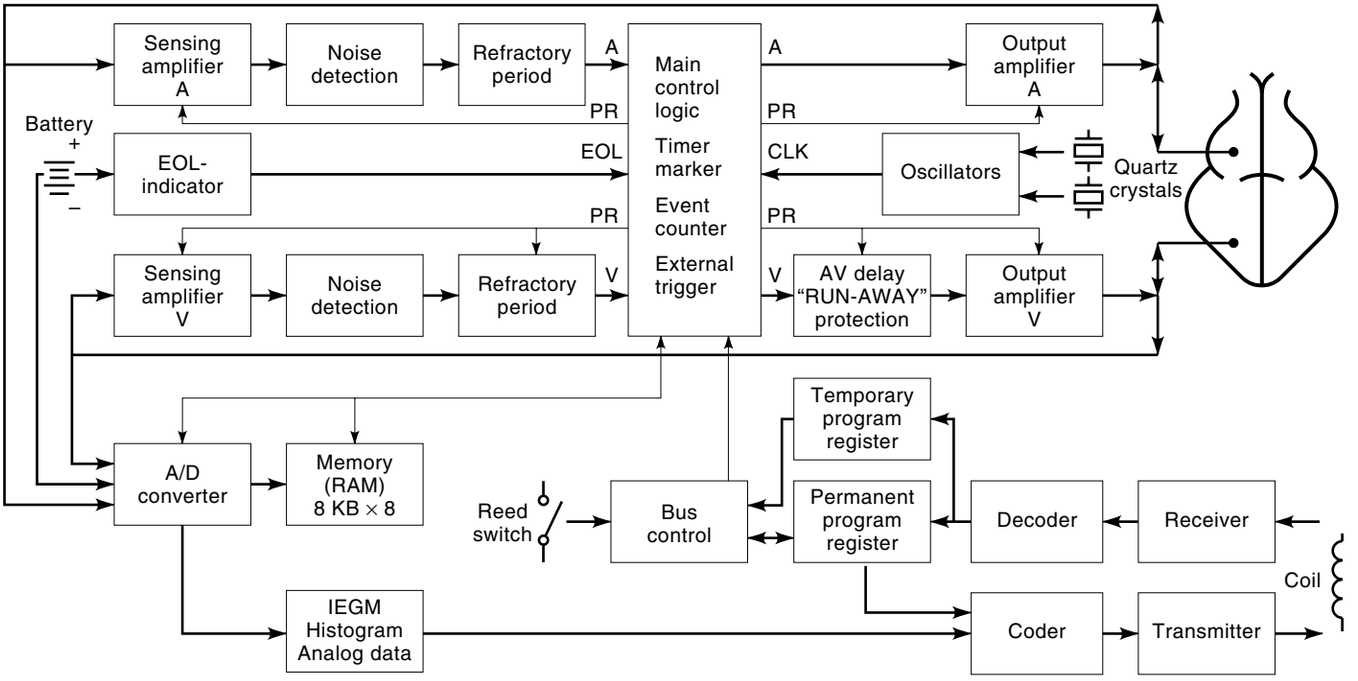

Figure 5. Block diagram of the circuitry of a multiprogrammable dual-chamber pacemaker. It shows the following major components: input and output stages for the atrial and ventricular channels, main control logic, memory for internal data storage, and the communication unit for bidirectional data transmission, which is activated by closing the reed switch with the magnet in the programming head.

rameters or intracardiac signals and such operating parameters as battery current, voltage, and internal resistance; electrode impedance; and patient information (12). The value of programmability not only lies in the possibility of postoperative corrections, but allows also an effective reduction of the variety of pacemaker types, lowering the overall costs involved.

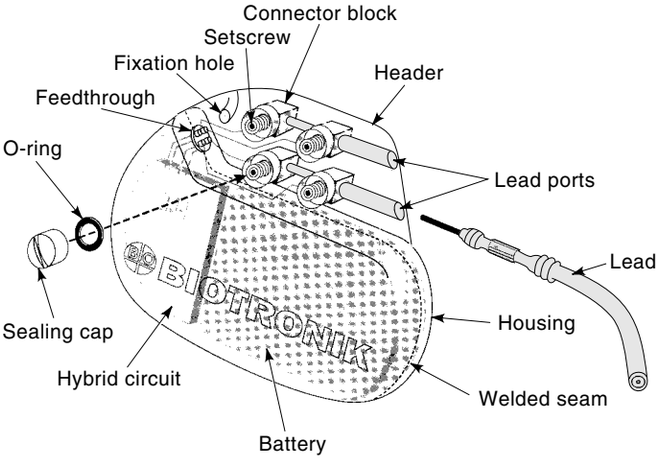

Figure 6. Major components of an assembled dual-chamber pacemaker. The hermetically sealed titanium housing contains the hybrid (left), which holds the IC and all other electronic components, and the battery (right), which occupies about two-thirds of the housing. Leads are connected to the device via the cast epoxy resin head.

Technical Realization of Circuits

Because the implant often has a life-supporting function, high demands are placed on the electronics in the pacemaker. Some of these expectations are extreme reliability and operating safety, the smallest possible and lightest construction, operation at low supply voltages of 2 V, and constancy of all function parameters, even with falling battery voltage as a result of discharging. These requirements are met by a host of special technical solutions for circuits and highly developed production processes.

Integrated Circuit. The biological demands for miniaturization and minimal energy consumption are best met through the monolithic integration of as many components as possible onto one chip. All analog and digital function blocks necessary for standard pacemaking are integrated onto one chip using low-voltage CMOS (complementary metallic oxide semiconductor) technology. The central control unit, the functional units for pacing and sensing, telemetry, charge pump, program amplifier, oscillator, and reference voltage sources are included in this group. The control signal is amplified with a two-level bandpass with several ranges of sensitivity. The pacing amplitude is created with the help of a charge pump in combination with a programmable voltage multiplier and is adjustable from 0.1 to 9.6 V. The programmability of closely stepped settings and the large range for adjusting pacing amplitude and sensitivity with separate programmability for the atrial and ventricular channel place great demands on the semiconductor technology of the pacemaker circuit. A 2 μm silicon gate technology was used. Approximately 100,000

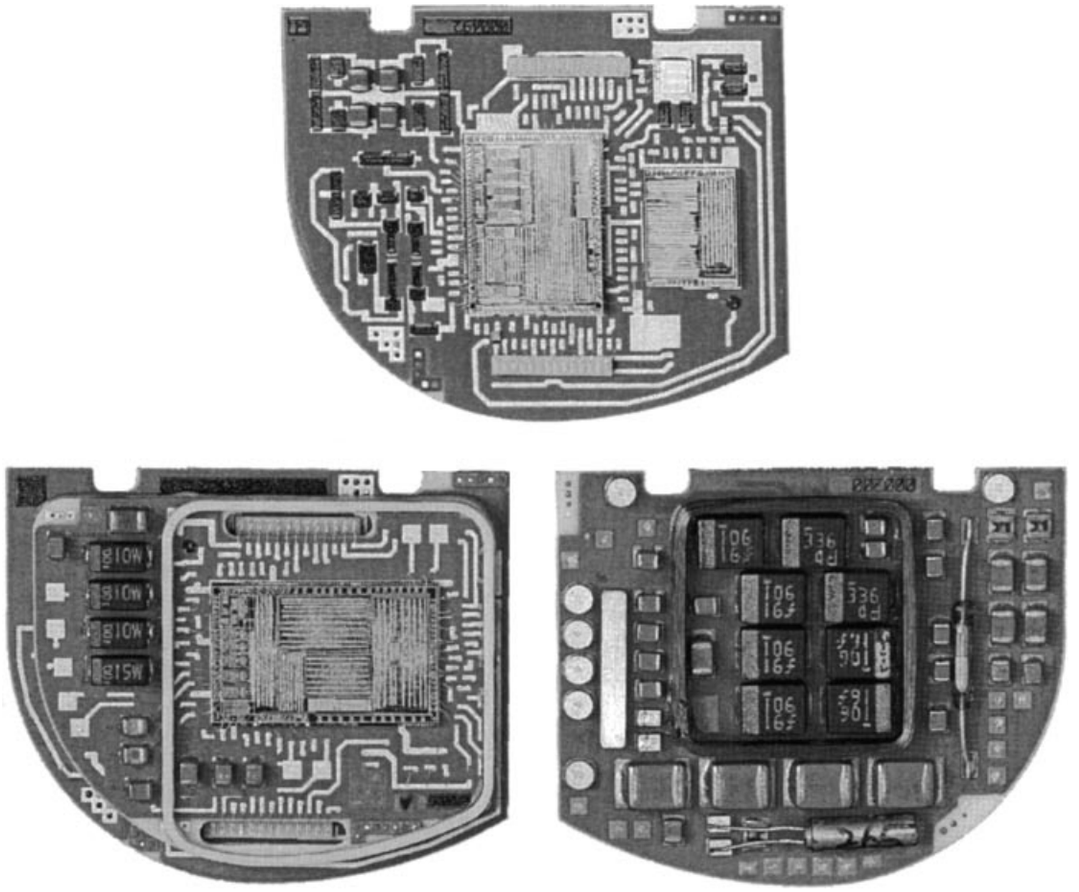

Figure 7. Hybrid circuit of a rate-adaptive dual-chamber pacemaker (INOS, Biotronik, Inc.). The back side (right) holds several discrete components such as quartz crystal, reed switch, telemetry coil, capacitors, and resistors. The front side (center) contains two VLSI chips (pacemaker and monitoring chips) and carries a daughter board (left) with a third VLSI chip for the rate-adaptation functions.

transistors were integrated on a surface with an area of 70 mm^2. The operating voltage ranges from 1.8 to 3.0 V. Current developments use technologies allowing structures between 0.3 and 0.8 μm.

Hybrid Design. As in many other fields of hardware and software development, modularity as a construction principle plays a key role in pacemaker technology. The previously noted complex functions of modern pacemaker systems are realized by individual technical modules composed of circuits. From here, a whole family of devices with different functions emerges easily. These devices are each tailored to the individual therapeutic needs and provide optimal and cost-effective therapy. The complexity of such circuits exceeds the present technical possibilities of a monolithic solution. Thus, integrated and passive components are joined by a hybrid circuit. Figure 7 shows the modular circuit construction of a completely assembled rate-adaptive dual-chamber pacemaker circuit using hybrid technology. The pacemaker circuit contains three VLSI components. The pacemaker chip is made up of the control logic, analog input and output amplifiers and telemetry; the monitoring chip is composed of the event counter and the trend monitor (Fig. 7, center). The third VLSI-chip mounted on a daughter board includes a microprocessor for rate adaptation functions (Fig. 7, left). Passive components including the telemetry coil, reed switch, and quartz crystal can be seen in Fig. 7, right. The versatile pacemaker chip can be applied with a dual-chamber system, as shown in the hybrid circuit, as well as in a single-chamber pacemaker. Likewise, the monitoring chip can be integrated into other systems. The chips are produced as application-specific integrated circuits (ASIC) using low-voltage CMOS technology. The no-load current is approximately 7 μA for the entire dual-chamber pacemaker circuit. With atrial and ventricular pacing at a rate of 60 bpm, approximately 30 μA are taken up from the lithium battery (2.0 Ah); that corresponds to an operation time of 8 years.

As a form of interconnection technology, hybrid technology plays a key role in producing electronics for implants. Its task is to create the connection between the different integrated components and the passive components. To meet the growing demands for reliability and packing density, production technology for manufacturing modern multilayer hybrid circuits has consistently been developed further. Laminate technology with dielectric foils allows the necessary production steps to be reduced. This is in contrast to thick film

multilayer technology, in which conductor track levels, including the insulating dielectric layers, are produced by repeated printing and sintering. With fewer production steps and by substituting screen printed for laminate dielectrics, a higher level of reliability is reached. Additional advantages are the possibilities to integrate passive components into the layered structure and fabricate a three-dimensional substrate by creating depressions. Both aspects lead to an increased packing density and therefore additional miniaturization.

Reliability and Quality Assurance. Reliability in the discussed monolithic circuit and its hybrid construction has been proven clinically in more than 600,000 implants, in which reliability can be attained with $\lambda = 10^{-7}$/h at a 90% confidence level for the hybrid circuit and $\lambda = 10^{-9}$/h for ICs and passive components. In pacemaker technology, this high reliability is not attained by the normal methods of redundancy of critical circuits and components. This is because operation time requirements can be fulfilled only via the current consumption aspect, because of the volume-limited battery capacity.

Instead, it is necessary to research specifically failure mechanisms and error sources and to eliminate them in the development phase as a preventative measure. Above all, it is important to provide consistent application of control measures during the different phases of production (13). This experience has led, for example, to special design rules during dimensioning of the current mirror circuits. This is because the design rules strongly influence the characteristics of the ECG, as well as measuring amplifiers, VCOs, and reference voltage sources. Especially critical production tolerance is also identified in this manner. A parameter drift from an ionic impurity in the semiconductor can be largely avoided by the exact control of the process parameters during chip production (14).

Quality assurance measures for pacemaker production include a 100% final control of all components, semifinished products, and the finished product. In general, the military standards (MIL-STD-883 and MIL-M-38510) are used for implantable devices. In some cases, the specifications even exceed these standards. The requirements of the standards (MIL-Q-9858 and MIL-STD-1772) must be met for the production of implantable semiconductors and hybrid circuits. All aspects of quality control and assurance are included in these measures. Standards set by the International Organization for Standardization (ISO), the ISO 9000 standards, are gaining importance worldwide. Quality assurance measures for the production process and measures for qualification and type testing are contained in the ISO 9002 guidelines. The ISO 9001 guidelines cover the realm of development, thereby having an effect on the design process. In addition to strict quality control during hybrid construction, it must be guaranteed that these high standards are being met in testing the materials applied.

Input Amplifier. The input or sense amplifier must detect the electrical intrinsic cardiac activity. That is, to amplify and filter the IEGM as recorded by the electrode and to sense the intrinsic activity (P waves in the atrium or R waves in the ventricular signal). The central control unit (see Fig. 5) turns off the amplifier during the pacing impulse (blanking). Protecting the amplifier and other components (e.g., the output amplifier) during use of an external defibrillator is accomplished by discretely designed input protection diodes. The amplifier circuit triggers a comparator, which senses via a threshold value comparison. The actual electrogram contains frequency components up to approximately 100 Hz. Higher frequencies originate from interference sources (e.g., from the muscle activity). To increase the selectivity, the input amplifier of the discussed dual-chamber pacemaker has a bandpass consisting of a fourth-order high-pass (80 dB per decade) and a second-order low-pass (40 dB per decade), and a center frequency of 70 Hz on the atrial and 40 Hz on the ventricular channel. The input amplifier is constructed similarly to the other analog circuits in SC (switched capacitor) technology (5,15). This offers a number of advantages with regard to the applicable semiconductor technology (e.g., CMOS) and improves the tolerances, especially for implants.

Control Logic. The digital control logic is housed on the pacemaker chip with the analog components. It must coordinate all activities of the pacemaker (sensing and pacing in one or two chambers) according to a predefined timing scheme, so that the synchronization of the ventricles with the atria is reestablished. The control logic is therefore realized as binary automaton, meaning it can assume different states depending on timing intervals and sensed signals. The course of control is influenced by various timing intervals. Minimum and maximum pacing rates are set by the lower rate interval (LRI) and the upper rate interval (URI). The lower rate interval (also the basic interval or the automatic interval) is the maximum time between two intrinsic impulses of the respective chamber during which no stimulus is triggered. The upper rate interval is the shortest interval between a sensed or paced event and a (new) stimulus. The AV delay in modern pacemakers varies according to two criteria. First, the AV interval is shorter after a sensed event than after a paced event to compensate for the delay between the atrial stimulus and the actual atrial depolarization (latency interval compensation). Second, the AV delay is shortened rate-dependently to mimic natural dromotropy, guaranteeing an optimal synchronization during higher heart rates (dynamic AV delay). The refractory periods for the atrial and ventricular channels (ARP and VRP, atrial/ventricular refractory period) are programmable in their length and ignore sensed signals during these periods. This prevents the QRS complex or the T wave of the previous stimulus as well as afterpotentials appearing after every stimulus from being misinterpreted as sensed events and falsely inhibiting the following stimulus. Through refractory period programming, certain physiological events are blanked out, preventing these signals from being interpreted as intrinsic events. A relatively short blanking period prevents false detection of hardware activities (i.e., by the stimulus in the other chamber) (16).

Output Amplifier. The tissue is stimulated with an impulse whose amplitude and pulse width are adjustable typically from 0.1 V to 9.6 V and from 0.1 ms to 2 ms, respectively. Both parameters are programmable for energy efficiency. The stimulus must be sufficiently high to depolarize the tissue. That is, to increase the membrane potential from its resting value of −85 mV beyond the threshold potential to approximately −65 mV. This triggers an action potential, which spreads throughout the entire myocardium. The necessary impulse energy varies on a case-by-case basis, depending on

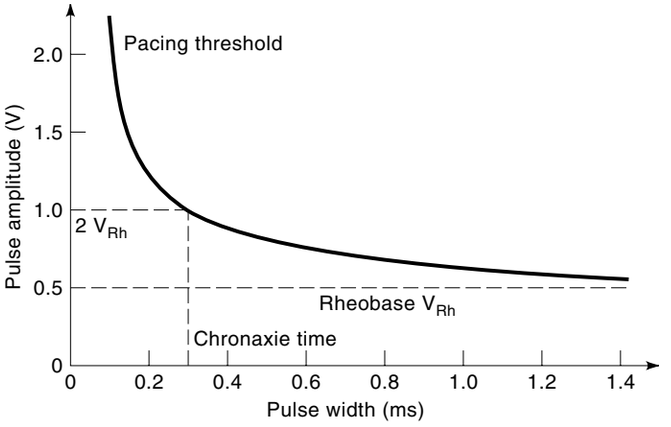

Figure 8. Chronaxie-rheobase curve showing the relationship between the pulse width and amplitude values necessary for tissue stimulation. Only typical values are shown; in practice, individual values have to be measured for each patient to determine adequate pacing parameters.

the exact position of the electrode, the thickness of the fibrotic tissue, the pacing threshold, and so on. By varying the impulse width and amplitude parameters, a chronaxie–rheobase relationship results. The graphical representation of this function (Fig. 8) connects pairs of values from both parameters that were determined experimentally for a certain pacing threshold. When the pulse width is increased up to infinity, the graph converges asymptotically toward the rheobase value. Chronaxie is the impulse duration corresponding to double the rheobase voltage. It can easily be observed that an impulse duration equaling the chronaxie at an amplitude of twice the rheobase is best from an energetic viewpoint. In practice, there is a 100% factor of safety (doubled pacing energy). One of the two parameters is doubled, preferably the impulse duration, because it can be adjusted by the circuit more simply. Consequently, an impulse amplitude equaling double the rheobase value and an impulse duration equaling double the chronaxie are normally chosen. The impulse delivery is realized by an output stage (pace amplifier), in which the capacitor that delivers the charge to the tissue (capacitive coupling) is charged between two stimuli. This allows charge neutrality to be reestablished by the subsequent repolarization process and minimizes irreversible chemical reactions. During an impulse, a charge of 0.1 to 20 μC is delivered. To increase the integration density, often one pace amplifier is used for both channels. Switching between atrial and ventricular electrodes is done by a multiplexer (5). Because the impulse amplitudes can be programmed up to a multiple of the battery voltage, the devices possess a voltage multiplier or charge pumps. These functions are also integrated onto the pacemaker chip.

TELEMETRY

Analog telemetry allows the bidirectional data transfer between the pacemaker and an external programmer. This enables a later correction of the pacing parameters during follow-ups, as well as an interrogation of the data stored in the internal memory of the pacemaker (e.g., patient-related data), the battery and electrode parameters, and a multitude of diagnostic data. This includes the number and histogram distribution of the paced and sensed events in each chamber that were recorded during the previous follow-up interval. These data provide the physician with valuable diagnostic information about the pacemaker function and changes in the patient's symptomatology. The stored data can be roughly divided into four categories—patient data, battery and electrode parameters, pacing parameters, and diagnostic information.

Patient Data

The patient data memory stores the most important information about the patient and the pacemaker. The date of implantation, the date of the last follow-up, information concerning the symptoms, etiology, and ECG indication, in the form of code letters according to an international code list, are some of these particulars. Others include the implanted electrode configuration, the initials of the patient, and the serial number of the pacemaker. Thus, the most crucial information can be retrieved in the case of an emergency, an unexpected change of the physician, or the loss of the pacemaker identification card.

Battery and Electrode Parameters

Precise, prevailing values of the battery voltage, the internal resistance of the battery, and the power consumption allow a correct estimate of the operation time to be expected. Data about the (real) lead impedance, which normally has a value around 500 Ω, indicate possible malfunctions such as breaks in the lead or insulation defects. Furthermore, the pulse amplitude, current, energy, and charge are displayed separately for the atrial and the ventricular channel.

Pacing Parameters

All rhythmological parameters, such as pacing mode (e.g., DDD), rates, AV delays, refractory periods, and hysteresis setting, are considered pacing parameters. During diagnostic examinations, temporary programs with other parameter settings need to be activated on a short-term basis. To simplify this process, some pacemakers possess two complete program memories. This makes it possible to switch quickly between two programs (e.g., within one cardiac cycle).

Diagnostic Information

This category includes the internal event counter with trend monitor. The event counter normally registers events that occur over very long periods, such as atrial sensing and pacing, ventricular sensing and pacing, or also ventricular extrasystoles (ventricular sensing outside the AV delay). The trend monitor graphically depicts the heart rate (paced or sensed) over time, where the temporal resolution can be selected within a wide range (several minutes to several days or even months). Frequently, it can be differentiated between a "rolling" or a "fixed" mode. Thus, either the oldest values are constantly overwritten by new values, or the trend recording stops after one complete run. The stored rates are not momentary values, but they equal the average value of the respective scanning interval.

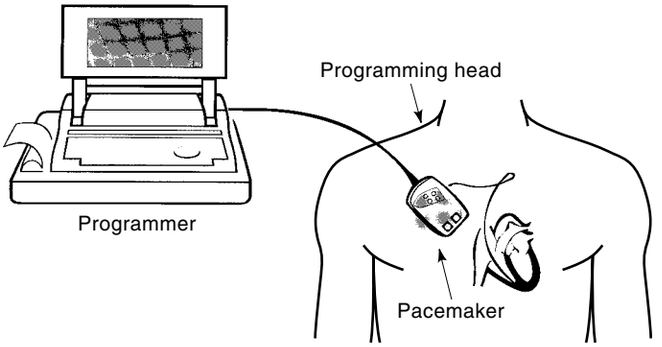

Figure 9. Bidirectional data transfer between pacemaker and programmer via the programming head by means of inductive telemetry, which is used to interrogate programmed parameters and stored Holter data from the pacemaker at the beginning of each follow-up and to reprogram it when necessary.

Aside from event counter and trend monitor, another application of analog telemetry exists for diagnostic purposes. The PHYSIOS TC (Biotronik, Inc.), for example, offers the option to transmit the filtered or unfiltered atrial and ventricular IEGM with markers to the programmer in real time. The sampling rate is 256 Hz for dual-channel and 512 Hz for single-channel operation. The transmitted IEGM and marker signals can be read on the monitor or by the programmer printer. They can also be read on a connected ECG recorder, which allows for the simultaneous display of these signals with the surface ECG. In this manner, the especially noise-free IEGM secures the diagnosis for atrial arrhythmias, simplifies the analysis of complicated ECGs, and recognizes muscle potentials.

Technical Realization

To interrogate and program the pacemaker, the programming head, which is connected to the programmer, is positioned over the pacemaker (Fig. 9). The magnet within the programming head closes a reed switch in the pacemaker, activating the transmission and the receiving mode. The components specific for telemetry are illustrated in the lower part of the block diagram in Fig. 5. The data are transmitted inductively between the coil within the programming head and the telemetry coil of the pacemaker, in most cases mounted on the hybrid circuit (Fig. 7, right). During data transmission, a temporary program paces with a constant rate (usually asynchronous) to avoid malfunctions resulting from incomplete data transmission. Because the relative positions of both coils are important for inductive coupling, modern systems facilitate exact positioning by indicating the optimum position using LEDs in the programming head.

Manufacturers do not use a unified coding procedure. The pulse-position coding is frequently used (17). Here, the information is transmitted by a sequence of pulses. One way is that the value of a parameter to be transmitted is coded either in digital or analog form by the distance of pulse flanks or of pulses of constant lengths. With digital coding, two different pulse distances are used (e.g., to code the binary values "0" and "1," which are transmitted in sequence, following a defined start coding). Some manufacturers send a certain access code in each data package, in addition to the parameter value. This access code is checked for exact agreement to exclude an erroneous programming by the wrong programmer, faulty transmission, or other interference signals (18). Also, a parity bit follows at the end of each data package, which is another of several safety measures during data transmission alone. The pulse sequence is subsequently amplitude-modulated to a carrier frequency, which corresponds to the resonance frequency of the telemetry coils. This frequency is not standardized, and it thus depends on the manufacturer. It is usually within a range of 10^4 and 10^5 Hz.

RATE-ADAPTIVE PACEMAKERS

The heart rate is the most important correcting variable used by the organism for increasing the cardiac output. This occurs under physical stress or various other influences resulting in an increased metabolic demand. As discussed earlier in this article, the large range of variation for the cardiac output illustrates how important an adequate heart rate adjustment is for maintaining a sufficient organ perfusion. The sinus-controlled and thus physiological heart rate adaptation (e.g., in the VAT mode with AV block) is maintained only for pacemaker patients showing neither a compromised sinus node function nor SA block nor atrial flutter or fibrillation. In these cases, a fixed-rate dual-chamber pacemaker is usually sufficient. But if adequate sinus rate is not present, as is the case with sick sinus syndrome, or if the rate increases only insufficiently under load conditions, as with chronotropic incompetence, then it is necessary to implant a rate-adaptive pacemaker. Even if there is not yet any chronotropic incompetence at the time of implantation, the physician should determine whether an affected sinus node is to be expected as a result of a progressing disease within the operation time of the implant.

The challenge for biomedical engineering consists of determining the metabolic demand with suitable sensors possessing high sensitivity and specificity. Consequently, the pacing rate can be adjusted to a sufficient degree and within physiologic response times. Figure 10 shows the principle behind rate-adaptive pacemakers using either corporeal or cardiac input. A number of sensors have been studied to date that are based on completely different physical measuring principles. These various sensors observe many different physiologic indicators. However, only some of them have attained any clinical significance.

Open- and Closed-Loop Systems

The sensor principles that have so far been studied can be classified according to several criteria as follows:

1. The control strategy in open- or closed-loop systems (19,20)
2. The origin of the signal in corporeal or cardiac control parameters (5)
3. The physiological relationship between the sensor signal and the activity of the autonomic nervous system in primary, secondary, or tertiary sensors (21)
4. The physical measuring principle (e.g., temperature, impedance, or potential measurement)

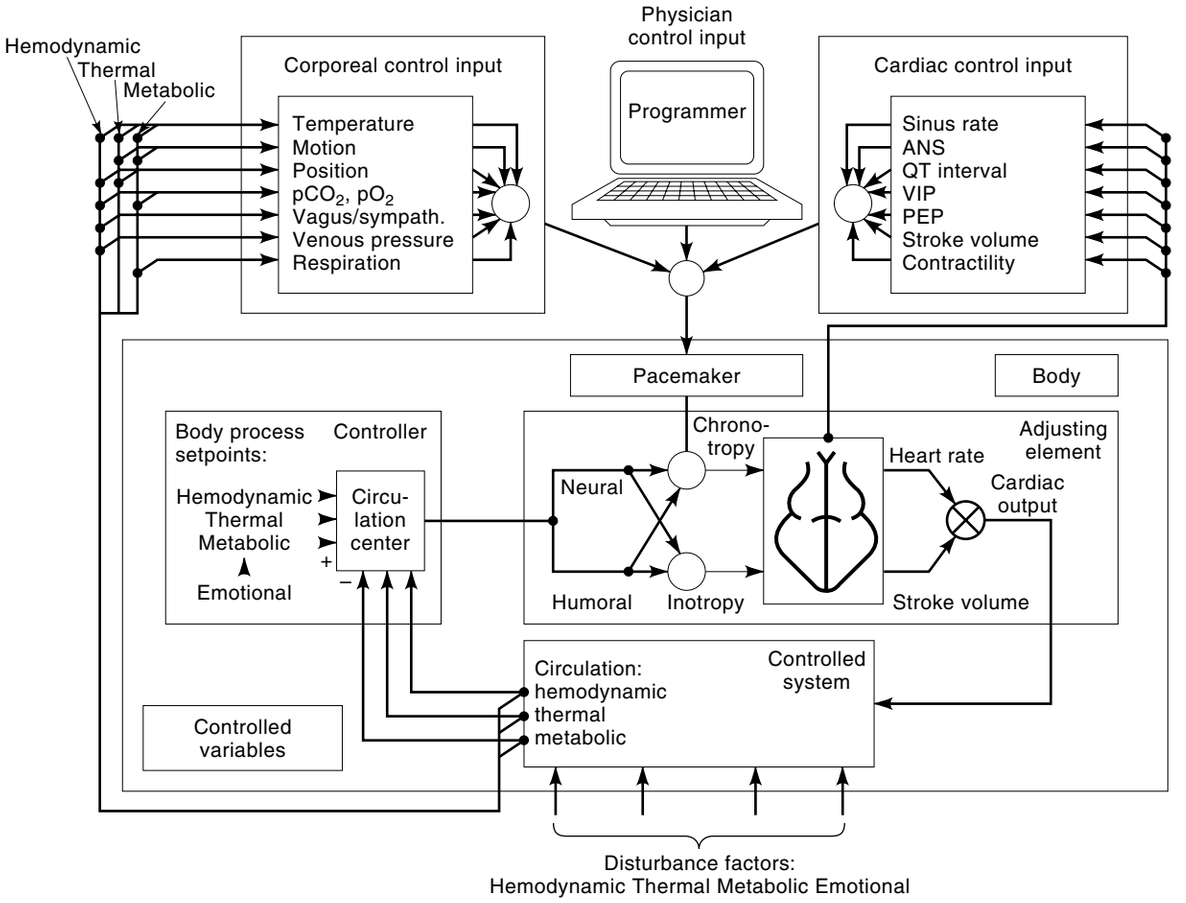

Figure 10. Principle of rate-adaptive cardiac pacing using corporeal or cardiac control parameters. The lower part of the picture shows the major components of the cardiovascular control system, while the upper part summarizes different strategies to reestablish chronotropic adaptation by the pacemaker.

Ultimately, the pivotal factor is the clinical quality of the sensor signal, specifically, up to which degree the physiological circulation regulation is restored for patient well-being. Based on this sole consideration, the superiority of the closed-loop systems over the open-loop systems is evident. The latter are characterized by the fact that only one variable disturbing the circulation is measured. One example is the physical activity detected by the mechanical motion sensor to determine the pacing rate from the sensor signal. With this approach, body movement is the input signal for rate control in obtaining a physiologic rate response.

The principal shortcoming of all open-loop systems is that no feedback and thus no successful physiological-based control exists, notwithstanding the accuracy of the executed rate response. Additionally, only the influence of one disturbance variable can be measured. Other disturbing influences remain unconsidered. In contrast, the pacing rate always reacts back upon the sensor signal in closed-loop systems, thus forming a closed control loop. These systems can be further divided into those with a purely metabolic feedback (e.g., the partial oxygen pressure sensor) and those with a feedback mediated by the autonomic nerves. The latter group is composed of systems that deliver a signal via cardiac measuring parameters. The signal depends on the myocardial contractility and thus on the nervous tone. With this signal, the natural control loop for heart rate adaptation can be closed again. Because the system-correcting variables that control the heart rate in a healthy organism are accessed, this group currently constitutes an ideal method for physiological rate adaptation. Such nervous system-controlled adaptation has an optimal amplitude and response characteristic that represents adequate reaction to influences from higher centers, (e.g., emotional stress). The following section outlines all relevant sensor systems for artificial rate adaptation that are currently undergoing a moderately large-scale testing or are being commercially distributed.

Corporeal Parameters

Activity. Rate-adaptive pacemakers equipped with an electromechanical motion or activity sensor within the pacemaker housing have experienced the widest distribution so far. Such a configuration determines corporeal activity or kinetic energy. To date, various constructions such as piezo-vibrators, capacitive sensors, or a movable sphere inside a coil have been used for the detection of mechanical motion. Because the

movements of the large muscles comprise the main part of the physical load, their kinetic energy is a suitable rate adaptation parameter (22–24). Another advantage is the easy clinical handling of such sensors. Because the sensor is located in the pacemaker housing, no additional probes or special electrodes are necessary. This system can be operated with standard electrodes (that are perhaps already implanted). Also, this sensor has short response times. Despite continuous improvements, the principal disadvantage of this concept does remain. Namely, only an external signal is used instead of an intrinsic, corporeal, circulation-related parameter. The external signal correlates with the actual, hemodynamic demand only in an indirect way, and it can be influenced by mechanical tremors, vibrations, and so on. Alternatively, some load conditions cannot be recognized at all (e.g., work involved in holding objects, standing, or psychological stress).

Blood Temperature. Another suitable parameter for rate adaptation that has also been used in commercially available pacemakers is the central venous blood temperature (25–27). The use of this parameter can be traced back to studies by Weisswange et al. (28). With physical motion, the central venous blood temperature (CVT) increases depending on the load because of the low efficiency of the musculature and the connected heat production. The CVT rises from 37° to 38.5°C with maximum physical activity. The temperature is measured with a high-resolution (0.025°C) thermistor integrated into the pacing electrode. The most important advantage of the temperature-controlled pacemakers is that the rate adaptation is based on a metabolically influenced parameter. This parameter also reacts to metabolic changes that are not exercise-related, such as fever, circadian deviations (a slight temperature decrease during nighttime), orthostasis, or even psychological stress. However, this is countered by disadvantages in response time and practicality. The temperature increase starts only with a certain delay after stress begins, and it occurs considerably more slowly than a physiological rise of the heart rate. The main disadvantage for clinical practice consists of the necessity of a special thermistor-electrode with a tripolar connection. On the other hand, this method approximates the actual metabolic demand much more closely than the motion sensors in spite of the fact that no central physiological control variable is measured, which means that a closed control loop does not exist.

Mixed Venous Oxygen Saturation (SO_2) and pH. Other metabolic parameters with special sensors are the mixed-venous oxygen saturation (termed SO_2) and the pH-value of the blood, the latter being tested only under nonclinical conditions. The mixed-venous oxygen saturation is measured by reflectance oximetry, where an integrated optoelectronic, glass-sealed sensor element is attached to the electrode at the height of the right atrium (29,30). The pH measurement is accomplished with an iridium/iridium oxide ring electrode. A silver/silver chloride electrode at the pacemaker housing serves as a reference (31). These two types of measurements have three disadvantages in common: a specific electrode is required; the response times are too slow for a short-term control, as is required by a rate-adaptive pacemaker; and the long-term stability is not guaranteed. One reason for this is that deposits that distort the result of the measurement form over time at the SO_2 sensor. The silver/silver chloride electrode for pH measurement also does not display long-term stability, and it is additionally problematic in its biocompatibility. Because of these results, these sensors have not been applied in commercially available implants to date.

Respiration. In contrast, rate-adaptive pacemakers based on minute ventilation measurements are presently offered by several manufacturers. As early as 1982, a rate-adaptive pacemaker that used the respiratory rate for rate adaptation was available (32). Respiratory rate and minute ventilation are determined via impedance measurements. Even though earlier devices required an additional electrode or special bipolar electrodes (with a very large distance between tip and ring) for this measurement, modern devices need only bipolar standard electrodes (33). To measure the impedance, subthreshold bipolar measuring current impulses are fed through the electrode ring, while the voltage between electrode tip and housing is simultaneously measured. Because of the low conductivity of air, the measured impedance rises during inhalation and falls during exhalation. With suitable algorithms, not only the respiratory rate but also the minute ventilation is determined from the gained impedance signal. The minute ventilation shows a much better correlation to the natural sinus rate than just the respiratory rate. However, no closed control loop exists in this system. Furthermore, motion artifacts impair the impedance measurement, and the rise in the rate occurs only with a certain delay.

Cardiac Parameters

Pressure Gradient. Patients with sick sinus syndrome have usually lost only chronotropy, but not the inotropic adaptation; that is, the increase in contractility conveyed by the sympathetic nerve still occurs under physical stress. But heightened sympathetic activity also occurs based on response by the ANS to other stimuli (e.g., emotional stress). Because of the thus triggered changes in the mechanogram of the muscle cell, the course of contraction and also the pressure curve for the right ventricle are modified. The maximum value of the first derivative of the right ventricular pressure (dp/dt_{max}) especially exhibits a good correlation with the natural sinus rate in some studies and is therefore attractive as a control parameter for rate adaptation. The pressure is measured by a pressure sensor that is integrated into the electrode, 28 mm behind the electrode tip (34). At the moment, several prototypes of the pressure rise-controlled pacing system are undergoing clinical trials (34,35). The correlation between sensor signal and load has been proven to be good; the response times are also physiological. The technical difficulty resides in the long-term stability of the sensor. This is a result of fibrin deposition and burrowing by the electrode into trabeculae of the ventricular wall, which can falsify the measurements. Thus, more studies are needed before applying these prototypes to the clinical setting. The research should focus on sensor long-term stability as well as on the reaction during ischemia, cardiac insufficiency, and simultaneous drug therapy. But the disadvantage of requiring a specific electrode remains.

Peak Endocardial Acceleration. A newly developed measuring system consists of a piezoelectric acceleration sensor integrated into the electrode tip, which directly detects the accel-

eration impulses of the adjacent heart wall (36). This new system exploits changes in contractility, in much the same way as is done with a pressure sensor, while avoiding the long-term problems associated with direct pressure measurement. A clinical trial with the first prototype provided a very good correlation of the evaluated maximum acceleration value, PEA (peak endocardial acceleration), with myocardial contractility. Thus, this maintains synchrony with sympathetic activity and the existing sinus rhythm (37). Because the measuring signal should not be distorted by the process of ingrowth by the electrode, a good long-term stability of the sensor is to be expected but must still be clinically proven. However, this measuring system also requires a special electrode with a head that has a significantly larger diameter than standard electrodes because of the integrated sensor.

QT Interval. In the search for physiologic measurement parameters that can be obtained with standard electrodes without an additional sensor, the IEGM is a consideration. This is a convenient value to use because the pacemaker already measures it through the pacing electrode for sensing intrinsic actions. Since 1983, the QT interval has been used as a control parameter for rate adaptation. That is, the time interval between the QRS complex of paced events, such as the pacemaker stimulus and the end of repolarization, namely the T wave in the IEGM (38). The QT interval shortens with rising metabolic demand, under stress, but also with a rising rate. Thus, this sensor signal displays a positive feedback. This normally disadvantageous behavior can be compensated by adjusting the transmission factor for setting the rate change per QT shortening (39). This transmission factor is not constant in the current generation of pacemakers but imitates the nonlinear relationship between ΔQT and ΔHR. The shortening of the QT interval is thought to be caused by the influence of catecholamines on the repolarization (19). Included in this influence is noradrenaline, the sympathetic cardiac nerve transmitter. Thus this sensor reacts not only to physical but also to psychological stress. This relationship also explains the good proportionality observed between the rate adaptation of the pacemaker and the amount of stress. The disadvantages of this sensor are the delayed increase at the stress origin and the brief continuation of a high rate after the stress has ended. Various nonmetabolic influences such as antiarrhythmic medication, ischemia, and changes in the electrolyte composition can influence the QT interval and thus the pacing rate. The relationship between rate and QT interval varies individually to a very large degree. It also undergoes temporal changes, requiring short follow-up cycles and frequent reprogramming. This sensor principle is used in clinical application. The positive feedback on the heart rate parameter is, however, a significant shortcoming.

Ventricular Depolarization Gradient. Besides the QT interval, other parameters of the ventricular IEGM were also studied (e.g., the ventricular depolarization integral). If the integral of the IEGM is formed over time, then the ventricular depolarization gradient is defined as the negative extreme value of this integral. Therefore, it corresponds to the integral of the IEGM in the depolarization phase (40). It is measured by a bipolar standard electrode. The ventricular depolarization gradient diminishes during stress and under catecholamine influence, and it increases during a rate increase. The parameter changes sufficiently fast at the initiation of stress and somewhat slower after it terminates. In the intact heart (i.e., with normal chronotropic adaptation), this parameter remains approximately constant. These favorable properties of the parameter, provided by the negative feedback of the heart rate, allow the construction of a closed system. There have been problems, however, because of paradoxical reactions to position changes (orthostasis). Also, certain drugs may give rise to other problems. Consequently, the system is not commercially available at the moment, but it is the subject of ongoing research. With the advent of the fractal-coated electrode, it has become possible to suppress almost completely the polarization artifact in the IEGM caused by the pacemaker stimulus. This enables a much more exact and undistorted measurement of the IEGM, opening up new perspectives in using the ventricular evoked response (VER) of the heart for physiological rate adaptation (41).

Stroke Volume. The changes in the contraction dynamics of the myocardium, resulting from a heightened sympathetic activity (increased inotropy), are expressed in other physiological parameters as well. Some of these are the stroke volume or the right ventricular preejection phase (PEP). Measuring methods determine the right ventricular volume by intracardiac impedance measurement. To date, catheters with 8, 6, 4, 3 or 2 equidistant ring electrodes have been used for intracardiac volume measurements (42–44). Even though good results have been achieved with such multipole catheters in the left ventricle, the irregular geometry of the right ventricle complicates the determination of a sufficiently exact volume. In addition, respiratory influences, movement or bending of the electrode during contraction, and variable AV-conduction times and intrinsic rhythm lead to compromised measuring results. A key error occurs with the transition from an upright to a supine position. The stroke volume increases as a result of a sudden increase in the venous return, to which the pacemaker would respond with a rate increase. In contrast to this, the heart rate decreases slightly with a normal circulatory regulation. This sensor has also not yet been introduced into commercially available systems.

Preejection Phase. The preejection phase consists of the electromechanical delay (from the QRS complex/stimulus to the beginning of the mechanical activation) and the isovolumetric contraction (presphygmic phase). This parameter shortens with increased contractility, but also with increased end-diastolic volume. It is thus suited as an indicator for physical as well as psychological stress. A direct dependence on the heart rate can be neglected for practical concerns. This parameter can also be derived from the intracardiac impedance measurement. Chirife (45) used a tripolar electrode for the volume measurement. The end of PEP is marked by the beginning of the ejection phase (i.e., by a sudden decrease in volume). Another approach was taken by Schaldach et al. using intracardiac impedance plethysmography (46). The measurement is performed with a unipolar standard electrode. In a method of measurement analogous to that of extracorporeal impedance plethysmography, a second parameter (PEP*) is obtained. This parameter is defined as the time interval between the ventricular stimulus and the point of the steepest negative rise of the unipolar intracardiac impedance. It closely correlates to PEP (47). The first generation of rate-adaptive pacemakers on the basis of PEP* confirmed the physiological significance of this parameter (48). They also re-

vealed technological difficulties in determining the exact time interval, mainly caused by limited temporal resolution of the scanning function in the digital portion of the circuitry. This measurement principle was then further developed and led to the concept of the ventricular inotropic parameter (VIP). Here, the inotropic state of the myocardium is directly determined from the morphology of the unipolar intracardiac impedance signal without the detour of a time interval measurement.

Ventricular Inotropic Parameter. The increased inotropy of the myocardium under sympathetic influence is controlled to a large degree by the increased influx of calcium. This heightened release of calcium, coming from the extracellular space and from the sarcoplasmic reticulum, intensifies electromechanical coupling. From a mechanical viewpoint, this process is expressed as an accelerated contraction (i.e., a higher contraction velocity). It is also expressed as a higher maximum value of the contraction power and, also, as an accelerated relaxation. The higher contraction velocity is the most interesting for its measurement technique; not only can it be captured by mechanical parameters like dp/dt_{max}, but it is also reflected in the unipolar intracardiac impedance signal. With a suitable algorithm, that of the RQ algorithm, the effective rise of the unipolar impedance is measured in a specially designed measuring window. It is then compared to reference values for rest and stress and used to calculate the pacing rate (5,49). This physiological principle of rate adaptation (based on nervous information) is already commercially available in the second pacemaker generation. It has shown very promising results in the clinical field in a large number of patients. Ambulatory stress tests prove an adequate rate adaptation concerning amplitude and temporal response characteristics. In addition to this, psychological stress tests, the rate course during everyday life activities (Fig. 11), and special pharmacological studies also confirm the close correlation of the measuring signal with nervous control (50).

Currently, a manual initialization of the algorithm for rate adaptation is necessary. The unipolar intracardiac impedance signal sometimes displays a drift over several months. This makes it necessary to check the initialization at certain time intervals and to renew it, if indicated. However, procedures are already underway that will initialize automatically after the implantation. These are also intended to update the pacemaker parameters continuously and automatically.

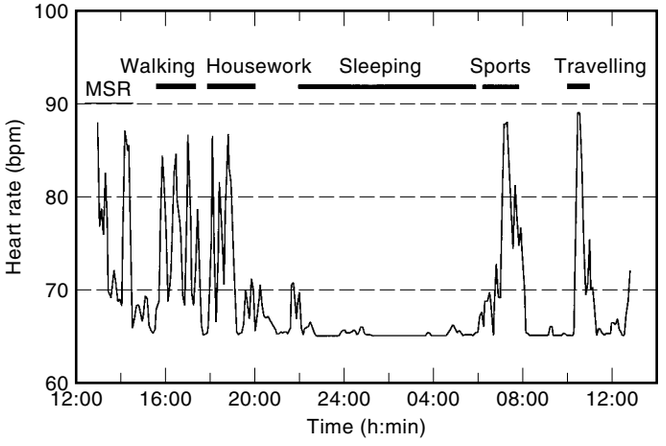

Figure 11. Twenty-four-hour trend of the adaptive pacing rate stored in the internal memory of the pacemaker. Rate adaptation based on unipolar intracardiac impedance measurement shows appropriate response to everyday activities.

Multiple Sensors

This overview of the various measuring signals has shown that every single sensor has some specific advantages and disadvantages for rate adaptation. For that reason, some manufacturers pursue the strategy to use two or more sensors simultaneously, offering the advantage of complementing each other as much as possible in their properties. A particularly attractive combination is that of the motion sensor and a metabolic sensor. The former quickly determines a load but only imprecisely measures the level, and the latter responds with a delay but detects the degree of stress more precisely and is less sensitive to external disturbances (e.g., tremors). Currently pacemakers that have a motion sensor combined with QT-interval measurement are available; others utilize the motion signal and minute ventilation measurement. The clinical results are promising (19,33), but it should not be overlooked that the integration of several sensors is connected to a higher consumption of power, an increased programming effort for the physician, and, quite relevantly, higher costs. Because of growing economic pressure and increasing time limitations for the pacemaker follow-up, the measurement of yet more measuring variables is questioned. Therefore, a different strategy is favored by other manufacturers.

If nervous activity, such as the sympathetic tone, can be successfully determined with sufficient exactitude (e.g., with the intracardiac acceleration sensor or the unipolar intracardiac impedance measurement), then access is established to the ANS and thus to a widely ramified and highly complex network of biological sensors (baroreceptors, chemoreceptors, etc.). Information from the corporeal intrinsic sensor system is thus used for rate adaptation that has already been processed in the circulatory center. This intrinsic sensor system determines the various inner and outer disturbances much more comprehensively and quickly, as well as more precisely than an artificial multisensor system. Moreover, it also captures nonmetabolic influences such as emotional stress. Consequently, it is to be expected that those systems measuring just one good indicator of nervous activity reliably will be superior to those measuring several other parameters with a lesser correlation.

CONCLUSION

In its comparatively short history, pacemaker therapy has undergone a rapid development. Today, the innovations allow the physician to treat complex heart rhythm disturbances with a therapy that is reliable and specific to the individual. Another advantage in contrast to drug therapy is that pacemaker therapy has less propensity to lead to side effects. While in the early years, the life-supporting function was the prominent focus, modern rate-adaptive dual-chamber pacemakers secure a high quality of life for the patient. This is because of their ability to reestablish the synchrony of atrial and ventricular contraction and their provision of physiological rate adaptation. With minimal dimensions and weight, the present implants possess a service lifetime that corresponds to the life expectancy of most patients.

Distant monitoring of pacemaker-dependent patients via telemedicine will further increase the safety of the patients in the future. Extended Holter functions of the internal memory will provide the physician with more precise diagnostic information. Considering time and cost limitations, the focus is no longer solely on quantity. Instead, the therapy-relevant information must be selectively extracted by a suitable choice of the parameters to be monitored, which is accompanied by expert systems support. These enhanced diagnostic features will allow pacemakers to monitor other functional aspects of the heart, such as medication monitoring or ischemia. An application that has already proven successful is allograft rejection monitoring of patients who underwent heart transplantation by means of the ventricular evoked response signal (51). To decrease the programming and follow-up efforts, automatic functions are increasingly used that guarantee an unvarying, optimal pacemaker function and thus enable the physicians to focus more attention on the patient. Some of these functions include the automatic monitoring and adjustment of the sensing threshold and pacing energy, which secures safe sensing and pacing with minimal power consumption. Further automatic functions will follow (e.g., automatic compensation of a possible sensor drift in a rate-adaptive system).

Paralleling this approach, several concepts are pursued to also draw tachycardic rhythm disturbances into the indication spectrum. Promising methods are antitachycardia pacing and multisite pacing. A direct stimulation of the afferent vagal nervous pathways in the myocardium can also contribute to the reestablishment of the neurohumoral balance. With the preventative measures mentioned, the access to neurohumoral parameters makes possible the recognition of life-threatening tachycardias at the early stages, and their suppression. This is done without having to trigger an electroshock by an implantable defibrillator. Access to the state of tone of the autonomic nervous system by intracardiac measuring methods will also make a major contribution to the therapy optimization for other applications, such as to ensure cardiac activity after a cardiomyoplasty (52).

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