New Dimensions and New Indications in Pacemaker Therapy

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Summary

The forty-year history of pacemaker (PM) therapy is characterized by the progress in pacemaker technology. Nowadays, the goal of pacemaker therapy is not only to save and prolong the patients' life but, moreover, to improve their quality of life. Therefore, the improvement of hemodynamics with different kinds of cardiac pacing represents the main point of interest. In this context, different types of atrial and ventricular pacing for the restoration of the normal atrial and ventricular activation pattern as well as for the prevention of the interatrial conduction delay and the avoidance of the deleterious effect of right-ventricular apical pacing on systolic and diastolic function are presented. The maximization of the hemodynamic benefit of AV synchrony by left sided AV resynchronization is performed especially in patients with interatrial conduction delay. In addition, the indications for pacemaker treatment are refined according to several cardiac disease. Certain pacing methods for patients with atrial tachyarrhytmias, HOCM, DCM, a long QT syndrome or neurocardiogenic syncope are discussed.

Key Words

Cardiac pacing, hemodynamics, new indications

Introduction

The forty-year history of pacemaker (PM) therapy is characterized by an improvement in the effectiveness of pacemaker stimulation. The task of PM therapy is to provide a sufficient heart rate, and to recognize and treat the disorder in hemodynamics, which forms the background for rhythm disturbances and causes complaints or decreases the life expectancy. The progress in pacemaker technology includes pacing leads, multiprogrammable pacemakers, non-invasive programmability and an expanded memory together with a Holter function.

The guidelines of cardiac pacing have been set up by the British Pacing and Electrophysiology Group (BPEG) [11]:

- ventricular stimulation is necessary in case of an existing or possible asystole,
- atrial stimulation is to be suggested if possible,
- rate adaptation is not necessary in case of chronotropic competency and for immobile patients,
- hysteresis should be used in order to preserve the sinus rhythm.

Factors influencing the pacemaker hemodynamics are:

- LV function,
- intra-, interatrial and -ventricular conduction delay or block,
- lead-tip position,
- antiarrhythmic effect of pacing.

There are many possibilities to improve the hemodynamic effect of cardiac pacing as shown in Table 1.

Atrial pacing

The optimal position of atrial leads is influenced by the following factors:

- diameter of the right and left atrium,
- interatrial conduction time (IACT),
- techniques of atrial pacing.

Atrium Ø < 50 mm: the conventional right-atrial (RAA) pacing may be appropriate with exception of a vagally activated lone atrial fibrillation [15,41].

Atrium Ø > 50 mm and signs of an atrial enlargement with abnormal IACT (> 100 ms): in this case the purpose of atrial pacing is to provide a synchronized

Method	Effect
Atrial Pacing	
Right atrial appendage (RAA)	Restoration of the normal atrial activation pattern
Dual-site right atrial (RA)	Prevention from interatrial conduction delay
Biatrial (BAD)	Antiarrythmic effect
Septal-biatrial	
Left atrial (LA) pacing via coronary sinus	
Ventricular Pacing	
Right ventricular apex (RVA)	Restoration of the normal ventricular activation pattern and avoidance of the deleterious effect of right-ventricular apical pacing on systolic and diastolic function
Right-ventricular outflow (RVOT)	
Multisite RV pacing (RVA / RVOT)	
Left-ventricular pacing	
Biventricular pacing	
Atrio-Ventricular Synchrony	
Left-sided AV synchronization	Maximization of the hemodynamic benefit of AV synchrony, especially in patients with interatrial conduction delay, prevention of diastolic mitral regurgitation (EF < 35%)
Optimization of the right-sided AV-delay (AVD)	
Left atrial pacing	
Optimal Rate Adaptation	
Closed loop sensors	Restoration of a normal heart-rate response to wide-range physiological stimuli
Dual sensors	Blood pressure optimization

Table 1. Methods to improve the hemodynamic effect of cardiac pacing.

activation of RA and LA by introducing the dual-site RA [35] and biatrial pacing [13,41] to clinical practice.

The special lead position in the atrium (interatrial septum and Bachman bundle) requires active fixation and echocardiography guiding management. The biatrial stimulation could be performed with a single lead from various sites of the interatrial septum. Encouraging initial results with these methods have already been published [29,38]. Part of the data originated from randomized multicenter studies but the number of patients is not big enough to draw an unambiguous conclusion.

Specific type of pacing - AV sequential stimulation with a single-lead system

Recently, the single-lead VDD pacing has become an accepted and widely used mode of PM therapy. The perfect atrial stimulation via atrial floating has not been solved completely. The Italian working group observed appropriate atrial stimulation with OLBI pacing in 225 patients during the 1-year follow-up [36]. LA pacing using the OLBI principle is still in clinical testing.

Using a special site as Bachmannn bundle pacing for atrial stimulation and prevention of atrial arrhythmias looks very promising [4].

Ventricular pacing

The right-ventricular (RV) position is the conventional solution. However, it has disadvantages, as shown in Table 2.

The above mentioned deterioration of the LV function can be further worsened by an LV enlargement and a weak LV function caused by myocardial infarction, cardiomyopathy, valvular disease, high blood pressure, etc. Because of these problems, various methods have been employed to improve the efficacy of LV function.

RV Outflow Tract (RVOT) and multisite RV (RVA/RVOT) pacing

The objective of RVOT pacing is to reduce the left-ventricular activation and the QRS duration. Giudici (1997) [18] observed an 21% improvement of the ejection fraction as an effect of RVOT pacing versus RVA stimulation in 85 patients with normal LV function suf-

Disorder	Effect
LBB pattern, altered ventricular activation	Increase of interventricular conduction time (IVCT) ⇒ increase of RV/LV asynchrony ⇒ delayed LV contraction ⇒ decrease of LV diastolic filling
Paradoxical interventricular septal motion	Decrease of global EF ⇒ failed exercise tolerance

Table 2. Hemodynamic effect of RV stimulation.

fering from sick-sinus-syndrome AV block and AV block after radiofrequency ablation (RF). Victor (1999) [39] presented a prospective randomized study with a limited number of patients implanted with DDDR pacemakers and both leads in a ventricular position. They had moderately decreased (EF = 40%) or poor (EF < 40%) LV function. No significant difference between RVOT and RVA stimulation could be determined during the 3-month follow-up.

The data in literature relating to the effectiveness of RVOT or multisite RV pacing are contradictory. This is most probably due to the mixed patient groups, the differences in LV function, anatomical site and mode of pacing. The estimation of the real hemodynamic effect of RVOT pacing can be verified by chronic prospective randomized hemodynamic examination after placing the bipolar leads in RVOT and RVA position, using DDDR equipment in patients with permanent atrial fibrillation and weak LV function (EF < 40%) [9].

Left-ventricular and biventricular pacing

RV stimulation together with a weak LV function has not fulfilled the hopes placed in it due to the atrial and ventricular desynchronization and the development of diastolic mitral regurgitation. To solve this problem, the restoration of AV synchrony and the resynchronization of ventricular activation are necessary. The atrial resynchronization abolishes the left-atrial activation delay caused by the interatrial conduction block (IACB), enables a timed atrial contraction and an appropriate LV filling [14]. LV and biventricular pacing both result in a significant increase of systemic blood pressure [7], in a sudden drop of the pulmonary capillary wedge pressure as well as of the V-wave amplitude. Further investigators verified the significant improvement of LV contractility and + dp/dt by a LV free-wall stimulation, which cannot be produced by either stimulating the RV or LV apex [10,22]. Based on this information, permanent left-ventricular pacing has already been introduced to clinical practice.

Hemodynamic benefit of AV synchrony

Interatrial (IACT), interventricular conduction time (IVCT) and PM hemodynamics

The right-sided AV sequential pacing together with an optimal PM setting can lead to a 10-30% increase of cardiac output in patients with normal IACT. However, in certain patients, the advantage of this setting has been lost. In these cases, the interatrial conduction block (IACB) (IACT > 100 ms) can easily be recognized on the ECG (P-wave > 120 ms, biphasic P-wave in II- III limb lead), causing a significant delay in LA activation, which cannot be optimized by right-sided AVD programming. During electrophysiological tests, it is possible to record via the esophagus the IACT, which represents the LA activation [31]. These findings are in close correlation with the enlargement of the left atrium [13]. The stimulation of the right atrial appendage (RAA) causes varying intra- and interatrial conduction delays [40] in certain patients.

The atrial stimulation can increase the normal PR distance due to the significant increase in paced inter-atrial conduction (PIACT) so that the contraction of LA takes place during the LV contraction. This is the hemodynamic basis of the pacemaker syndrome. The solution is the AV sequential stimulation, which can delay the onset of the LV contraction due to the increasing interventricular conduction time.

During P-wave triggered ventricular stimulation (VDD mode) with normal right-sided AVD, a significant LV

activation delay can develop. It consists of the P-wave detection delay (40 ms) and the PIVCT (100 ms) caused by the right-ventricular stimulation [3]. The PIVCT corresponds to the preejection-period (PEP) prolongation of the left ventricle. In order to avoid this, a shorter AVD should be programmed after P-wave sensing.
If during AV sequential pacing PIACT > PIVCT, AVD should be reduced, if PIACT < PIVCT, it should be prolonged [3].

The atrio-ventricular delay
The AVD amounts to the distance between the atrial (Ap) and ventricular (Vp) pacemaker spike, corresponding to the PR interval. Depending on the form of pacing, it corresponds to:
- the P-Vstim interval (As-Vp) in VDD pacing,
- the spike-R interval (Ap-Vs) in atrial pacing.

AVD, a programmable parameter of recent pacemakers, affects the pacemaker hemodynamics in three possible ways:
- AVD provides the optimal LV filling at rest during AV sequential pacing,
- a reduction of AVD after P-wave sensing (As-Vp) improves the effectiveness of right-sided pacing,
- dynamic (heart-rate dependent) AVD leads to optimal LV filling during exercise at a higher heart rate.

The information on the interrelation between IACT, IVCT and AVD in patients with a deteriorated LV function is essential, because the wrong programming of AVD would further worsen the left-ventricular performance due to ventricular desynchronization and improper LV filling.

The hemodynamics of rate adaptation

The heart rate is the one of the components of the cardiac output at rest and during exercise. A desirable increase in heart rate is influenced by the level of exercise, the physical fitness, disease and age of the patient. In P-wave-triggered pacemaker systems, the normal sinus-node function guarantees the patient an adequate heart-rate response. But, in cases of chronotropic incompetence, this heart-rate response depends on the type of sensor used and the setting of the rate adaptation. The optimal setting of the rate adaptation always has to be adapted to the individual needs of the patients, resulting in an increase of the stroke volume, thus producing the appropriate cardiac output [27]. Favorable results have been presented by closed-loop (CSL) sensors, based on measuring the change in the right-ventricular impedance (contractility) with help of a unipolar ventricular lead [25], and the mikroaccelerometer sensor (peak endocardial acceleration), included in the lead tip and measuring the demand of RV-contractility change [12].

Advances in pacemaker technology

Leads
Modern leads have been greatly reduced in size, nowadays even 4-5 F leads are available. The surface of the tip is 2-3 mm^2 with an increased micro-surface (carbon, platinum iridium, and titanium nitrite or their combinations), a larger capacitive double layer, which decreases the polarization and attenuates the endocardial signals and improves the current density surround the tip of the lead. High-impedance leads allow the reduction of the battery current drain and lead to lower pacing thresholds. With the new types of retractable active fixation leads the possible necessity of its extraction has been considered. Bipolar leads with linear bipolar connector (IS.1), and leads with built in rate adaptive sensors have been developed. A new achievement is a lead that can be used both for defibrillation and for antibradycardial pacing. Leads with a new design became necessary for LA and LV pacing [14,41]. Experiences of special leads with PTCA guiding catheter have been used for the development of leads for permanent LV pacing via CS [10].

Generator
Despite the expanded memory and the increased life expectancy of pacemakers, further decrease in the size of pacemakers has been achieved. Connectors for triple- or four-chamber pacing without a bifurcated Y connector is currently in clinical testing.

Programmability - Automatic functions
The use of "auto-" functions has been made possible by the drastic expansion of the PM memory. This results in a significant progress in the inspection of the pacemaker functions and the patient follow-up [8,28], see Table 3.

Holter function
The memory extension plays an important role not

Pacing Operation	Pacing Diagnostic	Follow-up Functions
Automatic set-up and programming - threshold tracking - capture detection - autosensing - AVD-hysteresis - dynamic AVD - hysteresis - PVARP	Antitachycardiac function based on beat-to-beat analysis - mode switching - pacemaker-mediated tachycardia detection & termination	Trends and histograms - heart rate - P-, R-, T- wave amplitude - sensor parameters - rhythm-disturbance analysis
Lead configuration Lead integrity	Neuronal syncope detection Sleep detection PM serial number	Threshold tests in both chambers VA conduction test Noninvasive electrophysiology

Table 3. Automatic and special functions of current pacemakers.

only for the detection of PM function but also for the determination of the type of rhythm disturbance, the mechanism of its onset and for the verification of the effectiveness of the therapy. This memory, already used in AICD, can take a prominent part in the therapy of atrial rhythm disturbances. Up to today, the heart-rate variability could only be used in AICD as a valuable indicator of the change in the vegetative tone [42].

New indications for pacemaker treatment

The representatives of the AHA/ACC, NASPE and the Society of Thoracic Surgeons have been revising the guidelines for PM implantation and antiarrhythmic devices every 7 years since 1984. The latest revision was presented in 1998 [20]. The experts of BPEG published similar principles in 1991 [11]. The Hungarian guidelines appeared in 1995 [34].

Pacing and sick-sinus syndrome
Andersen and co-workers [1,17] verified the superiority of single-chamber atrial pacing over single-chamber ventricular pacing. After 5.5 years, there was a persistent reduction in the incidence of atrial fibrillation and thromboembolism, the patients' life expectancy improved and the occurrence of heart failure decreased significantly ($p < 0.005$). This led to the conclusion that atrial-based pacing is recommendable for patients with sick-sinus syndrome and intact AV conduction.

The pacemaker therapy and atrial tachyarrhythmia
Permanent atrial fibrillation requires ventricular based pacing (VVIR or VVI mode). In patients with drug-resistant paroxysmal atrial fibrillation and IACB, multisite right-atrial and biatrial pacing prolonged the arrhythmia-free intervals [13,16,35,41]. In order to estimate the long-term effect of this type of pacing, multicenter prospective randomized trials have been performed. Initial results (42 patients) show a reduction in the incidence of atrial arrhythmia in the biatrial pacing mode without any real long-term benefit for this group of patients [26].

Pacing and hypertrophic-obstructive cardiomyopathy (HOCM)
Due to the character of the disease, AV sequential pacing can guarantee a remarkable decrease of the LV gradient with a full reactivation of RV with help of an individually programmed AVD. The reason for this is the reversal of the normal sequence of ventricular activation (the utmost last activation of the septal region) [18,30,32]. However, PM therapy is only one possibility of treating HOCM together with surgical and RF ablation leading to LBB (only successfully tested in animal studies) [21]. A prospective randomized trial, Pacing in Cardiomyopathy (75 patients), proofed the effectiveness of this PM therapy after one year [2].

New ways for pacing and dilatative cardiomyopathy (DCM)
According to hemodynamic findings, LV-based or biventricular AV sequential pacing is full of promise. The preliminary results of prospective randomized trials show positive effects of atrial synchronized

biventricular pacing in 68 cases of 81 patients [19]. During a period of 10 months, 7 patients died and 4 quit the study. The remaining patients showed a limited EF improvement together with a remarkable decrease of QRS duration and the interventricular mechanic delay. At the time of the implantation, 37% of the patients were classified as NYHA IV and 63% NYHA III, none of them as NYHA I-II class. After three months, the average NYHA enrollment was significantly lower, 60% of the patients became NYHA II, 15% NYHA I, 20% NYHA III and 5% NYHA IV class ($p < 0.001$). Similar improvement has been observed in Quality of Life Questionnaire Scores ($p < 0.001$) and noticeable improvement during the six-minutes walk ($p < 0.038$), as well.

Pacing and long QT syndrome (LQTS)

LQTS is a genetic disease. Individuals suffering from it are at risk of syncope and sudden cardiac death due to torsade-des-pointes ventricular tachycardia, developing because of sympathetic stimulation or excessive bradycardia [24]. The reason for this is an activity type triggered too early after the depolarization (EAD). The M cells from the middle zone of the heart muscle produce a repolarization inhomogeneity and are responsible for the onset of the torsade-des-pointes in bradycardia-dependent LQTS [5]. The therapy consists of beta-blockers, left-cervicothoracic ganglionectomy and permanent pacing. The increase of the heart rate with help of pacing shortens the QT interval, decreases the dispersion of refractoriness and EAD potentials. Beta-blockers are the basic therapy of LQTS. However, if they cause significant bradycardia or AVB, the implantation of a permanent pacemaker appears logical. Dual-chamber pacing should be used with a pacing rate programmed to normalize the QT interval. Implantable single- or dual-chamber AICD should be strongly considered for high-risk patients or in order to prevent sudden cardiac death.

Pacing therapy and neurocardiogenic syncope

The common characteristics of this syndrome include a hypersensitive carotid sinus and vasovagal syncope and consist of a reflex bradycardia and hypotension due to the transient disruption of the autonomic nervous system. Carotid massage and the tilt-table test are useful methods to characterize this disorder as cardioinhibitory, vasodepressor or a mixed form. The initial mechanism is often vasodepressor, then followed by vagally-induced bradycardia, which enlargens the drop in blood pressure. Thus, cardiac pacing is performed in order to avoid reflex bradycardia or sinus arrest and AVB. The AV sequential mode of pacing is preferable, but, in case of atrial fibrillation, VVI or VVIR pacing may be useful, too (ACC/AHA). The North American Vasovagal Pacemaker Study (NAVPAC) is a prospective randomized multicenter study with 46 patients implanted either with a dual-chamber pacemaker or no pacemaker at all. The implanted pacemaker had a special "rate-drop" algorithm, with which the sensed bradycardia is paced at a high initial heart rate, which is lowered gradually. This study has been interrupted prematurely as marked beneficial effect was observed due to pacing results. The DDDR pacemakers with closed loop sensors may be the appropriate pacing mode for the treatment of patients with malignant vasovagal syncope [37].

Pacing in elderly

There is a divergence in the opinion of the efficacy and the demand of AV synchrony and rate responsiveness in pacemaker therapy of elderly patients, age > 65 years. The purpose of the pacing in elderly (PASE) [23] was to examine the effect of dual-chamber rate responsive vs. single-chamber rate- responsive pacing on the health-related quality of life (QOL) in the elderly. Health-related QOL improved dramatically in both groups after pacemaker implantation. But no significant differences have been observed between the ventricular group and the dual-chamber group concerning death, stroke or hospitalization because of heart failure, or the development of atrial fibrillation and general health-related QOL. The favorable effect of AV-sequential pacing was only revealed in patients with sinus-node dysfunction. Nevertheless, these differences were considerably smaller than expected. Patients with an AV block did not show any clear benefit from dual-chamber pacing. Limitations of PASE are: missing comparison of the complication rate, the pacemaker longevity or costs. Furthermore, the number of patients was not large enough for a conclusive comparison of death incidence and major adverse effects. Unfortunately, there is no information on the favorable hemodynamic effect of individual AVD- and dynamic AVD programming. It is possible that the physical abilities of the elderly are limited so much by age and coexistent diseases that improvements in heart rate and cardiac condition show hardly any effect.

Pacing in AVB of degree I with hemodynamic disturbances

Marked first-degree AV block may be associated with a pseudo-pacemaker syndrome due to the proximity of atrial systoles to preceding ventricular systoles, this producing hemodynamic consequences similar to those associated with fast ventriculo-atrial conduction (< 160 ms) [27]. In this instance, atrial contraction occurs before the atrial filling is completed, induces diastolic mitral regurgitation, increasing capillary wedge pressure, and deteriorating ventricular filling, and results in the decrease of the cardiac output. Such a marked first-degree AV block may follow catheter ablation of a fast pathway resulting in a slow pathway conduction. Small uncontrolled trials have suggested symptomatic and functional improvement in pacing with PR intervals > 300 ms by decreasing the time of AV conduction [6].

Conclusion

The hemodynamic point of view is based on the technical development in PM therapy. The memory expansion made the pacemaker check together with the follow-up easier for the physician to handle. The AICD therapy combined with AV-sequential pacing opened a new dimension in PM treatment. Despite these achievements, the milestones of PM therapy, which significantly improve the patients' quality of life, are: a correct indication, an atraumatic surgical intervention and a pacemaker programming adapted to the individual patient. In order to draw appropriate conclusions on the effectiveness of the pacemaker therapy based on the hemodynamic view-point, further prospective crossover randomized studies are necessary.

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