Rate Response in Implantable Cardiac Pacemakers

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Modern cardiac pacemakers are equipped with a function that allows the heart rate to adapt to the current needs of the patient in situations of increased demand related to exercise and stress ("rate-response" function). Modern pacemakers are equipped with a number of functions and algorithms that adjust the basal rate of pacing to situations associated with increased demands of the body—this requires sensors for accelerometer-based measurements; measurements of minute ventilation; measurements of myocardial contractility; and the analysis of myocardial, transthoracic, and transvalvular impedances.

Keywords: cardiac pacemakers ; rate response

1. Principles of Rate-Response Algorithms

A typical implantable cardiac pacemaker consists of a pulse generator and one, two, or three leads that are implanted, depending on the patient's needs, endocavitary, into the muscularis of the right atrium, into the right ventricle, epicardially to the left ventricular wall, or directly or indirectly to the fibers of the conduction pathways or in their vicinity (stimulation of the bundle of His, stimulation of the left bundle branch area) [1][2][3]. Based on their construction, equipment, and technical capabilities, pacemakers are divided into classic subclavian-implanted (in most cases) systems, with leads inserted intravenously into the heart cavities, or leadless, endocavitary-implanted pacemakers [4]. The choice of type of pacemaker is made before implantation and is based on the indications for implantation, age, body structure (anatomical anomalies), comorbidities (diabetes, renal failure), and risk assessment of potential complications; additionally—in the case of patients previously treated with other cardiac implantable electronic devices—the presence of previous systems or components thereof (including abandoned or damaged leads), vascular patency in the planned course of electrode placement, and any history of past infectious complications will also be considered [5]. All currently produced pacemakers are equipped with a function to match the pacing frequency to the patient's current metabolic demand (a rate-response function). However, the principles of operation; scope of application; methods of recording the variability of metabolic, hemodynamic, and physical parameters; and the method of processing signals related to this function can differ [6]. The general principle of the rate-response function is that it senses a specific factor that signals the start of physical activity or the existence of a situation related to increased oxygen demand.

These pacemakers use built-in sensors to detect a signal that indicates the need for a faster heart rate and, in accordance with the programmed settings for the dynamics of the response and the permitted limit of the change in the pacing rate, calculates the number of sensor stimulations proportionally to the effort intensity; it increases the atrial (in pacing systems operating in single-chamber atrial-responsive pacing (AAIR mode) or dual-chamber sequential-responsive pacing (DDDR mode)) or ventricular (in single-chamber ventricular-responsive pacing (VVIR mode)) pacing rate to match the performed effort, up to the maximum pacing frequency limit defined by the parameter value (most often referred to as the "upper sensor rate") or until the effort ceases. In the parameters of the rate-response function, there is also a mechanism for setting the dynamics of a gradual return to the basic rate of pacing after the end of the exercise. This prevents sudden, significant drops in the stimulation frequency in situations where the effort is stopped abruptly. The parameters for the dynamics of increase and the dynamics of decrease, and for the limitation of the pacing rate, are programmable in order to individually adapt to the patient's age, condition, needs, and lifestyle, taking into account their health history (it is also possible for multiple and noninvasive modifications to be made using the programming functions) [7][8].

Each type of sensor (categorized by the factor to which it responds) has its own specific capabilities, advantages, and limitations. A common solution involves two different sensors combined in one system in order to increase the sensitivity and specificity of stimulus perception by the system, optimizing the stimulation frequency change under the influence of the received factor and reducing the susceptibility to disturbances caused by interference from other stimuli acting on the sensed parameters [9].

According to the order in which they sense and react to the body's increased demand for oxygen and the consequent need to increase the pacing frequency, the rate-response sensors can be divided into primary, secondary, and tertiary categories. The least physiological are the tertiary sensors, which detect parameters resulting from exercise, e.g., accelerometers. Secondary rate-response sensors detect parameters resulting from metabolic demand, e.g., minute ventilation. The most physiological sensors, termed primary sensors, detect parameters influencing cardiac function during exercise, e.g., closed-loop stimulation [10]. In terms of the sensed stimulus, the rate-response sensors can be divided into mechanical (accelerometer), electrical (impedance-based sensors), and algorithm-based (QT-interval, closed loop) categories.

2. Rate-Response Algorithms Based on Patient Activity

The simplest, most commonly used system for sensing a patient's activity and the related need to adjust the pacing rate to their effort is an accelerometer that is built into the pacemaker's pulse generator. In this type of sensor, the device detects the patient's movement on the basis of the change in the position of the pulse generator, i.e., the deflection that naturally accompanies the movement of the chest while walking or running. The device continuously counts the number and frequency of recorded movements. It then converts this information into a proportional change in the pacing frequency in accordance with the dynamics programmed for a given patient, as well as the difference between the baseline pacing rate and the maximum limit to which stimulation may be increased during exercise. This sensor, however, has several significant disadvantages: it responds to increased effort with a delay and it is susceptible to disturbances in the form of external vibrations unrelated to, or disproportionately related to, the patient's activity (e.g., while on a swing, riding over bumps, or riding a horse) [11][12].

The operation of an activity sensor based on the incorporation of a circuit with a piezoelectric crystal works similarly. In pacemakers with a rate-response function based on a built-in piezoelectric crystal, the sensed mechanical energy related to vibration, muscle tension, and body movement is converted into electrical signals, triggering an algorithm responsible for adjusting the pacing rate. Research studies have shown that sensors based on accelerometers more quickly and precisely select the frequency of stimulation appropriate to the effort than pacemakers with sensors based on the piezoelectric effect [11][13]. Despite this finding, a study that compared the primary endpoint of death or stroke and mortality, hospitalizations for heart failure, the incidence and duration of atrial fibrillation episodes, and the quality of life in patients with sinus node dysfunction (MOST Trial), found no statistically significant differences in patients with an accelerometer-based rate-response pacemaker when compared to patients with pacemakers with an embedded piezoelectric crystal. Interestingly, this study also observed a group of patients with blended-sensor pacemakers consisting of an accelerometer and piezoelectric circuit— this group of patients demonstrated significantly worse results in terms of quality of life and physical performance [14].

3. Rate-Response Algorithms Based on Minute Ventilation

Adjustment of the stimulation frequency can also be based on a minute-ventilation sensor, which acts as a physiological sensor of increased metabolic demand associated with stress or exercise. Minute ventilation, which is calculated on the basis of respiratory rate and tidal volume, correlates well with heart rate in patients without sinus node dysfunction; it may, therefore, serve as an ideal pattern to utilize for adjusting the pacing frequency to exercise in patients receiving cardiac pacing [15][16]. This system has also been successfully validated in pediatric patients [17][18]. Minute ventilation can be measured by assessing intrathoracic impedance due to fluctuating gas-to-tissue and -fluid ratios in the area throughout the respiratory cycle. In pacemakers, minute ventilation is based on monitoring changes in intrathoracic impedance measured in the circuit between the pulse generator and the tip of the pacing lead [19][20][21].

Unfortunately, this parameter has its limitations. It is susceptible to disturbances and changes in intrathoracic impedance that are not related to effort. Previously conducted measurements showed that the accuracy of this sensor may be impaired in situations of different body position (sitting vs. lying) and depending on the required effort (running vs. cycling) [22]. This sensor is also of limited use in patients with respiratory diseases [23]. A significant disadvantage of this solution is its susceptibility to interference associated with other medical equipment. There have been reports of inappropriate control of the pacing rate in patients with mechanical ventilation systems [24] and cardiac rhythm monitoring systems [25], and during transesophageal echocardiography [26]. There have also been reports of incorrect pacing frequency caused by sensor malfunction as a result of damage to the pacing lead [27][28]. In order to take advantage of the strengths and reduce the impact of the disadvantages of this system, a common solution is to combine a minute-ventilation sensor with an accelerometer-based sensor in a single pacemaker. This solution allows for the benefits of the physiological response of the minute-ventilation sensor (as opposed to the nonphysiological response of the accelerometer sensor), while also using a cross-check method that verifies the need to activate the rate-response algorithm using the observed movement recording by the accelerometer, reducing the risk of an inappropriate increase of the pacing rate in response to external disturbances [29][30].

Study results have shown that the use of this combination produces a greater improvement in heart rate scores compared to the use of an accelerometer alone; this is a measure that determines the risk of death in patients with an implanted cardioverter-defibrillator and allows for the identification of patients that may benefit more from rate-responsive stimulation [31]. The results for the use of two sensors are contradictory and inconclusive in terms of the impact on physical capacity and exercise tolerance for cardiac pacing, and thus this issue requires in-depth research to assess which patient types could benefit most from the use of combined responsive stimulation with two activity sensors [32].

4. Rate-Response Algorithms Based on the Analysis of the QT Interval

Electrocardiographic QT-interval-based sensors provide a completely different solution for analyzing physiological increases in the body's metabolic demand. These pacemakers continuously record the heart rhythm by calculating the potential difference between the poles of the pacing leads (bipolar pacing) or between the pole of the lead and the can of the pulse generator (unipolar pacing). This registration is called an intracardiac electrogram (EGM).

Correct registration of intracardiac EGM signals forms the basis for the proper functioning of these pacemakers. Based on the EGM recording, the pacemaker calculates the time from the occurrence and sensing of a native or paced impulse. This allows it to send stimulation impulses at the appropriate time and control the heart rhythm according to programmed settings. The pacemaker also makes changes to basic pacing and sensing parameters using EGM. By automatically adjusting the sensitivity of the electrodes by adjusting the low- and high-pass filters, the pacemaker reduces the risk of incorrect pacing that could be caused by following incorrect signals registered by the lead (e.g., sensing muscle potentials, electromagnetic interference, incorrect classification of the QRS complex due to double or triple counting, incorrect classification of the T-wave or atrial fibrillation wave).

Based on the EGM recording, the pacemaker can also automatically assess the effectiveness of stimulation during periodic tests of the pacing threshold. In the absence of a deflection corresponding to the excitation of the atrium or ventricle after sending the test pacing impulses, the pacemaker can register ineffective stimulation. It can then change the amplitude of the stimulation output, reducing the risk of asystole. Additionally, the accurate recording of beats by the EGM allows for the use of algorithms that can change the atrioventricular interval to limit the pacing of the right ventricle. Excessive stimulation of the right ventricle (i.e., pacing in a situation where atrioventricular conduction is preserved with a delay that does not affect the deterioration of hemodynamic parameters) increases the risk of developing poststimulating cardiomyopathy [33].

In the majority of currently used cardiac implantable electronic devices, it is possible to automatically manage the pacing of the right ventricle. This is achieved by gradually extending the atrioventricular (A-V) interval in order to evaluate whether a native ventricular beat can be detected after a sensed or paced atrial beat [34].

QT interval analysis is a tool for the management of pacing rate during exercise (rate response) based on electrographic recordings (EGM) [35][36]. This algorithm is based on analysis of the duration of changes in the QT interval during exercise and rest after sending a single unipolar impulse during ventricular depolarization [37]. Under exercise or stress conditions, myocardial contractility increases in response to autonomic nervous system regulation, resulting in a change in the duration of the QT interval corresponding to the period of ventricular repolarization [38][39][40]. The atrioventricular interval, depending on the native atrioventricular conduction time or the programmed A-V interval settings on the pacemaker, is also closely related to the QT interval [41][42][43][44]. Recent studies describe the phenomenon of QT adaptation as an abrupt change in the rate or interruption of atrial and ventricular pacing; this is indicative of the complexity of the phenomenon and the existence of many potential factors (extrinsic, such as pacing, and intrinsic, such as pharmacotherapy of conduction dysfunctions, electrolyte disturbances, or short- or long-QT syndromes) that can affect this parameter [45][46][47][48][49]. One of the disadvantages of this sensor type is the slow response to effort. Numerous attempts have been made to improve response time and to allow diversification of the rhythm and pacing frequency distribution to achieve a nearly physiological distribution of heart rate in a human undertaking various forms and degrees of intensity of exercise [50][51][52][53].

Unfortunately, pacing rate control based on the analysis of changes in the QT interval has been associated with a susceptibility to malfunction and inadequate acceleration or deceleration of pacing under nonexercise conditions affecting QT interval duration. Additionally, inappropriate control of rate modulation pacing has been reported in association with drugs that affect the duration of myocardial repolarization [54]. In patients with coronary artery disease, there is a particular need for care when using QT-based rate modulation pacing settings. In these patients, ischemic pain may induce a pacemaker response in the form of an increase in heart rate by increasing the adrenergic response, which carries a small risk of increasing pain in a vicious circle by increasing the heart rate [55][56][57].

In patients with an implanted pacemaker that modulates the pacing rate based on QT interval analysis, changes in the pacing rate have been observed both during and after fever [58]. Due to the ability to monitor subtle changes in the QT interval and the response to physiological changes associated with inflammatory processes, an attempt was made to use this method as a noninvasive tool for diagnosing early signs of rejection in heart transplant recipients; however, the trials did not result in a sufficient level of diagnostic sensitivity and specificity to allow the solution to be considered clinically useful [59]. As with the previously described sensors, the combination of two different methods for recognizing increased metabolic demand could eliminate the impact of the disadvantages and enhance the advantages of using algorithms based on the analysis of the QT interval. Currently used pacemakers are, however, not equipped for this type of monitoring of physical activity [6][60].

5. Rate-Response Algorithms Based on Closed-Loop Stimulation

An innovative type of rate-response sensor is based on the closed-loop stimulation (CLS) algorithm. The principle behind this method is the continuous observation (in a closed loop) of changes in unipolar intracardiac impedance related to the filling of the ventricles with blood in the diastolic phase and the change in the ratio of the volume of fluid (blood) to tissue (walls of the myocardial chambers) in the contraction phase, under the direct influence of stimuli from the autonomic nervous system [61].

In CLS systems, a series of subthreshold electrical pulses are sent to enable impedance measurements in the tissue immediately surrounding the tip of the pacing lead placed in the chamber. A pacemaker with a CLS system adjusts the pacing rate by continuously analyzing the rate of change in impedance associated with changes in myocardial contractility during increased metabolic demand caused by emotions, exercise, or other conditions. It then calculates the difference between gradient sums of actual and reference impedance measurements [62]. CLS sensors are one of the most physiological options among the currently used cardiac implantable devices because they detect and respond to parameters influencing cardiac function simultaneously with the changing demand, rather than secondarily after the recording of parameters resulting from exercise or metabolic demand. This ensures a proportionate improvement in physical capacity and allows daily living activities to be performed with less effort [63][64][65].

CLS (Biotronik, Germany) works based on the measurement of intracardiac impedance of the area of about 0.5–1 cm diameter around the ventricular electrode (blood and endocardial tissue), on the basis of which it builds a model of the instantaneous work of the heart. Changes in the impedance of the right ventricle are correlated with dP/dtmax of the right ventricle, which corresponds to the rate of contraction of the right ventricle. Thus, during the contraction of the heart, there is greater contact between the electrode and the endocardial tissue, which increases the impedance and, as a result, sends information about the need to increase the heart rate—i.e., the stronger the contraction, the greater the impedance causing the acceleration of the heart rate. Changes in intracardiac impedance are often illustrated by impedance curves, and changing the shape of these curves causes CLS activation. Despite the known mechanism of action of CLS and the undeniable benefits in counteracting vasovagal syndrome (VVS) syncope, it is not fully known what activates this algorithm during such an episode—it may be the acceleration of the activity and the increase in the force of contraction of the heart in the first phase of the presyncope state, which is a physiological response to prevent it. Activation of CLS in this mechanism also allows the minute volume to be maintained at the time of pressure drop during the vascular reflex. After the reflex (when CLS-activating factors have subsided), the cardiac pacing rate gradually returns to baseline values according to the pacing program. It should be mentioned that there are no universal recommendations for programming CLS in the case of VVS, and the program of the device should be set individually so that the patient does not feel discomfort due to the increased frequency of stimulation or its overlong duration. It seems that in cases of VVS, it may be beneficial to program a higher CLS activation [66][67][68][69].

Due to the principle underlying the CLS sensor, it characteristically reduces symptoms associated with syncope in patients with vasovagal syndrome. Several clinical trials have evaluated the use of CLS in patients with vasovagal reflex syncope, with a mean follow-up of 30 months, and 88% of patients experienced a reduction in symptoms associated with vasovagal syndrome after using CLS [70][71][72][73].

In accelerometer-equipped pacemakers, the rate-drop response (RDR) is used to prevent vasovagal syncope. This function is based on the short period of overstimulation after an episode of sudden decrease in heart rate is detected (cardiodepressive mechanism of vasovagal syncope).

The main disadvantage of this function is the late reaction. The rate-drop response is activated after the beginning of the vasovagal mechanism, which often starts with a hypotensive reaction. The pacemaker detects a decrease in heart rate, which can precede syncope as a result of hypotension. Consequently, patients with vasovagal syncope achieve only partial improvement in the form of reducing the number of syncopes and prolonging the prodromal period, allowing them to adopt a safer body position before the syncope.

Furthermore, the rate-drop response function is based on a nonphysiological, sudden increase in the pacing rate, which is sometimes not well tolerated by patients, interpreted as long-lasting (even up a minute) attacks of palpitations which accompany the feeling of upcoming syncope [74]. Closed-loop stimulation is based on continuous analysis of intracardiac impedance, which changes along with the heart's work cycle and under the influence of mechanisms that change myocardial contractility.

In clinical trials comparing the effectiveness of CLS and RDR in preventing vasovagal syncope, superior efficacy of CLS devices has been evidenced [70]. This effect was also observed in patients with an epicardial lead [75]. Consequently, in the latest European Society of Cardiology (ESC) 2021 pacing guidelines, the implantation of a CLS pacemaker in patients >40 years of age with severe, recurrent, unpredictable reflex syncope caused by asystole was placed in class I indications (recommended) [5][76].

Moreover, this sensor is capable of detecting and responding to fluctuating demands of cardiac output due to blood flow and electrolyte changes associated with hemodialysis renal replacement therapy [77]. In a retrospective analysis of patients diagnosed with paroxysmal atrial fibrillation with an implanted pacemaker with a closed-loop sensor, a lower burden of atrial fibrillation was observed when compared to patients with a pacemaker without rate response or with a different sensor [78][79].

The limitation of this method is the need to implant a right ventricular lead (an algorithm impossible to use in AAIR systems). Furthermore, some patients experience accelerated pacing that is unsuitable for their needs and individual tolerance range. Additionally, the use of negative inotropic drugs and the presence of postinfarction scars in the area of the implanted right ventricular lead may reduce the effectiveness of the algorithm [6]. Currently, this algorithm is used only in implantable cardiac devices from BIOTRONIK, Germany.

6. Rate-Response Algorithms Based on Peak Endocardial Acceleration

Another solution for using an accelerometer as the basis for a rate-response function is to optimize the pacing rate in response to isovolumic contraction (and the first cardiac tone) and isovolumic relaxation (and the second cardiac tone) intervals. Technically, this is performed by analyzing endocardial vibration sensed using an accelerometer built into the tip of the ventricular lead (usually ventricular, but it is also used in systems with an accelerometer lead placed in the atrium). This solution allows for the assessment of systolic isovolumic peak acceleration—mechanical activity of the heart which increases during adrenergic stimulation, a parameter of heart contractility. It can also be used to follow the changes in heart rate and demand during exercise. The disadvantage of this solution is the need to use a dedicated electrode compatible with the pulse generator (Sorin Group, Saluggia, Italy). This prevents this solution from being used in patients in whom there are no indications for replacement or additional implantation of the leads from previously used systems, even when replacing the pulse generator itself due to battery depletion [80][81][82][83].

7. Rate-Response Algorithms Based on Transvalvular Impedance (TVI)

An example of pacing rate modulation based on hemodynamic parameter analysis is the rate-response function based on measurements of and changes in transvalvular impedance (TVI). TVI is measured via electrical impulses in a circuit created between the ends of the atrial and right ventricular leads. This method is based on the fact that changes in the impedance of this area are associated with changes in the filling of the heart chambers with blood during the heart cycle. The TVI reaches a minimum value during atrial systole (which corresponds to the end-diastolic phase of the cycle) and a maximum at the end of the QT period (which corresponds to the end-systolic phase) [84][85]. The maximum TVI corresponds to the end-systolic volume and is sensitive to changes in cardiac contractility, which allows this solution to be used to express the autonomic nervous system's regulation of the heart in patients with chronotropic insufficiency [86].

Changes in the TVI waveform correspond to echocardiographic recordings of filling parameters used in the evaluation of myocardial contractility under the influence of right ventricular stimulation. This allows for an indirect assessment of changes in ventricular contractility with stimulation from the septal region compared to the apical region of the right ventricle [87]. Diagnostic information on trends in TVI, due to reliable correlation with hemodynamic parameters in preclinical studies, may prove valuable in cardiac disease therapy in patients with an implanted device [88]. This system is available in Medico (MEDICO S.R.L., Rubano, Italy) cardiac devices.

References

1. Steffen, M.M.; Osborn, J.S.; Cutler, M.J. Cardiac Implantable Electronic Device Therapy: Permanent, Pacemakers, Implantable Cardioverter Defibrillators, and Cardiac Resynchronization Devices. Med. Clin. North Am. 2019, 103, 931–943.
2. Vijayaraman, P.; Chung, M.K.; Dandamudi, G.; Upadhyay, G.A.; Krishnan, K.; Crossley, G.; Bova Campbell, K.; Lee, B.K.; Refaat, M.M.; Saksena, S.; et al. His Bundle Pacing. J. Am. Coll. Cardiol. 2018, 72, 927–947.
3. Ponnusamy, S.S.; Arora, V.; Namboodiri, N.; Kumar, V.; Kapoor, A.; Vijayaraman, P. Left bundle branch pacing: A comprehensive review. J. Cardiovasc. Electrophysiol. 2020, 31, 2462–2473.
4. Merkel, M.; Grotherr, P.; Radzewitz, A.; Schmitt, C. Leadless Pacing: Current State and Future Direction. Cardiol. Ther. 2017, 6, 175–181.
5. Glikson, M.; Nielsen, J.C.; Kronborg, M.B.; Michowitz, Y.; Auricchio, A.; Barbash, I.M.; Barrabés, J.A.; Boriani, G.; Braunschweig, F.; Brignole, M.; et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Europace 2022, 24, 71–164.
6. Trohman, R.G.; Huang, H.D.; Larsen, T.; Krishnan, K.; Sharma, P.S. Sensors for rate-adaptive pacing: How they work, strengths, and limitations. J. Cardiovasc. Electrophysiol. 2020, 31, 3009–3027.
7. Strobel, J.S.; Kay, G.N. Programming of sensor driven pacemakers. Cardiol. Clin. 2000, 18, 157–176.
8. McAlister, H.F.; Soberman, J.; Klementowicz, P.; Andrews, C.; Furman, S. Treadmill assessment of an activity-modulated pacemaker: The importance of individual programming. Pacing Clin. Electrophysiol. 1989, 12, 486–501.
9. Coman, J.; Freedman, R.; Koplan, B.A.; Reeves, R.; Santucci, P.; Stolen, K.Q.; Kraus, S.M.; Meyer, T.E. A blended sensor restores chronotropic response more favorably than an accelerometer alone in pacemaker patients: The LIFE study results. Pacing Clin. Electrophysiol. 2008, 31, 1433–1442.
10. Rickards, A.F.; Donaldson, R.M. Rate responsive pacing. Clin. Prog. Pacing Electrophysiol. 1983, 1, 12–19.
11. Candinas, R.; Jakob, M.; Buckingham, T.A.; Mattmann, H.; Amann, F.W. Vibration, acceleration, gravitation, and movement: Activity controlled rate adaptive pacing during treadmill exercise testing and daily life activities. Pacing Clin. Electrophysiol. 1997, 20, 1777–1786.
12. Lau, C.P.; Mehta, D.; Toff, W.D.; Stott, R.J.; Ward, D.E.; Camm, A.J. Limitations of rate response of an activity-sensing rate-responsive pacemaker to different forms of activity. Pacing Clin. Electrophysiol. 1988, 11, 141–150.
13. Bacharach, D.W.; Hilden, T.S.; Millerhagen, J.O.; Westrum, B.L.; Kelly, J.M. Activity-based pacing: Comparison of a device using an accelerometer versus a piezoelectric crystal. Pacing Clin. Electrophysiol. 1992, 15, 188–196.
14. Shukla, H.H.; Flaker, G.C.; Hellkamp, A.S.; James, E.A.; Lee, K.L.; Goldman, L.; Orav, E.J.; Lamas, G.A. Clinical and quality of life comparison of accelerometer, piezoelectric crystal, and blended sensors in DDDR-paced patients with sinus node dysfunction in the mode selection trial (MOST). Pacing Clin. Electrophysiol. 2005, 28, 762–770.
15. Slade, A.K.; Pee, S.; Jones, S.; Granle, L.; Fei, L.; Camm, A.J. New algorithms to increase the initial rate response in a minute volume rate adaptive pacemaker. Pacing Clin. Electrophysiol. 1994, 17, 1960–1965.
16. Li, H.; Neubauer, S.A.; Hayes, D.L. Follow-up of a minute ventilation rate adaptive pacemaker. Pacing Clin. Electrophysiol. 1992, 15, 1826–1829.
17. Celiker, A.; Ceviz, N.; Alehan, D.; Lenk, M.K.; Ozme, S. Comparison of normal sinus rhythm and pacing rate in children with minute ventilation single chamber rate adaptive permanent pacemakers. Pacing Clin. Electrophysiol. 1998, 21, 2100–2104.
18. Yabek, S.M.; Wernly, J.; Chick, T.W.; Berman, W., Jr.; McWilliams, B. Rate-adaptive cardiac pacing in children using a minute ventilation biosensor. Pacing Clin. Electrophysiol. 1990, 13, 2108–2112.
19. Cole, C.R.; Jensen, D.N.; Cho, Y.; Portzline, G.; Candinas, R.; Duru, F.; Adler, S.; Nelson, L.; Condie, C.; Wilkoff, B.L. Correlation of impedance minute ventilation with measured minute ventilation in a rate responsive pacemaker. Pacing Clin. Electrophysiol. 2001, 24, 989–993.
20. Duru, F.; Radicke, D.; Wilkoff, B.L.; Cole, C.R.; Adler, S.; Nelson, L.; Jensen, D.N.; Strobel, U.; Portzline, G.; Candinas, R. Influence of posture, breathing pattern, and type of exercise on minute ventilation estimation by a pacemaker transthoracic impedance sensor. Pacing Clin Electrophysiol. 2000, 23, 1767–1771.

21. Mond, H.; Strathmore, N.; Kertes, P.; Hunt, D.; Baker, G. Rate responsive pacing using a minute ventilation sensor. Pacing Clin. Electrophysiol. 1988, 11, 1866–1874.

22. Simon, R.; Ni, Q.; Willems, R.; Hartley, J.W.; Daum, D.R.; Lang, D.; Ward, K.; Gill, J. Comparison of impedance minute ventilation and direct measured minute ventilation in a rate adaptive pacemaker. Pacing Clin. Electrophysiol. 2003, 26, 2127–2133.

23. Dell'Orto, S.; Valli, P.; Greco, E.M. Sensors for rate responsive pacing. Indian Pacing Electrophysiol. J. 2004, 4, 137–145.

24. Nayak, A.K.; Aggarwal, K.; Flaker, G.C. Minute ventilation-sensor driven pacemaker related difficulty in weaning from mechanical ventilation: A case report. Mo. Med. 2001, 98, 181–183.

25. Lau, W.; Corcoran, S.J.; Mond, H.G. Pacemaker tachycardia in a minute ventilation rate-adaptive pacemaker induced by electrocardiographic monitoring. Pacing Clin. Electrophysiol. 2006, 29, 438–440.

26. Khunnawat, C.; Mukerji, S.; Sankaran, S.; Thakur, R.K. Echocardiography induced tachycardia in a patient with a minute ventilation rate responsive pacemaker. J. Interv. Card. Electrophysiol. 2005, 14, 51–53.

27. Sugiura, S.; Matsuoka, K.; Ikami, A.; Shioji, H.; Takasaki, A.; Koji, T.; Tanigawa, T.; Ito, M. An incomplete pacemaker lead fracture causing inappropriate pacing inhibition due to oversensing of the minute ventilation sensor pulses. J. Cardiol. Cases 2018, 18, 47–51.

28. Shekar, P.V.; Vignesh Rangaswamy, V.; Subramanian, M.; Atreya, A.R.; Yalagudri, S.; Chennapragada, S.; Saggu, D.K.; Narasimhan, C. High rate episodes in a dual chamber pacemaker: What is the mechanism? Pacing Clin. Electrophysiol. 2022, 45, 238–240.

29. Pilat, E.; Mlynarski, R.; Wlodyka, A.; Kargul, W. Influence of DDD rate response pacing with integrated double sensors on physical efficiency and quality of life. Europace 2008, 10, 1189–1894.

30. Gilliam, F.R., III; Giudici, M.; Benn, A.; Koplan, B.; Berg, K.J.; Kraus, S.M.; Stolen, K.Q.; Alvarez, G.E.; Hopper, D.L.; Wilkoff, B.L. Design and rationale of the assessment of proper physiologic response with rate adaptive pacing driven by minute ventilation or accelerometer (APPROPRIATE) trial. J. Cardiovasc. Transl. Res. 2011, 4, 21–26.

31. Richards, M.; Olshansky, B.; Sharma, A.D.; Wold, N.; Jones, P.; Perschbacher, D.; Wilkoff, B.L. Addition of minute ventilation to rate-response pacing improves heart rate score more than accelerometer alone. Heart Rhythm. 2018, 15, 1730–1735.

32. Padeletti, L.; Pieragnoli, P.; Di Biase, L.; Colella, A.; Landolina, M.; Moro, E.; Orazi, S.; Vicentini, A.; Maglia, G.; Pensabene, O.; et al. Is a dual-sensor pacemaker appropriate in patients with sino-atrial disease? Results from the DUSISLOG study. Pacing Clin. Electrophysiol. 2006, 29, 34–40.

33. Lu, W.; Lin, J.; Dai, Y.; Chen, K.; Zhang, S. The therapeutic effects of upgrade to cardiac resynchronization therapy in pacing-induced cardiomyopathy or chronic right ventricular pacing patients: A meta-analysis. Heart Fail. Rev. 2022, 27, 507–516.

34. Chen, S.; Chen, K.; Tao, Q.; Zheng, L.; Shen, F.; Wu, S.; Fan, J.; Xu, G.; Wang, L.; Zhou, X.; et al. Reduction of unnecessary right ventricular pacing by managed ventricular pacing and search AV+ algorithms in pacemaker patients: 12-month follow-up results of a randomized study. Europace 2014, 16, 1595–1602.

35. Baig, M.W.; Boute, W.; Begemann, M.; Perrins, E.J. One-year follow-up of automatic adaptation of the rate response algorithm of the QT sensing, rate adaptive pacemaker. Pacing Clin. Electrophysiol. 1991, 14, 1598–1605.

36. Connelly, D.T.; Rickards, A.F. Rate-responsive pacing using electrographic parameters as sensors. Cardiol Clin. 1992, 10, 659–669.

37. Connelly, D.T.; Rickards, A.F. The evoked QT interval. In Clinical, Cardiac Pacing, 1st ed.; Ellenbogen, K., Kay, G., Wilkoff, B., Eds.; W.B. Saunders (Elsevier): Philadelphia, PA, USA, 1995; pp. 250–257.

38. Johnson, N.P.; Holly, T.A.; Goldberger, J.J. QT dynamics early after exercise as a predictor of mortality. Heart Rhythm. 2010, 7, 1077–1084.

39. Frais, M.A.; Dowie, A.; McEwen, B.; Wyeth, R.P.; Kim, S.W. Response of the QT-sensing, rate-adaptive ventricular pacemaker to mental stress. Am. Heart J. 1993, 126, 1219–1222.

40. Horstmann, E.; Koenn, B. Temporal relationship between exercise and QT shortening in patients with QT pacemakers. Pacing Clin. Electrophysiol. 1989, 12, 1080–1084.

41. Ishikawa, T.; Sugano, T.; Sumita, S.; Toda, N.; Kosuge, M.; Kobayashi, I.; Matsusita, K.; Ohkusu, Y.; Kimura, K.; Usui, T.; et al. Optimal atrioventricular delay setting determined by QT sensor of implanted DDDR pacemaker. Pacing Clin. Electrophysiol. 2002, 25, 195–200.

42. Ishikawa, T.; Sugano, T.; Sumita, S.; Kimura, K.; Kikuchi, M.; Kosuge, M.; Kobayashi, I.; Shigemasa, T.; Endo, T.; Usui, T.; et al. Relationship between atrioventricular delay, QT interval and cardiac function in patients with implanted DDD pacemakers. Europace 1999, 1, 192–196.

43. Ishikawa, T.; Sugano, T.; Sumita, S.; Kosuge, M.; Kobayashi, I.; Kobayashi, T.; Yamakawa, Y.; Matsusita, K.; Matsumoto, K.; Ohkusu, Y.; et al. Changes in evoked QT intervals according to variations in atrioventricular delay and cardiac function in patients with implanted QT-driven DDDR pacemakers. Circ. J. 2003, 67, 515–518.

44. Ishikawa, T.; Sugano, T.; Sumita, S.; Nakagawa, T.; Hanada, K.; Kosuge, M.; Kobayashi, I.; Kimura, K.; Tochikubo, O.; Usui, T.; et al. Optimal atrioventricular delay setting determined by evoked QT interval in patients with implanted stimulus-T-driven DDDR pacemakers. Europace 2001, 3, 46–51.

45. Axelsson, K.J.; Gransberg, L.; Lundahl, G.; Vahedi, F.; Bergfeldt, L. Adaptation of ventricular repolarization time following abrupt changes in heart rate: Comparisons and reproducibility of repeated atrial and ventricular pacing. Am. J. Physiol. Heart Circ. Physiol. 2021, 320, H381–H392.

46. Shah, S.R.; Park, K.; Alweis, R.; Long, Q.T. Syndrome: A Comprehensive Review of the Literature and Current Evidence. Curr. Probl. Cardiol. 2019, 44, 92–106.

47. Hirao, H.; Shimizu, W.; Kurita, T.; Suyama, K.; Aihara, N.; Kamakura, S.; Shimomura, K. Frequency-dependent electrophysiologic properties of ventricular repolarization in patients with congenital long QT syndrome. J. Am. Coll. Cardiol. 1996, 28, 1269–1277.

48. Biernacka, E.K.; Kosior, D.A.; Zienciuk-Krajka, A.; Miszczak-Knecht, M.; Kempa, M.; Przybylski, A. Safety of antiviral and anti-inflammatory drugs prolonging QT interval in patients with coronavirus disease 2019: An opinion of the Heart, Rhythm Section of the Polish, Cardiac Society. Kardiol. Pol. 2020, 78, 493–497.

49. Barış, V.Ö.; Dinçsoy, B.; Gedikli, E.; Erdemb, A. Empagliflozin significantly attenuates sotalol-induced QTc prolongation in rats. Kardiol. Pol. 2021, 79, 53–57.

50. Den Heijer, P.; Nagelkerke, D.; Perrins, E.J.; Horstmann, E.; Van Woersem, R.J.; Niederlag, W.; Jordaens, L.; De Wilde, P.; Hameleers, A.J.; Boute, W.; et al. Improved rate responsive algorithm in QT driven pacemakers—Evaluation of initial response to exercise. Pacing Clin. Electrophysiol. 1989, 12, 805–811.

51. McGoon, M.D.; Shapland, J.E.; Salo, R.; Pederson, B.; Olive, A. The feasibility of utilizing the systolic pre-ejection interval as a determinant of pacing rate. J. Am. Coll. Cardiol. 1989, 14, 1753–1758.

52. Furman, S. Rate-modulated pacing. Circulation 1990, 82, 1081–1094.

53. Lau, C.P.; Freedman, A.R.; Fleming, S.; Malik, M.; Camm, A.J.; Ward, D.E. Hysteresis of the ventricular paced QT interval in response to abrupt changes in pacing rate. Cardiovasc. Res. 1988, 22, 67–72.

54. Dionisio, P.; Stroobandt, R.; Vandenbulcke, F.; Sinnaeve, A. Rate adaptive dual chamber pacing: Inappropriate rate response due to pseudomalfunction of the QT biosensor. Pacing Clin. Electrophysiol. 1999, 22, 668–671.

55. Lau, C.P.; Leung, S.K.; Lee, I.S. Delayed exercise rate response kinetics due to sensor cross-checking in a dual sensor rate adaptive pacing system: The importance of individual sensor programming. Pacing Clin. Electrophysiol. 1996, 19, 1021–1025.

56. Robbens, E.J.; Clement, D.L.; Jordaens, L.J. QT-related rate-responsive pacing during acute myocardial infarction. Pacing Clin. Electrophysiol. 1988, 11, 339–342.

57. Edelstam, C.; Hedman, A.; Nordlander, R.; Pehrsson, S.K. QT sensing rate responsive pacing and myocardial infarction: A case report. Pacing Clin. Electrophysiol. 1989, 12, 502–504.

58. Kaye, G.C.; Baig, W.; Mackintosh, A.F. QT sensing rate responsive pacing during subacute bacterial endocarditis: A case report. Pacing Clin. Electrophysiol. 1990, 13, 1089–1091.

59. Bainbridge, A.D.; Cave, M.; Newell, S.; Delaney, M.; Parameshwar, J.; Large, S.R.; Wallwork, J.; Grace, A.A.; Carey, N.R.; Schofield, P.M. The utility of pacemaker evoked T wave amplitude for the noninvasive diagnosis of cardiac allograft rejection. Pacing Clin. Electrophysiol. 1999, 22, 942–946.

60. Clémenty, J.; Barold, S.S.; Garrigue, S.; Shah, D.C.; Jaïs, P.; Le Métayer, P.; Haïssaguerre, M. Clinical significance of multiple sensor options: Rate response optimization, sensor blending, and trending. Am. J. Cardiol. 1999, 83, 166D–171D.

61. Coenen, M.; Malinowski, K.; Spitzer, W.; Schuchert, A.; Schmitz, D.; Anelli-Monti, M.; Maier, S.K.; Estlinbaum, W.; Bauer, A.; Muehling, H.; et al. Closed loop stimulation and accelerometer-based rate adaptation: Results of the PROVIDE study. Europace 2008, 10, 327–333.

62. Proietti, R.; Manzoni, G.; Di Biase, L.; Castelnuovo, G.; Lombardi, L.; Fundarò, C.; Vegliante, N.; Pietrabissa, G.; Santangeli, P.; Canby, R.A.; et al. Closed loop stimulation is effective in improving heart rate and blood pressure

response to mental stress: Report of a single-chamber pacemaker study in patients with chronotropic incompetent atrial fibrillation. Pacing Clin. Electrophysiol. 2012, 35, 990–998.

63. Chandiramani, S.; Cohorn, L.C.; Chandiramani, S. Heart rate changes during acute mental stress with closed loop stimulation: Report on two single-blinded, pacemaker studies. Pacing Clin. Electrophysiol. 2007, 30, 976–984.

64. Abi-Samra, F.M.; Singh, N.; Rosin, B.L.; Dwyer, J.V.; Miller, C.D.; CLEAR Study Investigators. Effect of rate-adaptive pacing on performance and physiological parameters during activities of daily living in the elderly: Results from the CLEAR (Cylos, Responds with Physiologic, Rate Changes during Daily, Activities) study. Europace 2013, 15, 849–856.

65. Lindovská, M.; Kameník, L.; Pollock, B.; Hoenen, S.; Bökelmann, T.; Spitzer, W.; Salbach, P.; Behroz, A.; Frey, A. Clinical observations with Closed Loop Stimulation pacemakers in a large patient cohort: The CYLOS routine documentation registry (RECORD). Europace 2012, 14, 1587–1595.

66. Schaldach, M.; Hutten, H. Intracardiac impedance to determine sympathetic activity in rate responsive pacing. Pacing Clin. Electrophysiol. 1992, 15, 1772–1786.

67. Schaldach, M.; Urbaszek, A.; Stöbel, J.; Heublein, B. Rate-adaptive pacing using a Closed-Loop, autonomic nervous system controlled pacemaker. JHK Coll. Cardiol. 1995, 3, 22–32.

68. Closed Loop Stimulation. Unique Physiological Rate Response for an Optimal Haemodynamic Performance. 200 146/A/2012. BIOTRONIK SE & Co. KG. Available online: https://www.biotronik.com/en-gb/products/cls (accessed on 19 January 2023).

69. Gopinathannair, R.; Olshansky, B.; Turagam, M.K.; Gautam, S.; Futyma, P.; Akella, K.; Tanboga, H.I.; Bozyel, S.; Yalin, K.; Padmanabhan, D.; et al. Permanent pacing versus cardioneuroablation for cardioinhibitory vasovagal syncope. J. Interv. Card. Electrophysiol. 2022, 65. Epub ahead of print.

70. Rattanawong, P.; Riangwiwat, T.; Chongsathidkiet, P.; Vutthikraivit, W.; Limpruttidham, N.; Prasitlumkum, N.; Kanjanahattakij, N.; Kanitsoraphan, C. Closed-looped stimulation cardiac pacing for recurrent vasovagal syncope: A systematic review and meta-analysis. J. Arrhythm. 2018, 34, 556–564.

71. Ruzieh, M.; Ammari, Z.; Dasa, O.; Karim, S.; Grubb, B. Role of closed loop stimulation pacing (CLS) in vasovagal syncope. Pacing Clin. Electrophysiol. 2017, 40, 1302–1307.

72. Tomaino, M.; Russo, V.; Giacopelli, D.; Gargaro, A.; Brignole, M. Cardiac Pacing in Cardioinhibitory Reflex Syncope: Clinical Use of Closed-loop Stimulation. Arrhythm. Electrophysiol. Rev. 2021, 10, 244–249.

73. Palmisano, P.; Dell'Era, G.; Russo, V.; Zaccaria, M.; Mangia, R.; Bortnik, M.; De Vecchi, F.; Giubertoni, A.; Patti, F.; Magnani, A.; et al. Effects of closed-loop stimulation vs. DDD pacing on haemodynamic variations and occurrence of syncope induced by head-up tilt test in older patients with refractory cardioinhibitory vasovagal syncope: The Tilt test-Induced, REsponse in Closed-loop Stimulation multicentre, prospective, single blind, randomized study. Europace 2018, 20, 859–866.

74. Chmielecka, M.; Myszka, Z.; Pytka, M. Cardiac pacing in vasovagal syncope in the light of the latest recommendations. Folia Cardiol. 2021, 16, 416–419.

75. Di Pino, A.; Caruso, E.; Censi, F.; Gaudenti, G.; Gargaro, A.; Calcagnini, G. Physiological rate adaptation in a child with chronotropic incompetence through closed-loop stimulation using epicardial leads. HeartRhythm Case Rep. 2015, 2, 36–39.

76. Nakai, T.; Ikeya, Y.; Tsuchiya, N.; Mano, H.; Kurokawa, S.; Nagashima, K.; Ohkubo, K.; Watanabe, I.; Okumura, Y. Benefit of Rate Response with Closed-Loop Stimulation in Patients with Difficult Hemodialysis. Int. Heart J. 2020, 61, 611–615.

77. Puglisi, A.; Favale, S.; Scipione, P.; Melissano, D.; Pavia, L.; Ascani, F.; Elia, M.; Scaccia, A.; Sagone, A.; Castaldi, B.; et al. Overdrive versus conventional or closed-loop rate modulation pacing in the prevention of atrial tachyarrhythmias in Brady-Tachy syndrome: On behalf of the Burden II Study Group. Pacing Clin. Electrophysiol. 2008, 31, 1443–1455.

78. Morillo, C.A.; Brignole, M. Pacing for vasovagal syncope: Tips for use in practice. Auton. Neurosci. 2022, 241, 102998.

79. Ikeda, S.; Nogami, A.; Inoue, K.; Kowase, S.; Kurosaki, K.; Mukai, Y.; Tsutsui, H. Closed-loop stimulation as a physiological rate-modulated pacing approach based on intracardiac impedance to lower the atrial tachyarrhythmia burden in patients with sinus node dysfunction and atrial fibrillation. J. Cardiovasc. Electrophysiol. 2020, 31, 1187–1194.

80. Occhetta, E.; Bortnik, M.; Marino, P. Usefulness of hemodynamic sensors for physiologic cardiac pacing in heart failure patients. Cardiol. Res. Pract. 2011, 2011, 925653.

81. Bordachar, P.; Garrigue, S.; Reuter, S.; Hocini, M.; Kobeissi, A.; Gaggini, G.; Jaïs, P.; Haïssaguerre, M.; Clementy, J. Hemodynamic assessment of right, left, and biventricular pacing by peak endocardial acceleration and echocardiography in patients with end-stage heart failure. Pacing Clin. Electrophysiol. 2000, 23, 1726–1730.

82. Senoner, T.; Barbieri, F.; Semmler, G.; Adukauskaite, A.; Rubatscher, A.; Schgör, W.; Stühlinger, M.; Bauer, A.; Pfeifer, B.E.; Fiedler, L.; et al. Long-term performance of an atrial lead capable of accelerometer based detection of cardiac contractility in patients receiving cardiac resynchronisation therapy. PLoS ONE 2019, 14, e0222269.
83. Plicchi, G.; Marcelli, E.; Parlapiano, M.; Bombardini, T. PEA I and PEA II based implantable haemodynamic monitor: Pre clinical studies in sheep. Europace 2002, 4, 49–54.
84. Di Gregorio, F.; Morra, A.; Finesso, M.; Bongiorni, M.G. Transvalvular impedance (TVI) recording under electrical and pharmocological cardiac stimulation. Pacing Clin. Electrophysiol. 1996, 19, 1689–1993.
85. Calvi, V.; Pizzimenti, G.; Lisi, M.; Doria, G.; Vasquez, L.; Lisi, F.; Felis, S.; Tempio, D.; Virgilio, A.; Barbetta, A.; et al. Hemodynamic Surveillance of Ventricular Pacing Effectiveness with the Transvalvular Impedance Sensor. Adv. Med. 2014, 2014, 307168.
86. Gasparini, G.; Curnis, A.; Gulizia, M.; Occhetta, E.; Corrado, A.; Bontempi, L.; Mascioli, G.; Francese, G.M.; Bortnik, M.; Magnani, A.; et al. Rate-responsive pacing regulated by cardiac haemodynamics. Europace 2005, 7, 234–241.
87. Taborsky, M.; Fedorco, M.; Skala, T.; Kocianova, E.; Pastucha, D.; Richter, D.; Petrkova, J.; Di Gregorio, F.; Barbetta, A.; Vaclavik, J. Acute effects of right ventricular pacing on cardiac haemodynamics and transvalvular impedance. Biomed. Pap. Med. Fac. Univ. Palacky Olomouc. Czech Repub. 2014, 158, 569–576.
88. Lionetti, V.; Romano, S.L.; Bianchi, G.; Bernini, F.; Dushpanova, A.; Mascia, G.; Nesti, M.; Di Gregorio, F.; Barbetta, A.; Padeletti, L. Impact of acute changes of left ventricular contractility on the transvalvular impedance: Validation study by pressure-volume loop analysis in healthy pigs. PLoS ONE 2013, 8, e80591.