# REVIEWS

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# Alternative Right Ventricular Pacing Sites

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**A** – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

## Abstract

**Background.** The main adverse effect of chronic stimulation is stimulation-induced heart failure in case of ventricular contraction dyssynchrony. Because of this fact, new techniques of stimulation should be considered to optimize electrotherapy. One of these methods is pacing from alternative right ventricular sites.
**Objectives.** The purpose of this article is to review currently accumulated data about alternative sites of cardiac pacing.
**Material and Methods.** Medline and PubMed bases were used to search English and Polish reports published recently.
**Results.** Recent studies report a deleterious effect of long term apical pacing. It is suggested that permanent apical stimulation, by omitting physiological conduction pattern with His-Purkinie network, may lead to electrical and mechanical dyssynchrony of heart muscle contraction. In the long term this pathological situation can lead to severe heart failure and death. Because of this, scientists began to search for some alternative sites of cardiac pacing to reduce the deleterious effect of stimulation. Based on current accumulated data, it is suggested that the right ventricular outflow tract, right ventricular septum, direct His-bundle or biventricular pacing are better alternatives due to more physiological electrical impulse propagation within the heart and the reduction of the dyssynchrony effect. These methods should preserve a better left ventricular function and prevent the development of heart failure in permanent paced patients. As there is still not enough, long-term, randomized, prospective, cross-over and multicenter studies, further research is required to validate the benefits of using this kind of therapy.
**Conclusions.** The article should pay attention to new sites of cardiac stimulation as a better and safer method of treatment (**Adv Clin Exp Med 2015, 24, 2, 349–359**).

**Key words:** artificial pacemaker, cardiac pacing, artificial, tricuspid valve insufficiency, heart failure, myocardial contraction.

The rapidly developing branch of cardiology – electrophysiology – is associated with constant innovation of invasive diagnostic and therapeutic methods. Since the discovery of implantable devices for cardiac pacing in 1957, these devices have become a common method of treating many arrhythmias. Stimulation also helps improve the quality of life and survival in groups of patients with MAS syndrome and advanced a–v block with bradycardia.

The survey estimated that in Poland there are over 100,000 people living with an implanted pacemaker, and the number of implantations is estimated at about 9,500 per year. The data from 2006 also says that about 180,000 patients are undergoing pacemaker implantation in the U.S. each year, and this number is constantly growing [1]. On the other hand, this procedure is associated with a lot of complications. Among the surgical ones we can find bleeding into the pericardium, pneumothorax and device infection. Complications related with chronic stimulation and the presence of electrodes in the anatomical structures of the heart are connected with blood clots on the electrodes, endocarditis, valve and ventricular dysfunction with heart failure and increased mortality [2]. The mechanism responsible for these changes has not been fully explained. It is believed that artificial stimulation results in abnormal, non-physiological electrical impulses conduction within His-Purkinje system and

leads to interventricular dyssynchrony and hemodynamic dysfunction [3]. When deciding to implant pacemaker researchers began to pay more attention to the place of the ventricular lead set in case to eliminate the problem of heart failure and valvulopathy in the future. Researchers also suggested that right ventricular outflow tract (RVOT), right ventricular septum (RVS), direct His-bundle (DHBP) or biventricular (BiV = CRT) stimulation are better alternatives to the classical method of right ventricular apex stimulation (RVA).

# Material and Methods

Medline, Web of Knowledge, Scopus and PubMed sources were used to search English and Polish reports published recently.

# Results

## Adverse Effects of RVA Pacing

The most common adverse effects of chronic RVA pacing are: iatrogenically accentuated intraventricular conduction delay, left ventricular electrical and mechanical dyssynchrony, left ventricular remodeling, abnormalities in myocardial histopathology, left ventricular dysfunction (both systolic and diastolic), congestive heart failure, myocardial perfusion defects and regional wall motion abnormalities, functional mitral regurgitation, increased risk of atrial fibrillation (in patients with sinus node dysfunction and normal baseline QRS duration), left atrial enlargement, promotion of ventricular arrhythmias, activation of sympathetic nervous system [4].

## Tricuspid Valve Regurgitation

Based on the results of clinical and pathological research, it was noted that the most common negative consequences of chronic RVA pacing are abnormalities of the tricuspid valve. The data gathered from autopsy studies confirmed previous assumptions about the presence of reacted--fibrinous lesions between the implanted electrode and endocardium tissues, particularly around the apex and tricuspid valve [5]. On the other hand, recent studies do not fully explain the impact of the implanted electrode on the presence of tricuspid regurgitation.

In 1964, Sobol et al. [6] were the first who demonstrated the presence of tricuspid and pulmonary regurgitation by using catheters and indicator substance. Sakai et al. [7], using Doppler and contrast echocardiography, observed the presence of tricuspid regurgitation in 45% of patients with implanted permanent pacemaker. The authors also analyzed 26 autopsy studies of permanent paced patients, revealing changes in tricuspid valve function in 42%. Other results were achieved by David W. Leibowitz et al. [8]. The authors revealed no influence of implanted electrode on the severity of tricuspid regurgitation in short-term observation. This situation may suggest that only prolonged stimulation can result in adverse effects on cardiac function. This was confirmed in the study by Wojciech Krupa et al. [9]. In a group of 124 patients with or without pacemaker the authors revealed statistically significant tricuspid regurgitation after at least 12 months of observation. Before this time no differences were noticed between the analyzed groups. On the other hand, the type of stimulation and transition of electrode did not directly affect tricuspid regurgitation. Moreover, risk factors and diseases that strongly aggravates tricuspid regurgitation are, besides electrodes in heart cavities, advanced age, female gender, lower body mass index, hypertension, atrial fibrillation, other valvular diseases, heart failure, myocardial infarct, left ventricular diastolic dysfunction, coronary artery disease, history of invasive or surgical revascularization, pulmonary embolism, bronchial asthma, chronic obstructive pulmonary disease, emphysema and respiratory induced pulmonary hypertension. Chronic overload of the right atrium made by tricuspid regurgitation causes stagnation in systemic circulation, which, in the long term, leads to congestive heart failure. Literature widely describes the problem of tricuspid regurgitation in patients with permanent pacemaker. Paniagua et al. [10] performed a very detailed and valuable analysis of over 37,000 echocardiographic studies to assess tricuspid regurgitation in permanent paced patients. A selected chronic stimulated group (excluding patients with pathologies that initially may cause tricuspid regurgitation) showed a statistically significant higher presence of tricuspid regurgitation compared to control group. Multivariate analysis of this group stated that independent risk factors of developing significant moderate and severe tricuspid regurgitation include the presence of pacemaker electrode in the right cavities, mitral regurgitation, the size of left atrium and left ventricular endsystolicdiameter. The main mechanisms responsible for this situation were strong fibrinous reactions of electrode adhered to endocardium and valves, iatrogenic valve perforation, abnormal intraventricular conduction and interventricular dyssynchrony or impaired left ventricular hemodynamic function caused by atrioventricular dyssynchrony. In this last case back

ventriculo-atrial conduction plays the main role in the loss of active phase of ventricular filling, which finally reduces cardiac output by 20–30%. A lot of available reports describe the problem of tricuspid regurgitation but only a few of them explain its prognostic value. Jayant Nath et al. [11] demonstrated a worse prognosis and annual survival associated with degree of tricuspid regurgitation mainly in aspect of worse left ventricular function and presence of pulmonary hypertension. The authors also stated that severe tricuspid regurgitation is associated with a worse prognosis and survival regardless of age, left and right ventricular systolic function, right ventricular dimensions and inferior *vena cava* enlargement.

## Left Atrium and Mitral Valve Dysfunction – Atrial Fibrillation

The atrial fibrillation is the most common arrhythmia in patients with heart failure (about 45%) and is associated with worse prognosis. On the other hand, chronic heart failure is one of the most common pathomechanism of the atrial fibrillation beside mitral valve dysfunction, heart ischemia, hypertension, obesity, thyroid gland dysfunction, chronic lung disease, inflammations (sarcoidosis) and genetic predispositions (in example mutation of the lamin AC gene associated with atria fibrosis). The pathomechanism of the atrial fibrillation is composed of structural changes within the atria tissue (fibrosis) made by different diseases and triggers that release the arrhythmia (reentry, provoked activity or pathological automatism). This situation leads to the activation of the rennin aldosteron angiotensin system (RAAS) and causes fibrinosis, adverse remodeling and loss of atrial muscle mass, which is the main pathomechanism of atrial fibrillation. There are varieties of single and multifocal triggers like dyselectrolitemia, hyperthyroidism, chronic stress or intense and prolonged exercise, some toxic substances like (alcohol and nicotine) that can provoke the incidence of atrial fibrillation. Stambler B.S. MD et al. [12] suggested that chronic RVA stimulation is associated with a higher risk of atrial fibrillation incidents and heart failure development in the case of left side cavities dilatation, short atrio-ventricular delay and accessory electrical impulses which acts like a trigger. The main potentially arrhythmogenic areas within the atria are parts around the veins where the atrial tissue connects to the vein tissue. These sites are typically the aim of the ablation procedure in order to eliminate the arrhythmia. It was also proved in many trials that dual chamber stimulation (DDD) with atrio-ventricular delay (preferable about 100–120 ms) significantly reduces incidents of atrial fibrillation. As the atrial fibrillation is one of the most typical risk factors of heart failure decompensation and is connected with poorer prognosis especially in group with reduced LVEF ≤ 35%, NYHA class III, IV, and QRS over 120 ms ESC Guidelines 2013 recommends CRT implantation in case of adequate rhythm control and improved left ventricular function (class IIa indication). In case of uncontrolled heart rate despite adequate medical treatment or incomplete biventricular pacing (BiV) atrio-ventricular junction ablation is also recommended (class IIa indication) [13].

In 2010 Rita Miranda et al. [14] continued problem of left atrium dysfunction. The authors first described acute mitral regurgitation complicated by pulmonary edema caused by RVA stimulation in short time observation. Moreover, changing to RVOT stimulation she received immediate improvement in mitral valve function with clinical signs of pulmonary edema regression. She explained this unusual situation as abnormal electrical and mechanical activation of each papillary muscle within left ventricle caused by interventricular dyssynchrony as result of RVA stimulation.

## Left Ventricular Heart Failure – Clinical, Hemodynamic, Neurohumoral Parameters and Quality of Life

A lot of publications refer adverse consequences of chronic RVA stimulation on cardiac function including left ventricular dysfunction, re-hospitalization in case of cardiac decompensation, development of heart failure and increased risk of death. In a study of Ewa Lewicka-Nowak et al. [15] with 90 months follow-up patients were randomized in 2 subgroups RVOT vs RVA. Clinical status was assessed using NYHA class, echocardiographic parameters of left ventricular function and heart valves, QRS duration and level of NT-proBNP in blood. Patients with initially normal left ventricular function were included into trial. The study confirmed superiority of RVOT over RVA stimulation. RVA group showed left ventricular systolic function deterioration with tricuspid insufficiency aggravation and heart failure symptoms in NYHA class exacerbation. Patients in the RVOT group had significantly lower natiuretic peptide (NT-proBNP) levels that reflect heart failure severity and they also had better intraventricular conduction parameters due to a reduction of QRS complex duration in ECG. In conclusion, researchers suggested that permanent RVA

pacing in patients with primary normal left ventricular function may lead to left ventricular and valve function deterioration. Moreover, they stated that RVOT pacing can reduce the intervetricular dyssynchrony effect which is probably responsible for cardiac remodeling process. Furthermore, lower BNP peptide levels in RVOT group were equal with better ventricular systolic function. Many studies confirmed these suspicions. Thambo Jean-Benoit et al. [16], using Doppler technique and exercise test, demonstrated in a 5-year follow-up that chronic RVA stimulation was associated with higher interventricular dyssynchrony, left ventricular adverse remodeling with dilatation, asymmetric muscle hypertrophy and limitation in physical activity tolerance. Data collected from these studies underline crucial meaning of correct sequences of heart activation and proper way and delay of electrical impulse propagation through His-Purkinie system in pathogenesis of cardiomyopathy and heart failure in chronically stimulated patients. In a study of Cláudia Drummond Abreu Guimaraes et al. [17] researchers revealed another problem of long-term RVA stimulation – neurohumoral dysfunction – resulting in higher morbidity and worse myocardial viability. Decompensated heart muscle is exposed on very high forces and tensions that act on internal walls of the cavities extending them and forcing the heart muscle to work harder (Starling rule). This situation increases blood and oxygen consumption and releases more natiuretic peptides to the blood circulation. The NT-proB-NP level in blood correlates with an overload of the cardiovascular system. Moreover, deficiency of the nutrition and oxygen changes the myocardial cells to anaerobic metabolism. This situation significantly reduces the ability of myocardium to contract properly – muscle cells are in shock – deteriorating mechanical and neurohumoral function of the heart, aggravating heart failure, supra and ventricular arrhythmias, causing fibrosis, adverse muscle remodeling and increasing the risk of sudden cardiac death. If this situation lasts too long, muscle cells die, releasing cardionecrotic enzymes (CK-MB, troponin) – this state is irreversible – high specialized muscle cells are replaced with connective tissue. But in some cases of oxygen stress, muscle cells possess the capacity to limit contractility, which reduces metabolic demand, thus allowing the cells to survive the unfavorable period and recover their function. In clinically stable patients without signs of heart failure, RVA pacing with related interventricular dyssynchrony was an independent factor of NT-proBNP level increase regardless of age and left ventricular function. On the other hand, there are some publications, such as Bruce S. Stambler et al. [18] that state no differences between RVA vs RVOT and biventricular (CRT) pacing method in patients with heart failure and atrial fibrillation in 9 months observation. Moreover, they also did not prove the superiority of these last 2 methods in improving the quality of life (QOL). A different period of observation explains the most possible mechanism of discrepancies across these studies. To develop stimulation-induced heart failure at least one year of observation is required.

## Pathomechanisms of Chronic-Stimulated Heart Failure Abnormal Blood and Adrenergic Myocardial Perfusion

E. N. Simantirakis et al. [19] showed that RVA stimulation, besides blood perfusion disorders in the area of stimulation, also causes disturbances in adrenergic conduction system. This data proves the theory of correlation between the specific place of stimulation and its adequate effect on electrical impulse conduction system and regional blood perfusion.

## Aberrant Pathway Activation – Interventricular Dyssynchrony

Right ventricular apex stimulation is an artificial way of heart stimulation through working muscle cells omitting physiological conduction pattern of His-Purkinie system. This situation reduces the spread of electrical potential and makes it more aberrant than through specialized conduction muscle cells within His-Purkinie system. Ventricular activation in this case becomes more heterogeneous with early activation near implanted electrode and increasingly delayed as it moves further from origin of stimulation. This results in interventricular dyssynchrony which finally leads to chronic heart failure. This pathomechanism of stimulation-induced heart failure was confirmed by Prinzen and Wyman et al. [20]. Probably the same mechanism is responsible for the aggravation of mitral and tricuspid valve regurgitation. Nonsynchronous and delayed papillary muscle contraction caused by iatrogenic RVA pacing can lead to leaflets closure time asynchrony, which may escalate their regurgitation. A lot of researchers claim also that interventricular dyssynchrony can cause disturbances in adrenergic nerve fibers conduction and abnormal blood perfusion in different parts of the heart muscle. All of this together with other mechanisms can be the pathogenesis of heart failure and premature death. A worse prognosis and

survival in patients with interventricular conduction disorders is a well-known situation, described especially by Axel Bauer et al. [21]. According to their study, wider QRS complex (greater than 120 ms) is associated with significantly higher mortality and is an independent predictor of mortality, particularly in patients with heart failure. The same results of poor prognosis related with QRS width were achieved in VEST study. The only situation in favor of apical pacing, where interventricular dyssynchrony may be accepted, seems to be pacing as a therapy for hypertrophic cardiomyopathy according to the European Society of Cardiology Guidelines 2013. Pacing creates pre-excitation of the right ventricular apex, which changes the ventricular contraction pattern and creates regional dyssynchrony. The result is late activation of the basal part of the septum and decreased LV contractility, which reduces the systolic anterior motion of the mitral valve and the severity of LV outflow tract obstruction.

## High Rate Stimulation and Its Chronic Nature

Another problem of chronic stimulation seems to be over-stimulation. Many studies confirmed the adverse impact of a high pulse rate on the survival and long-term prognosis. In 2002 results of DAVID study showed that permanent stimulated patients with heart failure and implanted cardioverter-defibrillator had a 60% higher risk of re-hospitalization or death than patients who were periodically stimulated [22]. Another work of Zhang et al. [23] demonstrated that in a group of 79 patients who underwent right ventricular pacing for more than 90% of time, 25% developed systolic heart failure within 8 years after implantation. It was also noted that, although chronically stimulated patients develop left ventricular systolic dysfunction similar to that of heart failure, the structure of their chambers does not become as dilated and reconstructed as in a classical case of heart failure. This suggests that we are dealing with a new, unique phenotype of heart failure – chronically--stimulated heart failure.

## Methods of Treatment

Long-term adverse effects of chronic RVA stimulation and the necessity of its extensive use forced researchers to develop various methods to minimize these side effects. The main solutions are: reduction frequency of stimulation, prolongation of atrio-ventricular conduction and pacing alternative sites of right ventricle e.g. right ventricular outflow tract (RVOT), septal (RVS), direct stimulation of His-bundle (DHBP) and biventricular stimulation (CRT).

## Reduction Frequency of Stimulation

One way to reduce the negative effects of chronic stimulation is to reduce stimulation rate. In 2005 Sharma et al. [24] analyzed DAVID study which showed the benefits in terms of mortality and re-hospitalization reduction in patients periodically stimulated (below 40% time of stimulation) compared to the control, which was the permanently stimulated group. Similar results were achieved in MOST study. A subgroup of 707 patients biventricular stimulated showed a statistically significant reduction in the frequency of rehospitalization and the number of atrial fibrillation incidents as a consequence of heart rhythm reduction [25]. What is more, a group stimulated more than 40% of time had worse results compared to periodically stimulated group (below 40% of time). Although the follow-up period was short and there were no connections between pacing rate and mortality, the endpoint of tachyarrhythmia reduction was significant. On the other hand, it is important to note that there are some groups of patients in which the stimulation rate reduction is contraindicated. In these groups other treatments can be safely used.

## Adequate Atrio-Ventricular Conduction Delay and Contraction Synchrony

However, stimulation with physiological conduction path is necessary for optimal cardiac function nevertheless atrio-ventricular conduction delay (AVD) is the same important parameter that causes normal left ventricular preload. The role of a-v conduction delay and its absence in the case of VVI pacing with loss of atrial function is controversial and not fully explained. It is well--known that both too short and too long a-v conduction results in incomplete LV filling causing "Pacemaker syndrome". This improper situation of simultaneous atrial and ventricular contraction is not favorable for optimal cardiac hemodynamic function. An unusual experiment on animals that compared place of stimulation and a-v conduction delay showed a significant positive correlation between left ventricular ejection fraction and near-normal values of a-v conduction delay. Decreasing this value was associated with left ventricular

deterioration. Researchers Cowell et al. [26], when comparing patients RVS and RVA stimulated with heart failure, demonstrated superiority of RVS method simultaneously with a short period of a-v conduction (50–100 ms) over RVA method in case of cardiac output. They found a significant factor of a-v conduction delay time (preferably about 100 ms) that can reduce right ventricular dimension and decrease incidents of atrial fibrillation. These studies demonstrated that cardiac depolarization sequence, impulse conduction time and a-v synchrony should result in cardiac output and interventricular synchrony improvement, mitral and tricuspid regurgitation reduction and is crucial for proper left ventricle function, especially in patients with heart failure. Each of these factors may act independently and can enhance the beneficial effect of other. There are also reports suggesting muscle tissue changes – fibrosis – in the area of prolonged stimulation, which probably leads to a-v conduction problems and, in consequence, to adverse changes of the left ventricular function. Researchers postulated that the degree of left ventricular failure is inversely proportional to the origin of His-Purkinje system stimulation and that proper electrical pathway is more important in hemodynamic function than interventricular synchrony. What is more, they demonstrated on animals that abnormal left ventricular hemodynamic parameters are directly proportional to the degree of stimulated-induced walls asynchrony. By stimulating different parts of left and right ventricle, he showed differences in left ventricular function depending on QRS complex width. Therefore, it is worth noticing that the more physiological stimulation the better adverse effects of RV pacing reduction. Over the years the way of stimulation changed from typical electrical to more hemodynamic. It happens that stimulation not only protects electrically unstable heart muscle, but it also has a positive influence on its hemodynamic function, especially in patients with heart failure. In this group every small improvement in cardiac output is crucial.

## Alternative Ventricular Lead Implantation Sites (RVOT, RVS, His-Bundle Pacing, CRT)

Based on anatomical landmarks of human heart, M.C. Giudici et al. [27] defined 4 fundamental alternative pacing sites. They distinguished:

1. Right ventricular inlet septal pacing: a) a place described as above at or below ring around anterior-septal leaflet of tricuspid valve, b) a relatively normal QRS morphology and axis.

2. Right ventricular infundibular septal pacing: a) stimulation proximal to pulmonary valve, distal or near linea supraventricularis, b) cause left branch bundle block and vertical axis.

3. Right ventricular outflow septal pacing: a) most often defined as RVOT, b) close to septal band in middle of interventricular septum, c) cause left branch bundle block and vertical axis.

4. Right ventricular apical septal pacing: a) stimulation proximal to septal conduction band, b) does not produce vertical axis.

These 4 definitions describe separate anatomical, radiological and electrophysiological places of ventricular lead implantation that should help clarify and standardize results.

Unfortunately, a number of published studies about right ventricular alternative sites have separate, sometimes mutually exclusive, results. The main reasons of this inconsequence are differences in exact electrode localization.

As we know from recently reports, RVOT became the most popular alternative site of lead implantation. But there are some studies that reveal differences within this method of implantation and achieved results. A work of A. McGavigan et al. [28], which characterizes exact implantation sites within RVOT, confirms those suspicions. In order to avoid mistakes and assess the exact implantation site strict criteria of implantation technique were set. According to these criteria 12-lead electrocardiogram and standard radiographic projections are necessary. Narrow QRS complex and negative deflection of first lead in ECG provide septal region. What is more, backward deflection of electrode in lateral radiographic projections (LAO and LL) in 100% indicates the septal site. Wide QRS complex and electrode deflected into the bottom wall specify free wall implantation. According to the above-mentioned criteria, from 150 patients included into the study of A. McGavigan et al. who underwent RVOT implantation, 18 had an electrode implanted below outflow tract. The majority of the remaining 132 patients (94%) had an electrode placed into the position of low-RVOT. From this group 81 electrodes were implanted in the area of septum and 51 into the free wall. The summarized research shows different electrode implantation results in relation to the surgeon. These discrepancies are the reason why the benefits of alternative pacing sites described in the literature are uncertain. In addition, work of McGavigan underlines crucial role of X-ray and ECG studies in determining the exact position of the electrode implantation.

## Right Ventricular Outflow Tract

The tip of the right ventricle is a widespread, easily accepted and standard site of right ventricular lead implantation. However, there is considerable evidence which points to adverse effects of long-term stimulation in this classical method, including interventricular conduction dyssynchrony and an associated higher risk of heart failure. Consequently, scientists devoted much more time and attention to finding other and more physiological sites of right ventricular stimulation that could reduce the unfavorable effects of long-term stimulation. From 3 available sites (RVOT, RVS and His-Bundle Pacing) the most common is the right ventricular outflow tract stimulation (RVOT). Many studies suggested that there is a sudden improvement in the left ventricular function and resynchronization process compared to the RVA method. In cross-over studies assessing RVOT vs RVA method Yamano et al. [29] showed better synchrony and coronary blood perfusion in the study group. This data is difficult to prove in short term observation, which means that only a long period of stimulation brings adverse hemodynamic effects. In a study of Victor et al. [30] there were no differences in the width of QRS, ejection fraction, NYHA class and exercise tolerance after 3 months observation between analyzed RVOT and RVA groups.

## Right Ventricular Septum

The RVS stimulation showed the potential benefits in comparison to the RVA method in many studies. Authors Cano et al. [31] showed ventricular contraction synchrony improvement in 32 patients RVS vs 28 patients RVA stimulated without improving the quality of life in NYHA class and exercise capacity. In contrast to previous reports, Cho et al. [32] found no differences in contraction synchrony between 2 analyzed groups – RVS vs RVA.

## Direct His-Bundle Pacing

Several small studies showed benefits in synchrony and left ventricular function during stimulation around His-bundle area vs RVA. Recent reports suggested that direct His-bundle stimulation with similar to proper intraventricular and interventricular conduction can be reached in 85%. Authors Zanon et al. [33] demonstrated that stimulation around His-bundle area improve synchrony, coronary blood perfusion and mitral valve function when compared to RVA method in a cross-over, 3-month observation study. Furthermore, Pramod Deshmukh et al. [34] showed that DHBP in a selected subgroup of patients with atrial fibrillation and dilated cardiomyopathy can reduce ventricular dimensions, improve interventricular synchrony and cardiac output.

## Biventricular Stimulation Cardiac Resynchronization Therapy

Another situation is stimulation 2 chambers at the same time – biventricular stimulation or CRT as an alternative method to single chamber pacing. This method is strictly recommended for patients with an indication for stimulation due to bradycardia or atrial fibrillation with adequate rate control (pharmacological or after atrio-ventricular junction ablation) and with chronic, advanced heart failure (LVEF ≤ 35%, NYHA functional class II, III or ambulatory IV despite adequate medical treatment and prolonged QRS duration over 120 ms). The best responders for CRT are patients with wide QRS complex, left bundle branch block, female sex, and non-ischaemic etiology of heart failure. According to the ESC Guidelines, CRT is not recommended for patients with chronic heart failure and short QRS duration under 120 ms (III B class indication). This method, when used in very specific indications, can improve atrio-ventricular, inter and intra ventricular synchronization and decrease the possibility of heart failure development in the long term, especially in patients with baseline impaired intraventricular conduction such as left branch bundle block or prolonged QRS duration over 150 ms. The superiority of biventricular pacing over classic RVA method was showed in a randomized, cross-over HOBIPACE study [35]. Research enrolled 30 patients with intraventricular conduction block and present left ventricular dysfunction. This study showed a significant improvement in left ventricular dimensions, ejection fraction, quality of life and physical capacity in CRT group vs RVA group just after 3 months observations. Researchers Brignole et al. [36], in a long-term study, analyzed a group of 186 patients after sinus node ablation and randomized them into 2 subgroups CRT and RVA. Tough endpoints such as probability of death, rehospitalization or heart failure decompensation were significantly against the RVA group. On the other hand, many questions remained unanswered. First of all, which patients are the best candidates for CRT implantation, keeping in mind that many of them do not present side effects of chronic stimulation. Moreover, how to select those patients who really take benefits from CRT? What is more, there

are many studies comparing CRT vs RVA groups, but there is none that compares CRT with other alternative methods of stimulation, such as RVOT or RVS. Perhaps the RVOT or RVS method will result in similar benefits as the more risky CRT procedure with related higher risk of inflammation, fibrosis, electrode and valves blood clots and vegetations and a higher probability of wall perforation. Is the benefit-cost ratio good enough to make CRT the method of choice and standard procedure of chronic stimulation? The following is the opinion of the European Society of Cardiology from 2013 on cardiac pacing and cardiac resynchronization therapy: "There is emerging evidence that *de novo* CRT implantation may reduce HF hospitalization, improve quality of life and reduce symptoms of HF in patients with history of HF, depressed cardiac function and a bradycardia indication for pacing. The benefit should be weighed against the added complication rate and costs of CRT devices and their shorter service life. The quality of evidence is low and further research is likely to have an important impact on our confidence in the estimate of effect, and may change the estimate."

Nevertheless, cardiac resynchronization therapy (CRT) has its place in the European Society of Cardiology Guidelines from 2013 as high class recommendation method [37].

To summarize, a number of studies demonstrate the benefits of selecting alternative sites of stimulation. On the other hand, several researches contradict these reports. This discrepancy makes us believe that the current studies seem to be relatively small with a short follow-up. Therefore, large, multi-center, randomized and prospective studies are required to clearly demonstrate the benefits of alternative sites stimulation.

## Safety and Efficacy of New Methods

Another problem is the technique of ventricular lead implantation. Used so far in RVA procedure, passive fixation between papillary muscles seems to be ineffective in case of RVS and RVOT, although it was associated with fewer complications of electrode dislocation. On the other hand, active fixation as a repeatable and safe method carries the risk of wall perforation and higher probability of electrode dislocation, especially in RVS and RVOT method, where the structure of the wall is thinner than in apex. Referring to the specific data about safety and efficacy of the new implantation techniques, we should not forget the work of Stephen C. Vlay et al. [38] who assessed 460 patients undergoing RVOT implantation for treatment effectiveness, complications and electrophysiological parameters. Implantation success was achieved in 84% over a 9-year follow-up and 92% in the last 4.5 year. No abnormalities were observed in the stimulation and sense parameters. There was 1 case of electrode dislocation. Long-term electrode stability and performance was satisfactory. No acute and chronic complications were associated with implantation procedure. Authors Richard J. Hillock et al. [39], based on many years of experience, reported 61% effectiveness of standard RVOT electrode implantation technique. These methods require active fixation and specialized "stylet" electrode with rear angulations. On the basis of available data, the authors estimated that the correct RVOT position can be achieved in 90% in the case of properly performed procedure by an experienced surgeon, and with the use of active fixation. From 316 implanted electrodes using traditional techniques both in RVOT and RVA, 7 dislocations were obtained. Additionally, there were few serious complications. On the other hand, excellent results were obtained by using the new "stylet-driven" type of electrodes and new active fixation techniques. In 500 cases an established septal position was achieved without any complications. In addition, correct sensing and pacing parameters without starting blocks were achieved. Authors Michael C. Guidici et al. [40] in a 5-year observation confirmed the safety and efficacy of pacemaker and defibrillation electrode implantation in RVOT position. In the above experiment there were no electrode dislocation cases, inappropriate shocks, cardiac sensing and pacing abnormalities. It was found that this method is safe, effective and potentially beneficial in the prevention of stimuation-induced heart failure. Moreover, Erdoan Okan et al. [41] proved in 38 months observation safety of RVOT pacing. Researchers analyzed parameters such as impedance, stimulation and sensing parameters, electrode dislocation. In regards to the anatomical location, RVOT method prevents against free wall perforation, pericardium inflammation and diaphragm or intercostals septum stimulation. The main problem associated with the new technique is to locate a precise implantation site in order to ensure easy and reproducible electrode placement. For this purpose, standard fluoroscopic projections and 12-lead electrocardiogram are crucial. European Society of Cardiology 2013 Guidelines, based on meta-analysis of 14 RCTs, present the benefits of pacing from alternative right ventricular sites compared to apical pacing in the case of better left ventricular ejection fraction, especially in the group of patients with initially reduced LVEF < 45% in at least a 12-month follow-up. The complication rate of non-RV apical pacing is similar to that of RV

apical pacing. On the other hand, because of non-significant difference in the group with preserved LVEF > 45% and uncertain results with respect to exercise capacity, functional class, quality of life and survival, the Task Force of ESC was unable to give definite recommendations until the results of larger trials become available. All in all, alternative ventricular lead implantation sites are considered to be the safest treatments under the condition that the appropriate techniques are used by a well-qualified medical personnel and with professional equipment. Keeping in mind that there is a constant need for continuing research and gaining experience about safety and efficacy of these new methods.

# Discussion

## Treatment Patients with Stimulation-Induced Heart Failure

It seems that improving both left ventricular systolic function and interventricular contraction synchrony can be the most effective method of treating chronically stimulated patients. It is proven that reducing the rate of stimulation, prolongation of atrio-ventricular conduction and alternative site stimulation can be crucial in prevention and treatment of patients with pacing-induced heart failure. Authors Foley et al. [42] demonstrated similar benefits in terms of left ventricular function, quality of life and clinical symptoms in both analyzed groups of patients – RV-stimulated with upgrade to CRT and initially CRT-stimulated. On the other hand, the European Society of Cardiology Guidelines from 2013 provide different recommendations for patients with indications for upgrading to CRT from conventional PM or ICD as a result of deterioration of heart failure secondary to high percentage of ventricular stimulation (I class indication) and *de novo* CRT implantation in patients with heart failure and indications for stimulation (II class indication) [43]. These recommendations are highly debatable. Therefore, if we want to set new pacemaker implantation standards that can simultaneously protect against heart failure development in the future, new alternative ventricular pacing sites should be considered as a method of choice. A consensus confirmed by long-term, randomized, prospective studies and appropriate patients selection to the researches is required. According to the recent studies, the first line beneficiaries of new therapy should be patients with advanced heart failure and intraventricular conduction disorders.

Alternative ventricular lead implantation sites are budding, along with improved treatment for patients requiring chronic stimulation. Electrophysiologists should be aware of these techniques, especially in patients with heart failure. There are many indications in which alternative pacing sites could replace previously used methods of right ventricular apical pacing, as a better alternative of chronic stimulation.

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