# Does right ventricular pacing increase the risk of ventricular arrhythmias in patients with an implantable cardioverter-defibrillator?

## Czy stymulacja prawokomorowa zwiększa ryzyko groźnych arytmii komorowych u chorych z implantowanym kardiowerterem-defibrylatorem?

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## INTRODUCTION

The use of therapy with implantable cardioverter-defibrillators (ICD) allows for significant improvement in survival in patients with systolic heart failure (HF), reducing both the incidence of sudden cardiac death and all-cause mortality [1–3]. Currently available devices, in addition to the discontinuation of life-threatening ventricular arrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF), also have the function of right ventricular (RV) pacing, which is particularly useful for the prevention of significant bradycardia in the period after discharge.

However, findings from clinical studies about pacemakers or ICD indicate that RV pacing in patients with left ventricular (LV) systolic dysfunction is associated with an increased risk of HF, increasing the frequency of hospitalisation and possibly death from this cause [4–6]. This effect may in part be responsible for the observed shift, in the era of the ICD, in the causes of death among patients with systolic HF, who currently most often die because of HF, while the arrhythmic death rate compared to previous observations has decreased [7]. But there are also reports suggesting that RV pacing with ICD may promote the occurrence of VT/VF episodes, requiring intervention of the device, which also would contribute to a possible increase in mortality and thereby reduce the prognostic benefits of ICD therapy [4, 5]. This problem seems to be very important, especially since a different number of episodes of ventricular pacing with an ICD may also occur in patients who do not have indications for permanent pacing. Patients with HF are in this regard particularly vulnerable, because due to the structural damage of the heart and the chrono- and dromotropic negative impacts of used beta-blockers and/or amiodarone, they are exposed to automatism and conduction disorders which facilitate RV pacing.

## RIGHT VENTRICULAR PACING AND THE OCCURRENCE OF VT/VF EPISODES

The possibility of harmful effects of RV pacing in patients with reduced LV systolic function with an ICD was pointed out after the announcement of the results of the Dual Chamber and VVI Implantable Defibrillator study (DAVID) which compared the effects between the application of a dual-chamber device programmed to DDDR mode with a base rate of 70/min, and a single-chamber device programmed to VVI 40/min mode, in a group of 506 patients with systolic HF. During this observation (median of 8.4 months), a higher incidence of the combined endpoint including death and hospitalisation for HF in patients with dual-chamber pacing was noticed, and a post-hoc analysis of the collected data showed that the reason for this was a much higher incidence of RV pacing in this group of patients [8, 9]. It should be noted that this group consisted of patients without indications for permanent pacing, so RV pacing here was a somewhat unintentional side effect of DDD mode with a high base rate of stimulation. In this study, however, the possible influence of a high percentage of such stimulation on the occurrence of episodes of ventricular tachyarrhythmias was not investigated. However, further observations have provided these findings.

Smit et al. [10] analysed a group of 456 consecutive patients without overt HF, but most of them had mild LV systolic dysfunction (mean LV ejection fraction [LVEF] 40%),

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who were implanted with an ICD. They found that an overall percentage of RV pacing > 50% was associated not only with a higher incidence of HF, but was also an independent predictor of ICD shocks. 25% of the surveyed patients experienced high-energy therapy, while in a subgroup stimulated over 50%, the interventions occurred in a larger number of patients (34% vs. 21%), and the time to the first intervention of device was shorter compared to the subgroup with the percentage of stimulation not exceeding 50% [10]. Post-hoc analysis of data from the MADIT II trial involving patients after myocardial infarction with LVEF ≤ 30% taking into account the 567 patients randomised to ICD implantation with known percentage of RV pacing also showed a higher probability of adequate ICD therapy (antitachyarrhythmic pacing and shocks) in the group stimulated at > 50% [4].

The results of these observations are very similar, despite significant differences in the characteristics of the examined populations. In the analysis of Smit et al. [10], patients with mild LV dysfunction receiving the ICD significantly prevailed in secondary prevention; in most cases, it was also a dual chamber system. The MADIT II trial involved patients with severe LV systolic dysfunction qualified for an ICD in primary prevention, and dual chamber systems were implanted in 46% of patients [4, 10]. It seems that a large amount of RV pacing in a population of patients with implanted ICD and reduced LV systolic function has not only the previously known adverse effect of favouring the progression of HF, but also has a clear pro-arrhythmic effect.

It is not clear what exact proportion of such stimulation is enough to induce the above-mentioned detrimental effects. In these observations, 50% was taken as the cut-off value, but the analysis of the distribution of the percentage of ventricular pacing in the surveyed populations indicates that, in fact, patients hardly stimulated were comparable (median of stimulation in stimulated subgroups ≤ 50% — 0% in the study of Smit et al. [10], and 0.2% in the analysis of data from MADIT II [4]) with those stimulated almost completely (medians of percentage of stimulation in stimulated subgroups > 50%, 96% and 95.6%, respectively). The study by Gardiwal et al. [11] provides relevant information in this regard. It evaluates the impact of the total percentage of RV pacing on the incidence of episodes of VT/VF in the group of 245 patients with implanted ICD, mainly in secondary prevention. In this case, the researchers assumed a very low cut-off point of 2% only, and found that in a stimulated group > 2% the time to first occurrence of arrhythmia was significantly shorter than in a stimulated group ≥ 2%, and the percentage of stimulation exceeding this cut-off point was an independent predictor of occurrence of VT/VF. Moreover, the incidence of arrhythmic episodes increased with an increase in the frequency of ventricular pacing in the overall surveyed population. On this basis, it can be assumed that a very small amount of ventricular pacing, and perhaps any RV pacing in patients with an implanted ICD, acts in an arrhythmogenic way and that the higher the percentage of stimulation, the greater the risk of incidents of serious ventricular tachyarrhythmias and intervention of the device. Some doubt as to the validity of this thesis may indeed occur during the analysis of the retrospective results of a subgroup of 715 patients from the INTRINSIC RV trial, published by Olshansky et al. [12], which suggest that a moderate percentage of RV pacing (10–19%) may be more favourable, i.e. giving both a lower risk of death and hospitalisation for HF and a lower incidence of ICD shocks than a very low percentage (0–9%). This study, however, included only patients with an implanted dual chamber ICD system programmed in DDDR mode, and the authors took into account the shocks and not, as in most studies, all VT/VF episodes, interrupted by the ICD. It seems that the main reason for these somewhat different conclusions are methodological differences, although it is possible that for some patients some amount of RV pacing ensuring restoration of normal atrioventricular synchrony could bring some benefits. There are also reports that undermine the relationship between the stimulation of the right ventricle and the incidence of episodes of ventricular arrhythmia. Stockburger et al. [13] analysed a group of 213 patients with HF, who had an ICD implanted, and they did not notice that the cumulative percentage of ventricular pacing equal to or in excess of 30% was associated with an increased occurrence of of VT/VF incidents.

However, this result should be treated with caution, since it may result from the fact that this study surveyed subgroups that differed significantly, taking into account the number of patients (the stimulated group ≥ 30% had only 24 persons, while the stimulated group < 30% consisted of 189 people), and the combined percentage of ventricular pacing in the total population was in general very low (median 0%, interquartile range 0–2.5%).

In summary, it is clear that most observations seem to favour the proarrhythmic effects of RV pacing in patients with an implanted ICD. Moreover, as the results of the prolonged eight-year observation of patients included in the MADIT-II trial demonstrate, this effect may be a secondary, after worsening HF, cause of adverse impact of RV pacing, which leads to a significant reduction of benefits from therapy using ICD [5].

## POSSIBLE MECHANISMS OF PROARRHYTHMIC ACTION OF RIGHT VENTRICULAR PACING

Stimulation of the right ventricle, causing abnormal, similar sequence of electrical activation of the muscle in ventricles of the heart as in the native block of left bundle branch, leads to the mechanical dyssynchrony of the contraction of the heart muscle and associated load variation of individual segments. Stress of the heart wall becomes the greatest within the lateral segments of the left ventricle, which are activated at the latest, because of the impact of the early contraction

of the interventricular septum, and the activation of this area during the end-systolic period when consequent load is the greatest. These changes can lead to atioasymmetrical hypertrophy of the LV muscle and disturbance of perfusion and oxygen utilisation in the myocardium (the increase in areas of late activation, the decrease in areas activated early), and also to regional changes in autonomic innervation [14, 15]. In addition, the secondary, in comparison to dyssynchony, load polarisation of individual areas of the left ventricle can induce changes in the expression of multiple proteins in cardiomyocytes, including those involved in the processes connected to the formation of arrhythmia, i.e. in the regulation of calcium homeostasis and the conduction of electrical impulses. In an experimental model, stimulation of right ventricle caused a significant decrease in the expression of ATP-ase of sarcoplasmic reticulum (SERCA2a), phospholamban and connexin 43 in the lateral wall of the left ventricle [16]. Reduced expression of connexin 43, which is the main protein of intercellular connections within the myocardium, in several observations, significantly increased susceptibility to ventricular arrhythmias, probably as a result of a one-way slowing down of conductivity and facilitation of the creation and circulation of any reentrant wave [17, 18]. The occurrence of ventricular arrhythmias may be also favoured by other above-mentioned abnormalities.

However, it seems that the development of potentially arrhythmogenic structural changes in the heart muscle requires a rather high percentage of RV stimulation. In stimulation with relatively low, or very low, frequencies, other mechanisms are probably involved. Himmrich et al. [19] pointed out the possibility of the induction of VT/VF, even by a single paced beat, caused by sudden changes in the length of cycle of rhythm of ventricles.

If the sinus rhythm is disturbed with a single premature beat, followed by a compensatory pause, then interrupted with a paced ventricular beat, the sequence of a short-long-short RR interval period is created, causing the dispersion of refraction periods within the muscle of the ventricle, which in favourable conditions might be the basis of arrhythmia, in particular, polymorphic ventricular tachycardia. In patients with anatomical substrate of ventricular arrhythmias in a post-infarction scar, the pause belonging to such a sequence can also favour the creation of functional block in one arm of a potential loop of tachycardia, while ending it the paced ventricular beat is being conducted through the other arm and at the end of the refractory period in the first arm returns, initiating VT in a reentry mechanism.

The aforementioned researchers observed episodes of ventricular tachyarrhythmia induced with ventricular pacing (PIT — pacemaker-induced ventricular tachycardia) in 26% of the 150 analysed patients with an implanted single-chamber ICD who had no indication for permanent pacing, but in 8.6% of patients, these were the only type of VT/VF episode. In the latter subgroup, the total exclusion of ventricular pacing resulted in the complete disappearance of episodes of arrhythmia, confirming their causality to unintended stimulation of ventricle with ICD [19]. Possible participation of the described mechanism in arrythmogenic effect of stimulation of the right ventricle is also confirmed by observations by Sweeney et al. [20], who analysed data concerning 136 episodes of VT/VF observed in 204 patients covered in the PainFREE Rx II and Entrust trial, and stated that incidents corresponding to PIT occurred in 3–5% of all patients, and formed, depending on the stimulation mode, 2.6–5.2% of all episodes of arrhythmia.

## CONCLUSIONS

Many findings indicate an adverse proarrhythmic effect of RV pacing in the population of patients eligible for implanting a ICD. Such stimulation may increase the risk of serious ventricular arrhythmias requiring ICD intervention, including high-energy therapy which worsen prognosis and quality of life, leading to a reduction of the benefits from an implanted ICD. Therefore, in this case it seems fully justified to recommend limiting RV pacing. For patients who do not require pacing, the best solution seems to be implantation of a single-chamber system programmed to VVI mode with a very low basic pacing rate or hysteresis of heart rate. Implantation of a dual-chamber device may be justified in patients with dysfunction of the sinus node requiring atrial pacing, but in this case, close attention must be paid to the possibility of unintentional stimulation of the right ventricle which should be maximally reduced with the support of algorithms promoting own atrioventricular conduction or enabling changes between DDD and AAI modes. For patients requiring ventricular pacing due to impaired atrioventricular conduction, implantation of an ICD with the function of cardiac resynchronisation therapy should be considered (or an upgrade to such a system in patients with an already implanted device), but it must be borne in mind that the benefits from this strategy are sufficiently documented only in terms of the reduction of the risk of progression of HF. The issue of a reduction in the number of episodes of VT/VF has not yet been clearly defined, and is still a matter of controversy.

This is reflected in the current European Society of Cardiology guidelines on HF, which recommend implantation of the cardiac resynchronisation therapy (CRT) system in patients with LV systolic dysfunction and an indication for permanent cardiac pacing, in NYHA III or IV functional class (Class IIa) and NYHA II (class IIb) only to reduce the risk of worsening of HF [21].

Biventricular pacing improves the uniformity of LV activation and reduces imbalance within the autonomic system, so it should reduce the risk of ventricular arrhythmias [22]. But, so far, a reduction in the number of VT/VF episodes after the upgrade of the ICD to CRT-D has only been observed in single studies, involving only small groups of patients [23, 24]. Results of other observations, including large clinical trials such as

MIRACLE ICD and REVERSE, did not show significant differences in the number of interventions of devices because of ventricular arrhythmias between the groups of patients with an ICD and ICD-CRT [25, 26]. Moreover, Thijssen et al. [27] analysed a group of 115 patients whose ICD system was upgraded by adding the function of resynchronisation due to progression of HF, and they noticed no significant decline in adequate therapy from the device in the surveyed population. The trend in this direction was present only among those in whom a response to CRT expressed in a decrease of end-systolic volume of the left ventricle has been observed, whereas patients not responding to resynchronisation experienced ICD interventions even more often than before replacing the device.

Perhaps, at least in some cases, when no improvement in the remodelling and function of the left ventricle is reached after CRT implantation, the proarrhythmic effect of stimulation from the branches of the coronary sinus predominates. This effect may be related to the reversed direction (i.e. from the epicardium to the endocardium) of depolarisation within the walls of the ventricle and the subsequently increased transmural dispersion of repolarisation.

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