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Dual-site right ventricular pacing. A rescue alternative in cardiac resynchronisation therapy implantation failure? More efficient stimulation for patients with borderline cardiac resynchronisation therapy indication? Less harmful ventricular pacing?

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Abstract

Permanent cardiac pacing is nowadays a widespread method for the cure of conduction system diseases, improving quality of life and often saving patients' lives. In the twentieth century, scientific efforts were focused on extending battery life, improving sensitivity and reliability, minimizing the dimensions of the device and restoring atrio-ventricular synchrony and rate response. However, there is more and more evidence for the deleterious influence of chronic right ventricular pacing especially apical (RVA) pacing. DANISH, MOST, CTOPP and DAVID trials have proven univocally that right ventricular pacing increases risk of heart failure, atrial fibrillation and even mortality in patients with chronic heart failure. Such knowledge inspires the quest for alternative pacing sites. Right ventricular outflow tract (RVOT) became the most favourable non-apical pacing site. Since 1995 there have been several reports concerning dual-site right ventricular pacing (DuVP: RVOT plus RVA pacing) proving its beneficial clinical and hemodynamic outcome especially in the case of unsuccessful left ventricle implantation for cardiac resynchronisation therapy (CRT). (Cardiol J 2007; 14: 224–231)

Key words: dual-site right ventricular pacing, bifocal right ventricular pacing, right ventricular outflow tract pacing, alternative ventricular pacing sites

Pacing hurts

The first successful transcutaneous human myocardial stimulation was performed in 1952 [1]. Endocavitary, transvenous ventricular pacing, which is presently the most widespread type of cardiac pacing, has been commonly performed since the nineteen-sixties. Scientific efforts were focused on extending battery life, improving sensitivity and reliability, minimizing the dimensions of the device and restoring atrio-ventricular synchrony and rate response. The consequences of chronic right ventricular (RV) pacing, especially apical pacing (RVA), were emphasized in the last two decades.

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However, over 80 years have passed since the first report on the harmful influence of chronic cardiac pacing. In 1920, Koch published an experiment which proved that right ventricular pacing caused its asynchronous systole [2]. Five years later, Wiggers pointed out that epicardial ventricular stimulation extended mechanical cardiac contraction time and lowered systolic arterial pressure and its first derivative (dP/dt) in the left ventricle compared with atrial stimulation [3]. Many years passed, and then in the early seventies attention was focused on hemodynamic effects of ventricular pacing. Wiggers' results were then confirmed by Boerth and Covell on denervated dogs' hearts [4]. Badke et al. [5] have proven, also on dogs' hearts, that every ventricular stimulation causing improper interaction between asynchronously contracting heart segments leads to a 20% decrease in systole effectiveness. Coronary blood flow and oxygen consumption in a paced ventricle is 30% lower in early-activated segments and 30% higher in later activated ones. This indirectly shows regional differences in workload [6, 7]. Permanent RV pacing lowers myocardial perfusion especially in the apex and inferior wall even without coronary arteries stenosis [8, 9]. Apical pacing extends relaxation time, shortens left ventricular filling period and causes ineffective interventricular septum (IVS) systole, just like in the presence of a left bundle branch block (LBBB); during LV contraction, IVS remains relaxed and bows to the blood flow which lowers heart stroke volume, impairs mitral valve function and increases end-diastolic left ventricular volume [10].

A decade before the crucial DAVID trial, in 1993, Saxon et al. [11] showed that heart failure mortality (HF) is increased three times in patients with implanted cardioverter-defibrillator (ICD) and heart failure. The DANISH study proved that atrial pacing (compared to ventricular VVI pacing) was associated with lower mortality, incidence of heart failure atrial fibrillation (AF) and thromboembolic events [12]. These surprising results were supposed to be due to asynchronous ventricular stimulation with present sinus rhythm (SR). However, the MOST study, comparing VVI with DDD pacing, revealed that atrio-ventricular pacing (called "physiologic") did not lower AF incidence and HF hospitalisation. These end points were associated with ventricular pacing percentage but not with pacing mode. The probability of HF increased when ventricular pacing share was greater than 40% while atrial fibrillation incidence rose simultaneously [13].

The CTOPP study, similar to the DANISH study, showed the superiority of DDD pacing over VVI only in AF incidence. Overall mortality and cardiovascular and thromboembolic mortality were similar in both groups [14]. The nail in the coffin of the safe ventricular pacing idea was the DAVID trial. Over 500 patients with left ventricular ejection fraction (LVEF) of 40% or less, with no need for permanent pacing and ICD indication, were randomised. They were assigned to a backup pacing group (VVI 40/min) or dual-chamber pacing group (DDDR 70/ /min). Ventricular pacing percentage was below 3% in the first group while about 60% in the other. So-called physiologic pacing turned out to be harmful in patients with heart failure — significantly increasing heart failure hospitalisation and mortality [15].

According to the presented data, we are allowed to state that permanent right ventricular pacing causes adverse heart remodelling, decreases contraction effectiveness, lowers coronary blood flow, which finally leads to greater heart failure and atrial fibrillation incidence, and even increases mortality. Current knowledge concerning right ventricular apical pacing was presented in detail in an article by Kutarski [16].

Primum non nocere: RVOT pacing?

Although the first endocavitary lead was placed (by Furman) in the right ventricular outflow tract (RVOT) [17] its apex remains the most favourable pacing site. Since the nineteen-nineties, there have been more and more reports concerning RVOT pacing. Karpavich et al. [18] in the canine heart in 1991 and de Cock et al. [19] in the human heart in 1992 showed the advantage of RVOT pacing over apical pacing. Placing the lead in the outflow tract is safe and feasible for an experienced physician [20–22]. Giudici et al. [23] noticed a 20% cardiac output improvement right after relocating the pacing lead from the apex to RVOT. This benefit continued during follow up. Tse et al. [24] reported no change in ejection fraction during outflow tract pacing, while in the case of apical pacing it decreased significantly. Moreover, an improve in cardiac output and left ventricle (LV) filling conditions was proven by Baszak et al. [25] RVOT pacing is advantageous, especially in heart failure patients, as shown by Kutarski et al. [26].

Primum non nocere: DuRV

Cardiac resynchronisation therapy (CRT) is nowadays a reputable treatment in patients with end stage chronic heart failure [27–29]. Unfortunately, 5–15% of attempts of CRT implantation are unsuccessful due to coronary sinus/cardiac vein

anatomy, high LV lead pacing threshold or phrenic nerve stimulation. Epicardial pacing is an alternative but requires a thoracotomy and general anesthesia in patients in NYHA III–IV functional class. There are some reports indicating that dual-site (also called bifocal) right ventricular pacing (DuRV = = RVA + RVOT) improves hemodynamics and may be useful especially in the case of left ventricular lead implantation failure (Fig. 1, 2).

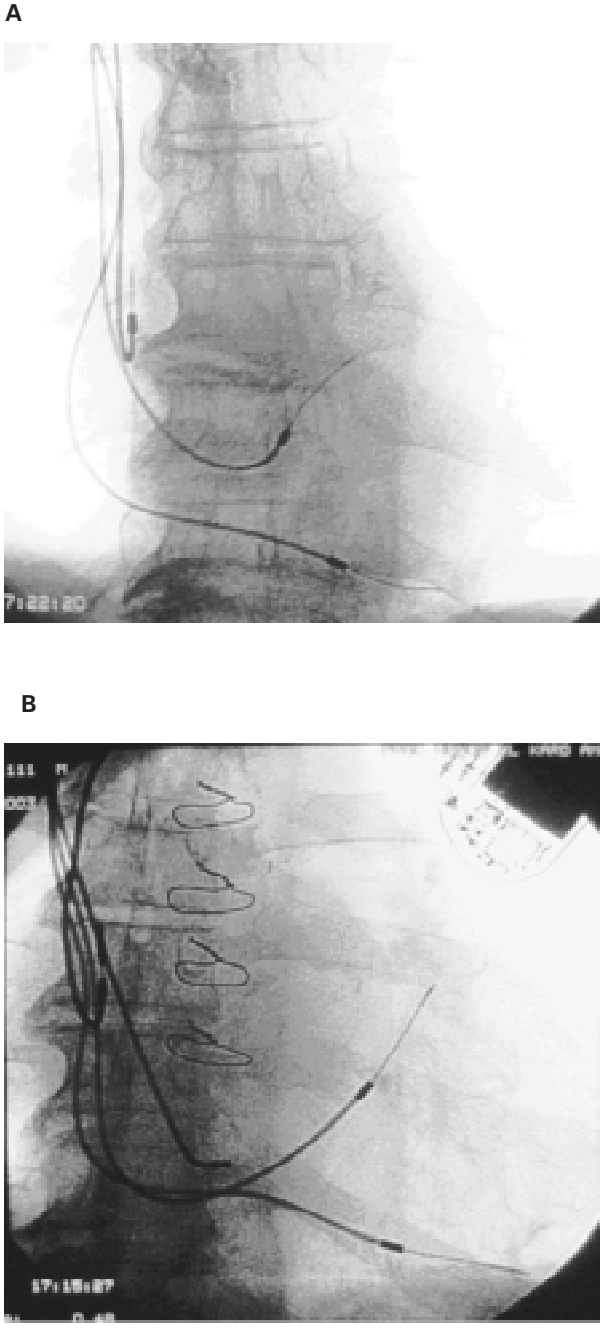

Figure 1. Dual-site right ventricular pacing: fluoroscopic view (**A**) and with bifocal right atrial pacing (**B**).

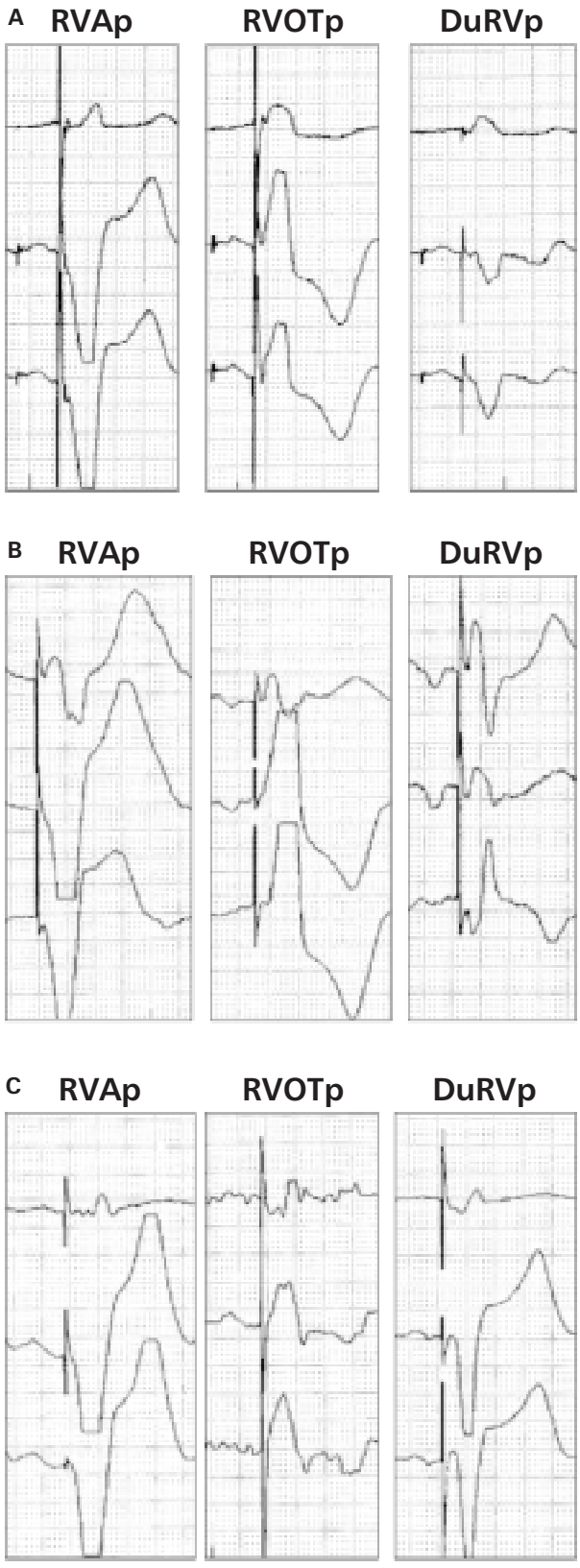

Figure 2. ECG (leads I, II, III) of three patients with apical (**A**), outflow tract (**B**) and dual-site (**C**) pacing. Major influence of ventricular activation pattern derives from the apical pacing which is due to retrograde ventricular activation via Purkinje fibers.

The first reports about DuRV were published in 1997 when Buckingham et al. [30] tested different RV pacing sites and their influence on cardiac output and QRS duration during EP studies in patients with intact left ventricle contractility. Dual-site RV pacing significantly shortened QRS length (duration) while cardiac output increase was insignificantly higher than in the case of apical pacing. Similar effects were reported by the same group of scientists a year later but in patients with LV dysfunction. In both cases, results were obtained after short, two-minute stimulation periods. Another objection is that AV delay was arbitrarily set to 100 ms in order to avoid native conduction [31] and fusion activation. Hochleitner et al. [32] observed the advantageous influence of such a short AV period in patients with drug resistant dilated cardiomyopathy (DCM), but further investigations did not confirm this concept.

In 2001, Pachon et al. [33] showed the advantage of bifocal RV stimulation not only over apical but also over RVOT pacing in a heterogeneous group of DCM patients. 39 patients (Chagas disease, ischemic heart disease, AV node ablation for tachycardiomyopathy; mean NYHA class 3.1) had cardiac pacemaker implantation with two leads in the right ventricle (RVOT and RVA) and one in the right atrium (excluding patients with AF). The ventricular leads were connected to conventional dual-chamber pacemakers. First, an active fixation ventricular lead was fixed in the high RV septum, the other active or passive fixation lead was placed in the apex. In AF patients, the septal and the apical leads were connected to the atrial and ventricular pacemaker connectors, respectively. In SR patients, it was necessary to use a Y-connector. The cathode of the ventricular channel was attached to the tip of the septal lead, and the anode was connected to the tip of the RV apex lead. This made it possible to pace bifocally, unifocally in RVA with unipolar pacing and unifocally in RVOT with bipolar pacing, when the pacing threshold was higher in RVA than in RVOT. NYHA class, quality of life (according to the Minnesota Living with Heart Failure Questionnaire), QRS duration, echocardiographic parameters (EF, cardiac output, mitral regurgitation, LV filling parameters, LA area) and LV contraction synchrony using radionuclide angiocardiography (in 6 patients) were evaluated to compare different pacing modes. Bifocal right ventricular pacing showed a statistically strong advantage over both pacing modes in each parameter. Quality of life (QOL) decreased after reprogramming to a conventional pacing in eight patients forcing the investigators to reprogram to DuRV pacing before the end of the 30-day follow-up.

Meznes et al. [34] applied dual-site RV pacing in 30 patients with Chagas disease HF (NYHA class III–IV) and atrial fibrillation. During the first 6 months of a 3-year follow-up, hemodynamic state increased to I–II NYHA class, LVEF increased and its end diastolic diameter decreased. However, after 6–12 months, all patients developed end stage heart failure in IV NYHA class, echocardiographic parameters were worse than before implantation and Holter monitoring revealed more than a ten-fold increase in severe ventricular arrhythmia percentage. Despite initial clinical improvement, the overall mortality in the first 6 months was 43% and during 3 years reached 76%, which corresponds with a natural history of Chagas disease. Six out of seven survivors had an ICD implanted. The mean time to therapy was ca. seven months. The authors do not try to explain the sudden collapse of significant clinical improvement after six months. Probably, it is due to the biological course of Chagas disease and coincidence of AF, the influence of which on cardiac resynchronisation therapy may be overwhelming.

An interim report of an ongoing BRIGHT study was presented during Cardiostim 2005. Forty patients with current CRT indications (NYHA class III, wide QRS complex, LVEF below 35%) received bifocal RV pacing systems implanted in one of several Dutch centres. A six-minute walking test, NYHA class, quality of life and LVEF were evaluated after at least seven months follow-up. Patients were randomised to backup VVI 40/min pacing or DuRV atrio-ventricular pacing groups. From the initial 40 implanted patients, only 26 of them have recorded complete follow-up. In this small group, the benefits were significant in favour of bifocal pacing in LVEF, quality of life scores and functional (NYHA) class. Moreover, five patients could not tolerate spontaneous conduction after a period of DuRV pacing. Unfortunately, until now there exists only initial analysis [35] and technical aspects report [36] of this interesting but controversial experiment.

Sodolski [37], during a temporal experiment, assessed the hemodynamic response of different right ventricular pacing sites (RVA *vs*. RVOT *vs.* DuRV) using impedance cardiography. Cardiac output, stroke volume, stroke index, cardiac index, aortic velocity and acceleration index were at their highest levels in the course of bifocal pacing, conversely to apical pacing. Kutarski et al. [38] proved in a subsequent experiment that an improvement

in systolic performance is observed especially in patients with impaired LV function.

Peichl et al. [39] examined electrical activation sequence caused by pacing from various sites using the Carto system. Of 20 patients with NYHA class III, 13 had CRT and 7 had DuRV pacemakers implanted. Left ventricular activation time (LVAT), interventricular delay (IVD) and QRS duration were evaluated during native conduction and during pacing from various sites (RVA, DuRV, BiV, LV). DuRV pacing shortened LVAT only in comparison with apical pacing. It did not decrease IVD or QRS time. There was no significant improvement in functional NYHA class in contrast to biventricular pacing during a six-month follow-up. These investigations, although conducted on a very small and heterogeneous group, suggest restraint in terms of treating DuRV pacing as an equal alternative to the cardiac resynchronization therapy.

Stambler et al. [40] did not find a clear clinical favour of bifocal pacing either. One hundred and three patients in functional II–III NYHA class with chronic atrial fibrillation had dual-chamber pacemakers with two RV leads (RVA and RVOT) implanted. The aim of this study was to compare the influence of different pacing sites on QOL, NYHA class, echocardiographic parameters and QRS duration. A group of 50 patients participated in a dual-site RV substudy (with 31 ms RVOT/RVA delay) between months 9 and 12 of follow-up. There was only a slight improvement in NYHA class (comparing to RVOT), besides there was no advantage of DuRV pacing.

The current is not all… Case reports

The majority of designed dual-site RV pacing publications are case reports describing individuals or small groups of patients after unsuccessful LV lead implantation

Chudzik et al. [41, 42], in two reports including 8 and 9 patients with bifocal RV pacing (implanted after unsuccessful CRT procedure), evaluated functional conditions using a six-minute walk test and NYHA classification and echocardiographic measurements: LVEF, stroke volume (SV), systolic (LVSD) and diastolic left ventricle diameter (LVDD), cardiac output (CO), cardiac index (CI), isovolumic contraction (ICT) and relaxation time (IRT), interventricular mechanical delay (IVMD) and ejection time (ET) and QRS duration. LVDD, SV, IRT, ET and QRS times remained unchanged. All other parameters and clinical markers improved significantly during a three-month period of bifocal pacing [41, 42].

Vlay [43] evaluated NYHA class in 22 patients after unsuccessful CRT implantation followed by using a DuRV pacing type. This is how the functional class advanced during a seven-month follow-up: (during a seven-month follow-up, the NYHA class improved as follows:) IV → I (n = 6 patients), IV → II or III → I (n = 10), IV → III or III → II (n = 3), no change in 3 patients [43]. Malinowski and Jacob [44] compared the clinical outcomes of CRT in patients with chronic AF and SR. Six of forty-nine patients had an additional lead implanted in RVOT after LV lead placement failure. DuRV patients improved in NYHA class and left ventricle ejection fraction, likewise CRT patients (results were statistically insignificant due to the small number of DuRV patients). QRS duration and mitral regurgitation (which was initially small in the DuRV group) remained unchanged. O'Donnell et al. [45], in a similar work in patients with sinus rhythm, showed that dual-site RV pacing reduces heart failure hospitalisation time, increases physical efficiency (NYHA class and six-minute walk test), improves EF, LV contraction synchrony and decreases mitral regurgitation and QRS duration time comparably to CRT in twelve-month follow-up. Like in the previous work, the DuRV group was incomparably smaller — 6 patients of 44.

The next papers are single case reports. Vlay and Kort [46] describe a 62-year old patient with an ICD and severe heart failure in III NYHA class. An attempt to implant a CRT system was unsuccessful due to coronary sinus anatomy, so a bifocal RV pacing system was applied. A clinical (II NYHA class, QOL) and hemodynamic (impedance cardiography) positive response and significant brain natriuretic peptide level decrease was observed within the first week after the procedure. However, after three weeks, all clinical parameters returned to initial levels. It turned out that due to Twiddler's syndrome, the RVOT lead dislodged. After replacement, the patient rapidly recovered, and after 12 months his NYHA class improved to I. The same author reports two patients whose NYHA class lowered by one and two levels after applying bifocal pacing but the follow-up period was very short (8 weeks) [47]. Satish et al. [48] describe a 46-year old patient with IV NYHA class heart failure, chronic AF and a permanent ventricular pacemaker implanted seven years previously. He had a CRT successfully implanted and improved to II NYHA class. However, after 17 months, CRT was replaced by DuVP due to a high LV threshold and battery depletion. During 12 weeks of follow-up, the patient remained in II NYHA class.

Technical aspects

The implantation procedure was similar in most of presented works. First, the active or passive fixation ventricular lead was placed in the RV apex. The other one was implanted in the high RV outflow tract, which was identified with fluoroscopy (the active fixation lead was screwed in just below the pulmonary trunk valve) and with ECG (positive QRS complexes in II, III, aVF and negative or biphasic in I). The atrial lead was usually placed in the right atrial appendage. Pachon et al. [33] used dual-chamber pacemakers with a Y-connector, as described above. In other cases, CRT dedicated pacemakers were used in patients with sinus rhythm while in AF patients the RVOT and apical leads were connected to the atrial and ventricular connectors of a dual-chamber device, respectively. In all cases, pacing and sensing parameters were within acceptable ranges. Ventricular signal amplitude was usually slightly lower in RVOT than in RVA. An "interventricular" delay (i.e. RVOT-RVA delay) was programmed, according to the limits of the pacemaker, between 0 and 50 ms — the outflow tract lead was paced as the first one. In O'Donnell's report, it was optimised echocardiographically and ranged between 4 and 36 ms. In dual-chamber pacemakers the lowest delay (A-V delay) possible was programmed (10–31 ms). The atrio-ventricular delay was set short to avoid native ventricular activation.

Summary

According to large, properly designed trials, there is no doubt about the deleterious influence of right ventricle apical pacing. Modern pacemakers are equipped with algorithms minimizing ventricular pacing, but in patients with conduction system disease there is no way to exclude it. Cardiac resynchronisation therapy, which eliminates, or at least reduces, ventricular asynchrony, is a solution for a narrow group of patients who may not have typical indications for permanent pacing. There are more and more enthusiasts of alternative pacing sites. Until now, there have not been randomised trials proving the advantage of dual-site ventricular pacing over apical or RV outflow tract pacing. However, reports published to date, especially works describing hemodynamic improvement after CRT implantation failure or keeping positive response after replacing CRT by DuRV pacing, let us assume that bifocal pacing is hemodynamically efficient (or at least less harmful than RVA pacing). Obviously, the presented data do not entitle us to treat DuRV as an equivalent to CRT, but it may be a solution for patients who have pacing indications and heart failure before the "CRT stage" and an alternative when LV lead implantation fails.

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