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Pacing for Long PR: Who, Why and How?

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The story repeats itself. In 2009, David A Kass a pioneer in experimental CRT research, said "Remarkably, CRT was mostly developed and tested in patients first, and the speed at which the concept was translated to an approved clinical therapy was unusually quick" (1). Indeed, few years have elapsed between the first clinical report by S Cazeau et al (2) and clinical recommendations in international guidelines (3). In the meantime, randomized clinical trials, MUSTIC and MIRACLE in particular provided evidence of clinical efficacy. Animal experiments came later and allowed "understanding how CRT works at the molecular and cellular levels" (1)

The story was nearly similar for pacing therapy in long PR syndrome. In the early nineties, observational data suggested that by solely correcting major AV dyssynchrony, standard DDD pacing dramatically improved symptoms and cardiac performance (figure 1) in patients with isolated long PR syndrome (4). Despite lack of stronger clinical evidence, the ACC/AHA/NASPE 1998/2002 guidelines issued a Class IIa recommendation for permanent DDD pacing in patients with "First-degree AV block with symptoms suggestive of pacemaker syndrome." (3). Experimental evidence arrives to-day, 20 years later and is welcome (5)

In this issue of Europace, Salden F et al. aim at investigating pacing therapy for heart failure (HF) patients with the so-called atrioventricular dromotopathy (i.e. isolated AV conduction delay > 230ms with no CRT indication). They elegantly evaluated the effect of PM therapy for AV coupling restoration using a three-step approach: 1) computational simulation analysis, 2) HF porcine model and 3) clinical study enrolling HF patients. Importantly, the hemodynamic effect of AV coupling restoration was also assessed depending on right ventricular (RV) or bi-ventricular (BIV) pacing in both animal and human models. Acute hemodynamics were invasively measured through a pressure volume loop catheter introduced into the LV. Non-invasive cardiac function evaluation was performed using echocardiography included the E- and A-waves analysis and diastolic mitral regurgitation (MR). First, authors

confirmed that in patients with normal heart and long PR, restoring a “physiological” AV coupling (i.e. AV interval at 150ms) improves LV filling and reduces MR. Second, HF porcine animal’s experiments demonstrated that a mean AV interval at 157 ± 7 ms was associated with the largest improvement in LV stroke volume due to a dual effect of increased filling flow and reduced diastolic MR. Data also showed that the hemodynamic gain with AV coupling recovery is modulated by the ventricular pacing strategy since RV pacing limits this benefit with smallest stroke volume and LV filling flow compared to BIV. Lastly, a proof-of-concept study was performed in a cohort of 20 HF patients with severely reduced LVEF ($29\pm 6\%$), prolonged PR interval of 261 ± 32 ms and relatively narrow QRS (123 ± 19 ms). DDD device was programmed with paced AV-delay above 100, 75, 50 and 25% of patient’s PR interval. Authors showed that restoration of AV-coupling with BIV pacing at an AV-delay of 50% of intrinsic PR interval (i.e. 137 ± 30 ms) resulted in a significant increase of LV filling time and decrease of MR fraction. Additionally, LV pressure-volume loops analysis demonstrated that BIV coupled with a 50% AV delay of intrinsic PR interval was associated with the greatest LV stroke volume and stroke work. As previously reported, RV pacing limited this positive hemodynamic effect due to ventricular dyssynchronization. Authors conclude that these results could open a new area of pacing strategy in HF patients without CRT indication.

First-degree AV block

In the general adult population, the prevalence of 1-st degree AV block is estimated 2-3% but it has been shown that PR interval may normalize over time in up to 30% patients (6). The prognostic impact of long PR is still debated but was generally associated with an increased risk of major cardiac events. However, this was not confirmed in the largest observational study published so far (6). The excess risk may only concern certain categories of patients, mainly HF patients (7).

The isolated long PR interval syndrome

First-degree AV block can occasionally be associated with severe symptoms and major exercise intolerance, even in patients without structural heart disease. Patients prone to develop long PR syndrome are characterized by a marked PR prolongation (> 300 msec) at rest and the loss of physiological adaptation to heart rate on exercise. During exercise, PR remains stable or even increases as the RR interval shortens. In the extreme, the P wave can blend into the repolarization or even the R wave of the previous cycle, creating mechanical equivalent of 1:1 VA retrograde conduction. The hemodynamic consequences of very long PR interval at rest and the acute benefits of VDD pacing are illustrated in figure 1

In such patients, the benefit of standard DDD pacing with optimized AV synchrony may outweigh the negative consequences of RV pacing-induced LV dyssynchrony. It is known that pacing induced cardiomyopathy is of rare occurrence in normal heart patients. Thus, standard RV-DDD pacing may be an acceptable and straightforward option for symptom relief. However, in an idealistic view of long-term cardiac function preservation, other ventricular pacing configurations could be discussed, either BIV as proposed for all patients by Salden et al (5), or His-pacing as suggested by Keen et al (8). We can regret that His-pacing has been not tested by Salden et al (5).

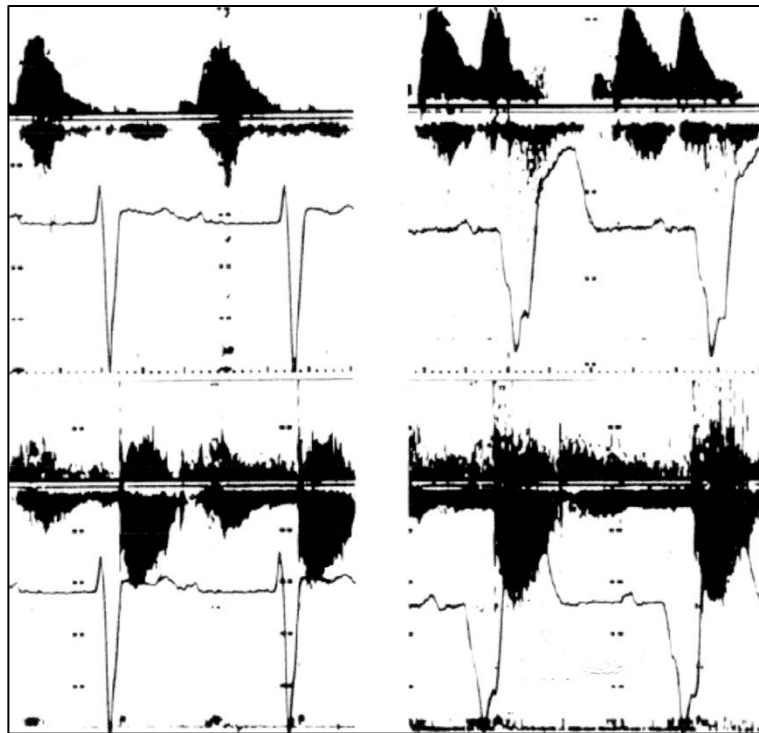


Figure 1: Male, 72 yrs, LVEF=55%, NYHA functional class III, Severe exercise intolerance. ECG: stable sinus rhythm (HR=69 bpm) with very long PR interval (400 ms). Pulsed Doppler echocardiography with simultaneous recording of transmitral blood flow (upper part) and LV ejection flow (lower part). During normal sinus rhythm (left pannel), the ventricular filling time is very short (300 msec) with an E wave alone. During temporary VDD pacing (right panel) with optimized AV delay coupling (150 msec), filling time increases by 35%. An ample and well synchronized A wave reappears. Aortic VTI increases by 30% despite complete ventricular capture.

HF patients with long PR

Baseline PR interval is an independent predictor of unfavourable outcomes in HF patients candidate to CRT but it has not been shown to predict the clinical response to DDD-BIV pacing (7). However, in non-LBBB patients, a post-hoc analysis from MADIT-CRT suggests that patients with prolonged PR (≥ 230 msec) may derive significant clinical benefit from DDD-BIV, when implantation may be deleterious in patients with normal PR (9). Few data are available in HF patients with prolonged PR but QRS duration < 130 msec. Salden et al.(5) investigated this population and clearly demonstrated that AV delay optimization resulted in acute hemodynamic improvement. Nonetheless, the choice of the ventricular pacing strategy strongly influences the benefit of restoring the AV-coupling since RV pacing, which likely creates intra-ventricular dyssynchronization, offsets the hemodynamic effect of an optimal AV-delay compared to BIV. This study may be a step toward extending CRT to a new population of HF-patients with prolonged PR and “narrow” QRS. However, acute hemodynamic data do

not mean clinical evidence. We may regret that in a first approach, simple surrogate markers like NYHA functional class, NT- pro BNP level or VO2 max were not evaluated by the investigators following PM implantation. Further clinical studies are required to assess the long-term clinical benefit of the Sadler's pacing strategy and eventually, become a guideline's recommendation.

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