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Original Article

How can we identify the optimal pacing site in the right ventricular septum? A simplified method applicable during the standard implanting procedure

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Abstract: Aims: A short paced (p) QRS duration (d) can be a marker for selecting the most appropriate RV pacing site. Although this could be achieved by continual 12-Lead ECG monitoring, such a technique is not applicable during pacemaker (PM) implantation. The purpose of this study was to validate a method for identifying the optimal site for RV septum pacing using simple markers derived from few real-time ECG leads and fluoroscopy (F). Methods and results: An overall of 304 measurements of pQRSd in different RV sites was performed in 102 patients undergoing PM implant. In accordance with F position the lead placement was classified high, medium, and low septum. Paced electrocardiographic/fluoroscopic parameters (q-wave/negative QRS in lead I, notching in limb leads, R/S wave in lead II, QRS precordial leads transition, and F septal segments pacing site) were analyzed to predict short pQRSd (≤ 160 ms). Logistic regression analysis showed that pQRSd > 160 ms was predicted by presence of pQRS notching in limb leads (OR = 3.24, p < 0.001), and with negative amplitude of QRS in lead II (OR = 2.53, p = 0.03). Short pQRSd (≤ 160 ms) was observed with mid F position (OR = 0.31, p < 0.001) and with the presence of a q-wave/negative QRS in lead I. Conclusion: In RV septum pacing, simple QRS markers of few limb leads (lead I/II) added to F position are usefull to identifying the optimal site to place the RV lead.

Keywords: Ventricular pacing, septal pacing, ECG

Introduction

The septal areas, particularly the mid-right ventricular (RV) septum and the RV outflow tract (RVOT), have been proposed as alternative pacing sites to RV apical pacing, theoretically leading to a more physiologic electrical conduction to the left ventricle (LV) and therefore to a more physiologic contraction [1]. However, some studies have demonstrated that the standard fluoroscopic (F) view alone has inherent limitations in defining the optimal site of the RV septum because of the extensive area and variable anatomy [2, 3]. Considering that RV septum is a relatively large area [3] it has been suggested to replace the term RV septal pacing with the broader term "RV non-apical pacing". The multiplicity of possible lead positions in such an alternative pacing site might explain the conflicting and controversial results reported in previous studies [4-7]. Paced (p) QRS duration (d) may reflect homogenization of contraction and it is a surrogate marker of dyssynchrony. Thus, the degree of electrical dyssynchrony induced by RV pacing can be estimated by the duration of the pQRSd [8-10]. Moreover, some studies have demonstrated that patients with a long pQRSd may be at high risk of adverse cardiac events including heart failure [8-10]. A long pQRSd can result despite the non-apical placement [11] because the lead might pace a non-favorable septal segment. Thus, the alternative to RV pacing should be the optimal septal segment and not any position in the septum. However, such approach needs continuous 12-lead ECG monitoring, thus making the pro-

cedure longer and much more complicated compared to the standard one. In order to keep the procedure as simple and fast as possible, we aimed to find few reliable real-time markers during pacemaker (PM) implant to identify the optimal anatomical locations for septal lead placement.

Methods

This prospective observational study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the local etic committee. All patients provided written informed consent prior to enrollment in the study.

Consecutive patients with standard indication to permanent PM implantation were eligible for enrollment. Exclusion criteria were significant valvular disease (mitral or aortic regurgitations of grade ≥ 2), congestive heart failure or LV ejection fraction (LVEF) < 55%. Twelve lead ECG was predisposed in each patient to measure QRSd of the native and pQRSd complex in each pacing site during the procedure. Fluoroscopic positions of the lead, together with the corresponding 12-lead ECG, were recorded for each tested pacing site.

Implanting procedure

RV septal pacing was performed using standard 58 cm 7-French bipolar steroid-eluting active-fixation leads [(Medtronic CapsureFix® Novus 5076) Medtronic Inc., Minneapolis, MN, USA] in all the patients. The ventricular lead was loaded with a stylet fashioned with a generous curve and a bent distal portion with posterior angulation. In the posterior-anterior (PA) projection, the lead was advanced into pulmonary artery and with the stylet fully inserted, the lead was then retracted from the RV outflow tract/high septal to low or apical septal. In the PA fluoroscopic projection, we arbitrarily divided the RV septum into 3 zones: (1) upper zone (one-third from the top of the RV between the pulmonary artery bulge and the roof of the tricuspid valve); (2) middle zone; (3) lower zone (one-third from the bottom of the RV). The local endocardial activation was recorded in each segment and VOO pacing was performed. The left and right anterior oblique view (45 degrees) were used to confirm that the lead was successfully placed in the RV septum and not on the free wall. As reported in our previous study [12] by the local bipolar activity we evaluate the QRS-local endocardial activation (Q-endo) delay defined as the interval between the onset of the QRS complex and the local activation into each segment. The screw was definitively deployed at the septal segment with the shorter pQRSd and the lowest Q-endo delay measured during spontaneous activation within the mapped segments.

Data collection

The 12-lead ECG derived from each septal pacing site was performed during forced RV pacing (VOO, 85 bpm) carried out at twice diastolic threshold and analysed off-line. The following pQRS parameters were evaluated: (1) pQRSd. (2) Amplitudes of Q, R, and S waves in limb lead II. The net QRS amplitude in lead II was calculated as R - (Q + S), and was used to define whether the QRS was positive, isoelectric or negative. A positive vector was defined as R - (Q + S) > 1/2 R. A negative vector was defined as (Q + S) - R > 1/2 S. As long as the dominant deflection was not more than twice as much as the reverse deflection, the vector was considered isoelectric [R - (Q + S) ≤ 1/2 R or (Q + S) - R ≤ 1/2 S]. (3) Presence of a q-wave or a negative QRS in lead I. (4) Presence of QRS "notching" in the limb leads (**Figure 1A**). (5) QRS transition in the precordial leads. Transition was defined as the lead with R < (Q + S) amplitude.

At these different sites the endocardial activation was also measured during spontaneous ventricular activation. So the local bipolar activity was recorded to evaluate the Q-endo delay defined as the interval between the onset of the QRS complex and the local endocardial activation during spontaneous ventricular activation. QRS onset was evaluated in the 12-lead electrocardiographic (ECG) recordings, and the local activity was defined as the (early) largest and steepest (faster) local bipolar potential recorded from the endocardial lead.

All measurements on ECG were performed by an independent operator. The measurements were performed manually using the digital callipers of a multichannel electrophysiology (EP) analysis system (Cardiolab, Pruka GE, Milwaukee, WI, USA). The electrograms were filtered at 30-500 Hz. Measurements were taken at a sweep speed of 100 mm/s. QRSd

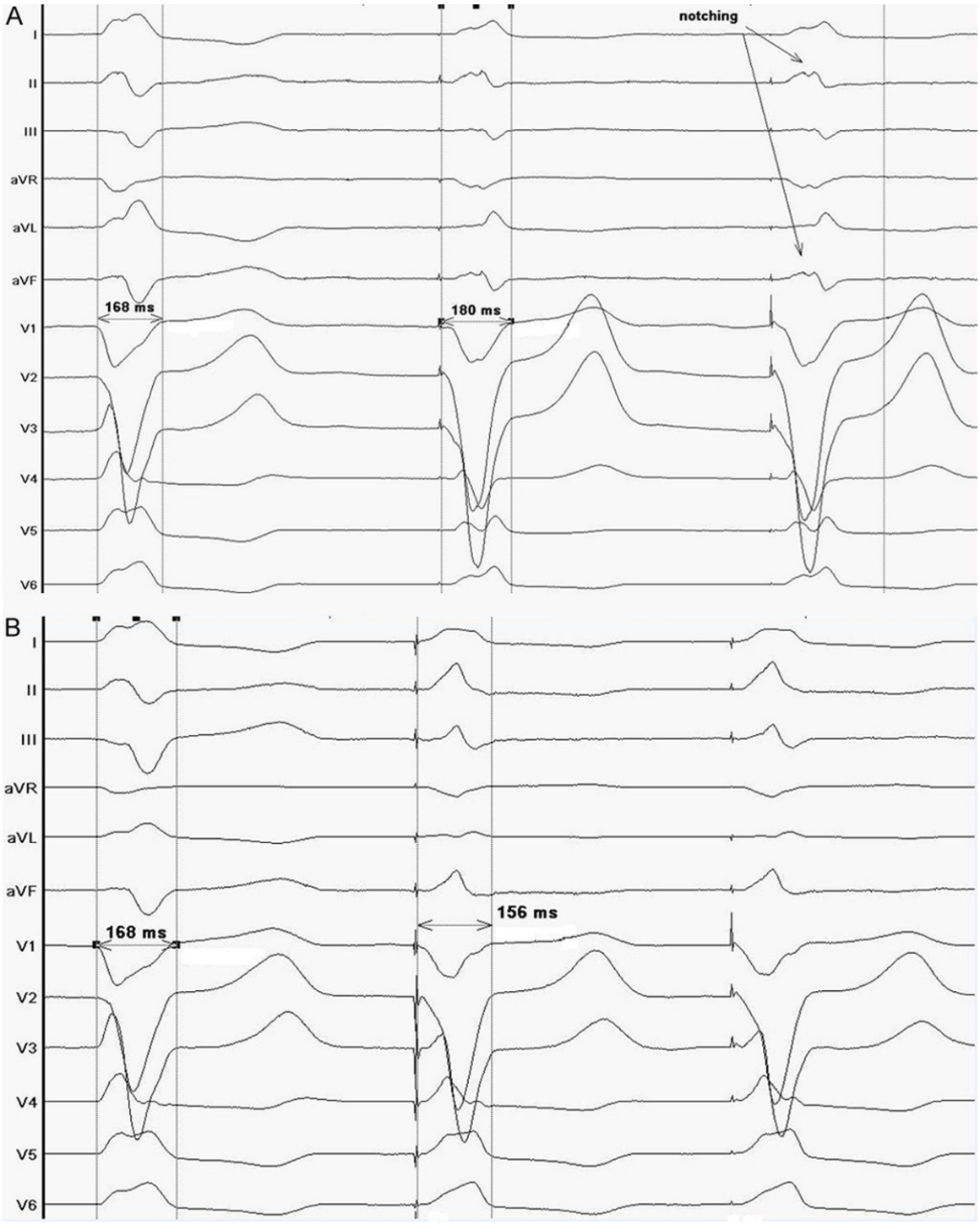

Figure 1. Twelve-lead ECG recordings during spontaneous (first beat) and paced (following two beats) from different right ventricular septal pacing sites in a patient with baseline left bundle branch block. Pacing from septal resulted in a notched R waves in inferior leads II, III, and aVF. In this site a longer paced QRS was measured (A). With a different septal position notched R waves in inferior leads were not observed; a shorter paced QRS duration was measured (B).

(native and paced) were measured manually using calipers among 12-lead recordings ECG. The lead recording the widest QRS was used for the analysis.

Table 1. Paced QRSd (≤ 160; > 160 ms) versus baseline clinical datas

	P QRS ≤ 160 ms n = 147	P QRS > 160 n = 157	p
Clinical data			
Gender (male)	73 (49.7%)	95 (60.5%)	0.057
(female)	74 (50.3%)	62 (39.5%)	
Age (yrs)	78.6 ± 8.5	78.7 ± 7.3	0.902
Hypertension	123 (83.7%)	121 (77.1%)	0.148
Coronary disease	24 (16.3%)	36 (22.9%)	
Baseline Electrocardiograpic data			
QRS width ms	126.9 ± 24.3	145.4 ± 26.8	0.001
Normal QRS	71 (48.5%)	55 (35.0%)	0.05
Complete RBBB/Bifascicular block	46 (31.3%)	67 (42.7%)	
Complete LBBB	30 (20.4%)	35 (22.3%)	
PM indication			
AVB	105 (71.5%)	114 (72.6%)	0.459
SSS	42 (28.6%)	43 (27.4%)	

LBBB = left bundle branch block; RBBB = right bundle branch block; RVS = right ventricular septal; Bifascicular block = RBBB and left anterior/posterior hemiblock. AVB = atrial ventricular block (included atrial fibrillation with low heart rate); SSS = sick sinus syndrome.

Table 2. Paced QRSd (≤ 160; > 160 ms) versus paced electrocardiographic/fluoroscopic characteristics

	P QRS ≤ 160 ms n = 147	P QRS > 160 n = 157	p
Paced QRS characteristics			
Lead II positive	80 (54.4%)	65 (41.7%)	0.009
Lead II isodifasic	31 (21.1%)	27 (17.3%)	
Lead II negative	36 (24.6%)	64 (41.0%)	
Notching limb leads: NO	95 (64.6%)	65 (41.4%)	0.001
Notching limb leads: YES	52 (35.4%)	92 (58.6%)	
Lead I positive	94 (63.9%)	127 (80.9%)	0.001
Lead I negative/isodifasic	53 (36.1%)	30 (19.1%)	
Precordial leads transition	4.9 ± 1.1	4.9 ± 1.1	0.827
Endocardial mapping (Q endo ms)	29.8 ± 14.1	53.3 ± 18.3	0.001
Fuoroscopic view segments			
High septal	26 (17.7%)	44 (28.0%)	0.001
mid septal	88 (59.9%)	53 (33.8%)	
Low septal	33 (22.4%)	60 (38.8%)	

Q-endo = delay between onset of QRS and the local bipolar activation.

Statistical analysis

All data are presented as mean ± SD. Patients were divided into two groups based on the pQRSd (> 160 ms and ≤ 160 ms). The pQRSd resulting from RV septal pacing were also analyzed versus baseline and clinical caractheristics (age, gender, hypertension, coronary disease), baseline Electrocardiographic data (QRSd, normal intraventricular conduction, RBBB and LBBB), pQRS characteristics (presence of a q-wave or a negative QRS in lead I, notching in the limb leads, positive or isoelectric/negative amplitude in lead II, QRS transition in the precordial leads) and Q-endo delay and fluoroscopic septal position (high, mid and low).

The chi-Square test was used to assess the association between qualitative variables, whereas analysis of variance (ANOVA) with post hoc Sheffè test were performed to compare quantitative variables and assess correlation by means of Pearson's regression coefficient (r). A multivariate logistic regression analysis with a forward stepwise option was performed to select independent variables able to predict longer pQRSd during RV septal pacing.

A two-tailed $P < 0.05$ was considered significant. A SPSS v.21 (SPSS Inc., Chicago, IL,USA) and STATISTICA v. 10 (StatSoft Inc., Tulsa, OK, USA) were used for all computations.

Results

The study prospectively enrolled 102 consecutive adult patients (43 female, 42.2%). All patients underwent permanent RV septal pacing for standard bradycardia indications, between September 2011 and February 2012. PM indications were: second-degree atrioventricular (AV) block/third-degree AV block in 47 (46.1%), sick sinus syndrome (SSS) in 30 patients (29.4%) and atrial fibrillation with low heart rate in 25 (24.5%).

Table 3. Paced electrocardiographic and fluorsocopic characteristics that predict longer pQRSd (> 160 ms)

	OR	95% CI	p
QRS notching in limb leads	3.24	1.89-5.55	< 0.001
Negative QRS in lead II	2.53	1.09-5.87	0.03
Mid septal F position vs high septal	0.31	0.16-0.60	< 0.001
Low septal F position vs high septal	0.56	0.21-1.45	< 0.23
Q-wave or negative QRS lead I	0.60	0.33-1.08	0.09

Baseline intraventricular conduction disturbances [complete right bundle branch block/bifascicular block (RBBB) or left BBB (LBBB)] were present in 66 patients (64.7%); RBBB and LBBB respectively in 41 (40.2%) and 25 patients (24.5%). Thirty-six patients (35.3%) had intact intraventricular conduction (normal QRS).

An overall of 304 measurements of pQRS characteristics in different RVS sites were performed. A lead placement into each septal segment (high, mid and low septal) was attempted in almost all patients (100/102 patients). In accordance with PA fluoroscopic projection segment definition 70, 141 and 93 measurements were performed respectively in high, mid and low septum.

Variables influencing pQRSd

Mean pQRSd was 160 ± 17 ms. The pQRSd measurements were divided into two groups [pQRSd ≤ 160 ms (n. 147; mean 145 ± 7 ms), pQRSd > 160 ms (n. 157; mean 173 ± 12 ms)]. All patients in the analysis did not have history of heart failure, with LVEF = 57 ± 6%. Baseline clinical and ECG data are shown in **Table 1**. Longer pQRSd was associated with gender (male), the baseline presence of RBBB, ischemic disease and longer baseline QRSd.

Table 2 shows the pQRS characteristics, Q-endo delay and septal segments (by fluoroscopy) associated with longer pQRSd. The presence of a negative lead II, notching in the limb leads, positive lead I, a high or low septal placement and longer Q-endo delay were associated with pQRSd ≥ 160 ms.

Predictors of pQRSd ≤ 160 ms

The presence of a q-wave or a negative QRS in lead I, presence of QRS notching in the limb leads, positive, isoelectric or negative amplitude in lead II, QRS transition in the precordial leads, and septal segments fluorospic view (high, mid, low) were assessed by multivariate stepwise logistic regression analysis to determine their independent association with pQRSd during RVS pacing. Paced QRSd > 160 ms was associated with the presence of pQRS notching in the limb leads, with negative amplitude of QRS in lead II. Paced QRSd ≤ 160 ms was observed with mid fluoroscopic position. Although not significantly, the presence of a q-wave or a negative QRS in lead I was also associated with shorter pQRSd. QRS transition in the precordial leads did not predict pQRSd. **Table 3** shows the values of OR with 95% CI. The presence of QRS notching in the limb leads resulted as the strongest predictor of the longer pQRSd. **Figure 1** shows the different pQRSd in accordance with the presence of notching.

Paced QRS d versus Q-endo

When the Q-endo delay was added to the above mentioned variables in the multivariate stepwise logistic regression analysis the following predictors of pQRSd were observed: pQRSd > 160 ms was associated with the presence of pQRS notching in the limb leads (OR = 3.01, 95% CI: 1.70-5.32; P < 0.001), Q-endo delay > 50 ms (OR = 8.53, 95% CI: 4.32-16.81, p < 0.001) and with negative amplitude of QRS in lead II (OR 2.50, 95% CI: 1.02-6.13, p = 0.046). Shorter pQRSd (≤ 160 ms) was observed with mid fluoroscopic position; mid compared with high septal (OR = 0.38, 95% CI: 0.19-0.75, p = 0.005); low septal fluoroscopic position compared with high (OR = 0.69, 95% CI: 0.25-1.92, p < 0.48). The presence of a q-wave or a negative QRS in lead I was not associated with pQRSd shortening or lengthening (OR = 0.65, 95% CI: 0.34-1.28, p = 0.19). The addition of Q-endo delay (< 50 ms) increased the prediction of pQRSd from 66% to 72% of cases. If the Q-endo is analyzed as a continous variable the corrected prediction of pQRSd increases up to 79.2%. In **Figure 2** the correlation between Q-endo delay and pQRSd is categorized by the notching and fluoroscopic septal segment. A Q-endo delay < 50 ms, a mid fluoroscopic position and QRS limb leads without notching identified the large majority of measurements (54/61, 85.5%) with QRS ≤ 160.

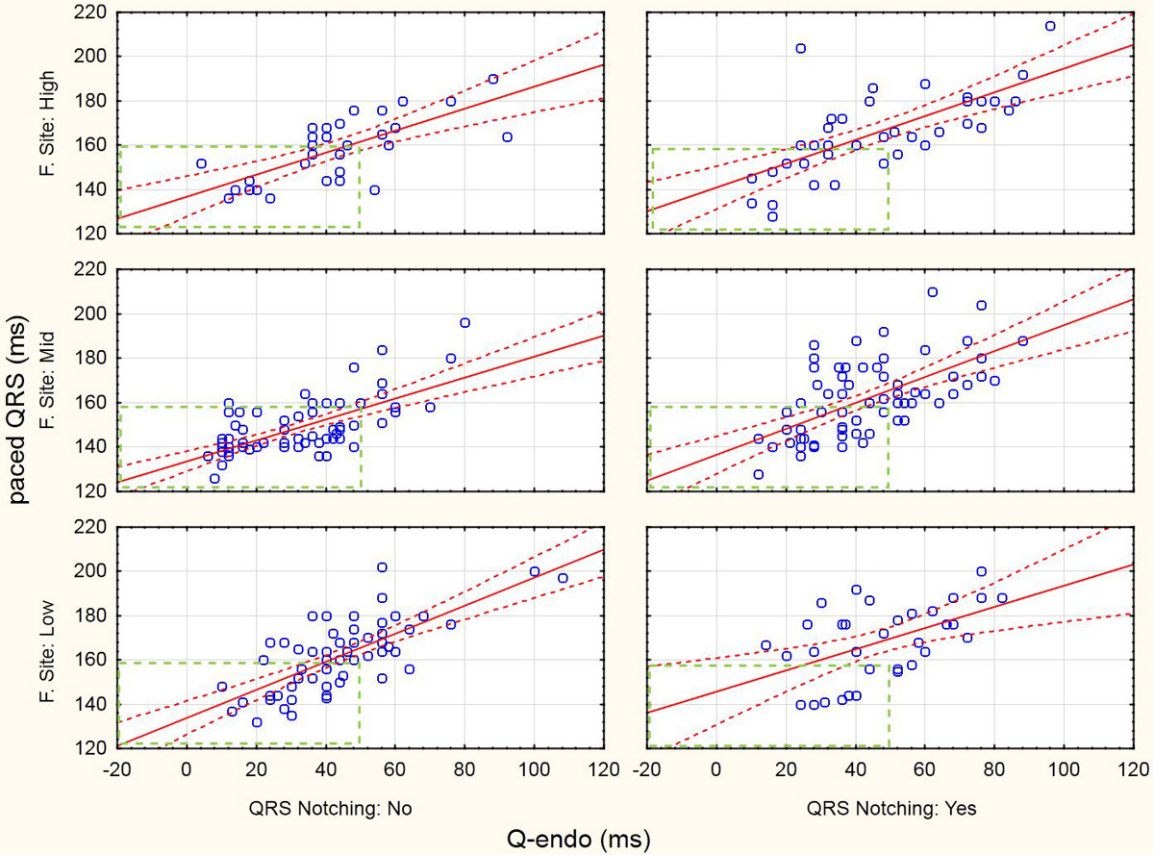

Figure 2. Relationship between the paced QRS duration and Q-endo delay in according to fluoroscopic segments (high, mid and low septal) and paced QRS characteristics (presence of notching in limb leads). A Q-endo delay < 50 ms, a mid fluoroscopic position and a QRS limb leads without notching (green outlined boxes) included almost the totally of QRS ≤ 160 measurements (54/61, 85.5%). F = fluoroscopic; Q-endo = delay between onset of QRS and the local bipolar activation; QRS notching = QRS notching in limb leads.

Intrapatient changes of pQRSd

Out of the 102 enrolled patients, a shortening of pQRSd (≤ 160 ms) among the mapped septal segments, was observed in 70 patients (68%). In 33 (32%) of patients the pQRSd there was no change moving the lead within different septal segments. Of these patients, 20 presented a very short pQRSd, whereas 13 patients showed a very long pQRSd independently of the lead septal position.

Local endocardial activation (Q-endo)

Different Q-endo delays were recorded in the RVS during spontaneous activation according to the baseline pattern of intraventricular conduction disturbances. The value of local activation recorded in patients with normal QRS, LBBB or RBBB were respectively (15.7 ± 6.3, 16.1 ± 6.5, 35.3 ± 10.4 ms). The values recorded in normal intraventricular activation and LBBB patients were significantly lower compared to the values measured in RBBB patients (ANOVA F = 53.3; $p < 0.0001$; post-hoc : normal QRS vs LBBB, $p = 1.00$; normal QRS vs RBBB, $p < 0.0001$; LBBB vs RBBB, $p < 0.0001$). The correlation between Q-endo delay and pQRSd was $r = 0.68$, $p < 0.05$. The correlation between Q-endo and pQRSd in the three subgroups of intraventricular conduction disturbances was $r = 0.78$ ($p < 0.05$), $r = 0.81$ ($p < 0.05$) and $r = 0.70$ ($p < 0.05$) respectively in normal QRS, RBBB and LBBB.

Discussion

Our study demontrates that few ECG markers (from leads I and II) combined with selected site driven by fluoroscopy can identify sites with pQRSd ≤ 160 ms during RV septal pacing. The data suggest that a mid-septal segment should be preferred. In this case the pQRS should not show a notching in the limb leads and should

also not show a negative amplitude of QRS in lead II. Moreover, a q-wave or a negative pQRS in lead I should be obtained. The addition of endocardial mapping such as an earlier local endocardial activaction (Q-endo) increases the ability to reach pQRSd ≤ 160 ms. The combination of above mentioned markers in our multivariate model correctly predict the pQRSd ≤ 160 ms outcome in 79.2%.

The presence of a q-wave or a negative QRS in lead I has previously been attributed to septal pacing [13, 14]. However, studies that tried to characterize the septal pacing defined by fluoroscopic have demonstrated that ECG pattern can not clearly define the pacing site and no single ECG criteria can reliably distinguish pacing the mid-septum from the anterior wall [3, 7, 15, 16]. Although a non-apical pacing is often associated with shorter pQRSd compared to RV apical pacing, some studies have demonstrated no differences [11] and an important intra and inter-patient variability of pQRSd in RV septal pacing was found [15, 17, 18]. This can be explained by the large variability in lead placements due to the large septal area which is consistent with the controversial results reported during permanent RVS pacing [4-7]. There are differences in the lead targets for the selected septal pacing site among the trials and there is no clear evidence that any of these septal sites are better than an RV apical one [1]. In our study, pacing from high RV septum (RVOT) resulted in longer pQRSd compared to mid-septal zone. Keeping in mind such considerations we focused on practical markers driving the lead placement in septal site characterized by shorter pQRSd.

Paced QRS duration (cut-off value)

Previous studies demontrated that the incidence of heart failure hospitalization increased with pQRSd [7-9]. Since a wider pQRSd has been demonstrated to be an independent predictor of new-onset HF [7-9], we planned this study with the goal to get short pQRSd. Patients were divided into two groups according to the duration of pQRS (pQRSd: ≤ 160 ms; pQRSd: > 160 ms). This pQRSd cut-off value was arbitrarily selected accordingly to the distribution of values in our population (mean 160 ± 17 ms) which resulted similar to other studies [14, 16]. Shukla et al. [10] reported the risk of HF hospitalization in different quartiles of the pQRSd; an important increase of incidence of HF hospitalization for pQRSd ≥ 160 ms was observed. Furthermore, a pQRSd of ≥ 165 ms was associated with an increased risk of HF after RV apical pacing in the study of Zhang et al [8]. In a previous study published by our group [12] a shorter pQRSd was associated with a more physiological LV activation which resulted in a better electromechanical activation.

Clinical implications

In the routine PM implantation a minimal number of simple markers from ECG lead I/II and fluoroscopy are enough to drive the optimal placement of RV septal lead. The ECG approach described in our study needs only few leads to assess morphology and QRS duration.

Randomized trials are currently in progress to evaluate whether the mid or high septum offers advantages over the RV apex, but the validation of the final lead position might remain an issue [1, 19]. Nevertheless, an approach based on simple real-time ECG markers during implantation combined with standard F views leading to shorter pQRSd may overcome the obstacles related to the complex anatomy of the RV chamber. Although many patients with preserved LVEF can tolerate RV pacing for many years [20] without relevant side effects, finding the optimal RV pacing site is mandatory. Optimizing the pacing site by reducing the pQRSd or avoiding very large pQRSd can represent a way of preventing cardiac disfunction in the long term.

It was more difficult to achieve lead placement into upper zone of septal. This explains the lower rate in lead placements in high septal segment compared to mid and low RV septal.

Our study was an observational study run on a relatively small sample size. Due to the methodogical limitations of a non-randomized study design our results must be taken as hypothesis-genereting and need to be confirmed in a larger scale randomized study collecting long-term clinical data.

Conclusion

Leads I and II, together with fluoroscopy view, can provide usefull information for selecting the optimal pacing site corresponding to a QRS duration shorter than 160 ms.

A mid-septal fluoroscopic-driven position associated with a QRS without negative lead II,

notching in limb leads and a q-wave or a negative QRS in lead I are the optimal markers.

Disclosure of conflict of interest

None.

Abbreviations

AV, atrioventricular; F, fluoroscopic; LVEF, left ventricular ejection fraction; LAO, left anterior oblique; LV, left ventricle/ventricular; LBBB, left bundle branch block; OR, odds ratio; PM, pacemaker; pQRSd, paced QRS duration; Q-endo, QRS-local endocardial activation; RAO, right anterior oblique; RBBB, right bundle branch block; RVOT, RV outflow tract; RV, right ventricle/ventricular; SD, standard deviation; SSS, sick sinus syndrome.

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