Nonselective His Bundle pacing with a biphasic waveform. Enhancing septal resynchronization

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Abstract

Aims. His bundle pacing has shown to prevent detrimental effects from right ventricular apical pacing (RVA) and proved to resynchronize many conduction disturbances cases. However, the extent of His bundle pacing resynchronization is limited. An optimized stimulation waveform could expand this limit when implemented in His bundle pacing sets. In this work, we temporarily implemented RVA and Nonselective His Bundle pacing with a biphasic anodal-first waveform (AF-nHB) and compared their effects against sinus rhythm (SR). **Methods.** Fifteen patients referred for electrophysiologic study with conduction disturbances, cardiomyopathy and ejection fraction below 35% were enrolled for the study. The following acute parameters were measured: QRS duration, left ventricular activation (RLVT), time of isovolumic contraction (IVCT), ejection fraction (EF), and dP/dtmax. **Results.** QRS duration and RLVT decreased markedly under AF-nHB (SR: 169±34 ms. vs nHB: 116±31 ms, $p<0.0005$) while RVA significantly increased QRS duration (SR: 169 ms vs RVA: 198 ms, $p<0.05$) and did not change RLVT (p=NS). Consistently, IVCT moderately decreased under AF-nHB (SR: 238 ms vs RVA: 184 ms, $p<0.05$ vs SR) and dP/dtmax showed a 93.35 [mmHg] average increase under AF-nHB against SR. Also, T-wave inversions were observed during AF-nHB immediately after SR and RVA pacing suggesting the occurrence of cardiac memory. **Conclusions.** AF-nHB corrected bundle branch blocks in patients with severe conduction disturbances, even in those with dilated cardiomiopathy, outstanding from RVA. Also, the occurrence of cardiac memory during AF-nHB turned up as an observational finding of this study.

Keywords: His bundle pacing, severe conduction disturbances, resynchronization, biphasic waveform

Condensed Abstract

We implemented a biphasic anodal-first stimulation waveform for nonselective His Bundle pacing (AF-nHB) with high efficacy at correcting bundle branch blocks (BBB). With this pacing paradigm, 100% LBBB cases were corrected, including those from nonischemic dilated myocardiopathy patients. Also, cardiac memory accompanied QRS normalization in some cases.

What's new?

- A systematic analysis for a biphasic anodal-first stimulation waveform temporarily implemented in a nonselective His Bundle pacing protocol (AF-nHB).
- AF-nHB would allow activation of a greater extent of myocardial tissue.
- AF-nHB corrected 100% LBBB cases including those from nonischemic dilated myocardiopathy patients.
- New T-wave inversions were found during AF-nHB immediately after SR and RVA pacing, suggesting the occurrence of cardiac memory.

1. Introduction

It has been widely evidenced that right ventricular apical (RVA) pacing elicits asymmetrical ventricular hypertrophy, ventricular dilatation, abnormal fiber arrangement, increase of myocardial cathecolamines and perfusion disturbances, among other deleterious effects [1, 2]. As a consequence, many efforts recently focused on the search of alternative stimulation sites to overcome some of the aforementioned problems. In that line, His bundle pacing appeared as a promising option. Its first attempts were carried out by Narula et al. in the seventies [3], however, technical issues postponed this technique as a method of permanent cardiac pacing. Only in the last decade, much evidence emerged reporting the septum as an ideal site for pacing, either in acute or chronic studies [4-9]. Because His bundle pacing respects the anatomical paths of electrical conduction in the heart, there is full agreement on its beneficial effects for patients without conduction disturbances [10-11]. Furthermore, not only bradycardia patients would benefit from His bundle pacing, but patients referred for cardiac resynchronization therapy (CRT) too. In particular, it is rather promising the possibility to resynchronize with only one lead, simplifying the technique and shortening implantation times. In fact, 30-40% of CRT patients are reported as non-responders, as measured by symptom improvement, left ventricular (LV) remodeling, and/or reduced mortality [12].

Late in the 90s, Thakor et al. reported some of the beneficial effects of anodal excitation of cardiac tissue, such as an increased conduction velocity, related to faster upstrokes of the action potentials [13]. In 2007, Lloyd et al. demonstrated that anodal pacing activates a larger volume of myocardium than cathodal pacing of identical intensity [14].

Moreover, tissue depolarization would start at some distance from the lead tip once the anodal stimulus is terminated [15], recalling the concept of virtual electrode [16]. However, anodal pulses are linked to higher stimulation thresholds, almost doubling those from cathodal pacing. Fortunately, biphasic configurations, specifically anodal-first stimulation, proved to lower these thresholds to values similar to those from cathodal pulses while preserving the benefits of anodal excitation [13].

We therefore postulate that an optimized stimulation configuration in terms of extent of captured tissue, velocity conduction and stimulation threshold would facilitate recruitment of latent His-Purkinje tissue. With that purpose in mind, we compared electrical, mechanical and hemodynamic responses to acute RVA and nonselective His Bundle pacing with a biphasic anodal-first waveform (AF-nHB) in patients with severe conduction disturbances.

2. Materials and methods

2.1. Population study

The study enrolled 15 patients (66±13 y.o., 5 women) referred for electrophysiological study with severe conduction disturbances, namely LBBB or RBBB associated to left anterior fascicular block, all of them with mean ejection fraction (EF) of 32%. Table 1 displays the baseline characteristics for the study population. Eleven out of fifteen patients presented LBBBs with QRS durations greater than 150 ms, of which seven showed nonischemic dilated cardiomiopathy. Three remaining patients showed RBBB associated to left anterior fascicular block, all of them with Chagas disease and only one patient presented left anterior hemiblock with long history of arrhythmic events and hypertrophic myocardiopathy. All patients qualified for heart transplantation and underwent an electrophysiologic study for cardiodefibrillator indication.

2.2. Definitions and measures

QRS duration and left ventricular activation (RLVT) together with ejection fraction (EF) and isovolumic contraction time (IVCT) were assessed during sinus rhythm (SR), temporary RVA and AF-nHB pacing. QRS duration was measured from stimulus artifact to latest QRS offset when AF-nHB pacing, otherwise from the earliest QRS onset to the latest QRS offset. RLVT was defined as the time from native QRS onset or stimulus onset (when AF-nHB pacing) and intracavitary activation in the most distal LV wall mapped by catheter in coronary sinus [17]. Also, left ventricle diastolic diameter was echocardiographically assessed.

2.3. Waveforms

For AF-nHB, a biphasic, anodal-first configuration was chosen, with a pulse width of 0.5 ms per phase. Phases were monophasic with the anode connected between tip and ground and the cathode connected between ring and ground. Ground was connected to a pad ground located beneath the patient. Each channel output consisted of the discharge of a resistance-capacitor circuit. In order to lower the RC constant and get a square wave as much as possible, each electrode (tip and ring) was connected to two output channels in parallel. Then, a specially designed, quad-configured pacing cable was connected to a Blazer II EPT 4mm Boston Scientific stimulation catheter. Figure 1 (left panel) shows the stimulation waveform as applied in the catheter. Notice that each phase had its subthreshold recovery to avoid electrode polarization. RVA was configured as standard: unipolar, cathodal stimulation, 5V amplitude and 1 ms pulse width.

2.4. Pacing protocol

To ensure consistent pacing, pacing rates were 10 beats per minute higher than the underlying intrinsic rate or 90 beats per minute if the patient intrinsic rate was less than 80 beats per minute. If the subject was in sinus rhythm, dual-chamber (DOO) pacing with an atrioventricular delay of 60 ms was used. Maximum fluoroscopy time was set to 15 minutes for the search of the narrowing stimulation site. Elapsed that time, the case was classified as a failed attempt. Pacing site was defined when the Blazer catheter recorded His potentials and ventricular deflections, preferably with no atrial contribution. Once achieved these conditions, the catheter slightly moved around to find QRS narrowing. Figure 1 (right panel) shows a right anterior oblique 45º fluoroscopic view comprising the stimulation sites (red circles) for every patient and a representative placement of a quadripolar stimulation catheter in His zone, a decapolar catheter in coronary sinus and a Millar pressure transducer in the left ventricle, which was utilized to monitor left ventricular pressure on 11 out of 15 patients during SR and AF-nHB.

Finally, the study was approved by the Ethics Committee of the "Instituto de Investigaciones Medicas Dr. Alfredo Lanari". In all cases, patients were thoroughly informed and provided written informed consent.

2.5. Statistical analysis

Data are presented as Mean(SD). All measures were obtained from an average over ten consecutive beats. The D'Agostino-Pearson normality test was applied to quantify the discrepancy between the parameters distributions and an ideal Gaussian distribution. Since normality was not achieved, the Wilcoxon sign rank test was used to compare paired data (pacing against SR). When $p<0.05$, differences were considered statistically significant.

3. Results

QRS narrowing with AF-nHB pacing was evident in each patient (Table 2). Average intrinsic QRS duration was 169±34 ms. Average AF-nHB QRS duration was 116±31 ms, reducing basal QRS duration about 30% ($p<0.005$). Similarly, AF-nHB reduced in average 44% RLVT ($p<0.005$) and 23% IVCT ($p<0.05$) with respect to SR, whereas RVA moderately increased QRS duration (SR: 169 ms vs RVA: 198 ms, $p<0.05$) and did not change RLVT (RVA vs SR, p=NS). Mean time to find the stimulation site was 8.4±2.4 minutes and in no case this time exceeded 13 minutes. The average threshold was 3.87 V_{peak}. It is worth mentioning that accessory evaluation in the first 8 patients was accomplished to decide the biphasic configuration throughout the study. In order to do this, anode was alternatively connected to the tip or the ring with anodal-first and cathodal-first settings respectively. The anodal-first configuration with the anode connected to the tip produced a 3.56 V narrowing threshold, whereas the remaining configurations showed higher thresholds by about 4.25 V.

Notice that AF-nHB narrowed QRS durations to 145 ms in two cases with relatively high thresholds (5V and 4V). In the remaining cases AF-nHB narrowed QRS complexes to 120 ms or less. A representative ECG and electrograms from the coronary sinus mapping catheter (CS_{12}-CS_{910}) under RVA and AF-nHB on a LBBB patient can be found in figure 2, top panel. Notice the significant QRS narrowing and advance of RLVT and IVCT under AF-nHB and the slight widening of QRS complexes under RVA. In order to compare regular and biphasic His bundle pacing, figure 2 bottom panel exemplifies the differences between 0.5 ms, 5V monophasic cathodal stimulation and 1ms, 2.5 V_{peak} biphasic anodal-first stimulation in the hisian zone. Under regular pacing, slurred QRS complexes are evident in Leads I, III, aVL and aVF (middle panel) together with QRS durations similar to SR (left panel), while AF-nHB evidence narrow QRS complexes.

Surprisingly, discordant T-waves were found during AF-nHB, immediately after SR and RVA in two and three cases respectively. Figure 3 shows two cases showing 12-lead electrocardiograms in which cardiac memory was involved. At the top panel, AF-nHB vs RVA pacing is displayed. Note how the AF-nHB T-waves on V1 to V6 follow the QRS polarity from the LBBB pattern induced by RVA. At the bottom panel, AF-nHB vs SR is displayed, showing paced negative T-waves in leads V1-V2-V3, consistent with basal QRS polarity originated by the left bundle block.

Finally, LV pressure was recorded by means of a Millar pressure transducer in 11 out of 15 patients evaluated under SR and AF-nHB only. LV pressure was continuously monitored during 5 ON/OFF cycles of AF-nHB paced and SR beats. dP/dt_{max} presented in average a higher level for AF-nHB versus SR (816.55±252.65 mmHg/s vs 909.90±261.25 mmHg/s, p=NS), with individual raises in 8 patients, no change in two (a change of 50 mmHg/s or lesser) and decrease in one patient (Table 3). Despite the trend, dP/dt_{max} was not statistically significant. Notice the uptrend for AF-nHB, with 72% of patients increasing its dP/dt_{max} 70 mmHg/s or greater.

4. Discussion

The main finding of this work was the high efficacy of the AF-nHB pacing, implemented with an anodal-first waveform, at correcting bundle branch blocks on patients with severe conduction disturbances, especially those with nonischemic dilated cardiomiopathy. Previously, evidence about activation of diseased His-Purkinje tissue by means of His bundle pacing was reported, but with poorer performance. Recently, Lustgarten et al. demonstrated QRS narrowing by direct His-Bundle pacing (DHBP) in 7 out of 10 patients, although only 4 showed nonischemic dilated cardiomiopathy, and it was not fully clear in which patients DHBP failed [6]. Also, Barba-Pichardo et al. reported their experience on patients with bundle blocks and widened QRS complexes, with a 52% success rate for temporary DHBP and a 29% success rate for permanent DHBP [4,5]. Moreover, patients from [5] had an average ejection fraction higher than our patients in Group I (52% vs 31%). In 2013, Barba-Pichardo et al. achieved QRS normalization in 13 out of 16 LBBB patients [8] and Vijayaraman et al. reported a 76% correction in patients with infra-nodal AV block with permanent HBP [9].

Anodal stimulation relies on the capture of an enlarged myocardial area [14] with depolarization starting in “virtual cathodes”, slightly far away from the stimulation electrode [15]. This gap between the electrode and the depolarization wavefront, mimicking a virtual electrode effect [16], could act as a bypass over blocked conduction tissue, making easier to find the stimulation site. Moreover, since these virtual cathodes lie along the fiber orientation it is also sensible to expect an increased conduction velocity with consequent improved contractility under anodal stimulation. Thakor et al. related this increased conduction velocity to faster upstrokes in the action potentials [13]. In the same work, however, the anodal setting required the highest stimulation thresholds, almost doubling those for cathodal configurations. The addition of the cathodal phase after the anodal one was meant to lower the stimulation threshold [13].

However, which of the phases captures the myocardium (if only one) remains unclear. By bringing together the anodal and cathodal mechanisms, there would be an enlargement of the depolarization wavefront from the ring surroundings to adjacencies of the tip in such timing that both phases could capture myocardium synergistically. However, this is only a speculation and specific experiments should be designed to get insight into the exact mechanisms of biphasic excitation.

The average peak threshold found in this work is coherent with those in the literature. In [6] thresholds were closer to ours, with 3.1V for standard pacing and 4.2V for reverse bipolar pacing, in both cases with active fixation mechanisms. Others ruled out thresholds above 2.5V, but this was on a permanent pacing basis [5]. We believe that the thresholds obtained in this work will certainly improve when applied on screw-in catheters within a permanent pacing protocol.

Even though not significantly, the hemodynamic changes accompanied AF-nHB, increasing dP/dtmax in eight out of eleven patients. From the remaining three, dP/dtmax did not change in two and decreased in only one patient (Table 3). This is consistent with Catazariti et al., who compared acute hemodynamic data among DHBP, nonselective His bundle pacing and RVA pacing, showing improvement of LV function for the two former over RVA pacing, with no statistical difference when DHBP was compared to nonselective His bundle pacing [18].

Finally, it was documented the occurrence of discordant QRS complexes and T-waves during AF-nHB immediately after SR and RVA pacing, recalling the concept of cardiac memory (CM). The occurrence of CM during AF-nHB pacing is interesting, since CM is normally evident in sinus rhythm, when normal myocardial activation resumes after ventricular pacing cessation. In this work, QRS normalization occurs during AF-nHB, and so do CM changes. Recently published studies support our findings with reports of T-wave inversions during His bundle pacing certainly linked to CM in selective His capture without RV fusion and less certainly in the setting of RV fusion [19-20].

4.1. Study limitations

Due to the temporary implementation of nonselective His Bundle pacing, safety and efficacy of the biphasic waveform was not possible. However, preliminary 90-days follow-ups on 15 *Romey Marsh* sheeps implanted with Insignia devices at maximum output (6.5V, 1ms/phase) for RVA and AF-nHB presented no significant histological differences between groups, showing similar fibrosis, trauma and inflammatory infiltration levels in the tip and ring areas.

Regarding device energy consumption, we believe that electrode active fixation would lower voltage thresholds found in this work for temporary pacing. However, design of batteries that allow higher energy consumption without significant shortening of their lifespan would be desirable.

5. Conclusions

Nonselective His Bundle pacing implemented with a biphasic anodal-first waveform (AF-nHB) would facilitate electrical correction of severe bundle branch blocks, allowing QRS normalization in each patient in this study. Mechanical parameters accompanied electrical changes, although a specific study involving more echocardiographical parameters would be desirable to fully understand the mechanical resynchronization elicited by the AF-nHB pacing carried out in this study. Three patients turned out as hemodynamic non responders since dP/dt changed inconsistently with their own electrical and mechanical improvement. Finally, it was documented the occurrence of discordant T-waves during AF-nHB, accompanying QRS normalization.

Conflict of interest: none declared

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Table 1: Baseline characteristics of the population study.

Characteristics	n(%)	Treatment
Age (y.o.)	66±13	NA
Women	5(33)	NA
Non ischemic dilated cardiomiopathy	7(46)	Digitalis, ACE inhibitors, BB diuretics, spirolactone
Ischemic cardiomiopathy	4(27)	ACE inhibitors, digitalis, diuretics spirolactone
Chagasic cardiomiopathy	3(20)	ACE inhibitors, amiodarone, diuretics
Hypertrophic cardiomiopathy	1(7)	BB

BB: beta blockers, ACE inhibitors: Angiotensin Converting Enzyme Inhibitors.

Table 2: Response to AF-nHB and RVA pacing modalities with respect to SR. Electrical and mechanical parameters on the entire population study. Bold indicates nonischemic dilated myocardiopathy patients. $^{\S}p<0.005$ vs SR, $^{*}p<0.05$ vs SR.

Na$_V$ [V]	**SR**		**AF-nBH**		**RVA**		**IVCT**			**EF**		
	QRS	**RLVT**	**QRS**	**RLVT**	**QRS**	**RLVT**	**SR**	**AF nBH**	**RVA**	**SR**	**AF nBH**	**RVA**
4	134	115	80	46	151	117	245	175	210	52	58	41
2.5	98	76	90	51	146	107	275	180	250	41	50	55
5	**224**	**170**	**145**	**88**	**237**	**190**	**365**	**275**	**345**	**17**	**25**	**19**
4	145	71	115	76	195	120	130	140	245	50	54	49
7	**204**	**135**	**145**	**58**	**225**	**141**	**195**	**155**	**200**	**18**	**25**	**21**
3.5	**176**	**135**	**120**	**54**	**217**	**137**	**235**	**255**	**285**	**16**	**25**	**18**
4	**210**	**110**	**136**	**68**	**230**	**141**	**270**	**195**	**280**	**32**	**37**	**33**
3	**190**	**137**	**95**	**68**	**224**	**134**	**265**	**160**	**275**	**29**	**35**	**31**
7	143	112	113	76	188	133	250	220	290	36	40	NA
4	171	61	122	59	173	100	155	122	180	37	42	NA
2.5	**205**	**155**	**105**	**78**	**210**	**170**	**350**	**260**	**320**	**20**	**30**	**24**
4	**170**	**134**	**120**	**52**	**200**	**123**	**240**	**155**	**255**	**25**	**30**	**22**
3	162	112	122	70	204	142	270	185	260	36	39	33
2.5	150	90	120	74	195	120	135	130	245	45	57	49
2	**160**	**120**	**122**	**51**	**180**	**130**	**195**	**155**	**200**	**24**	**28**	**24**
Mean	169	116	117§	65§	198*	134	238	184§	256	32	38	32
SD	34	30	18	12	27	23	69	48	46	12	12	13

Na$_V$: QRS Narrowing threshold [V$_{peak}$]. QRS: QRS duration [ms]. RLVT: right to left ventricular time [ms]. IVCT: isovolumic contraction time [ms]. SR: sinus rhythm. AF-nBH: Anodal-first Nonselective His Bundle pacing. RVA: right ventricular apical pacing.

Table 3: Hemodynamic response to AF-nHB stimulation. Individual dP/dt$_{max}$ for those patients evaluated with a Millar pressure transducer. Notice the uptrend for AF-nHB, with 72% of patients increasing its dP/dt$_{max}$ 70 mmHg/s or greater. Mean(SD) values are shown in the last grey shadowed row in bold. Average increase represented 11% from basal dP/dt$_{max}$.

dP/dt$_{max}$ SR [mmHg/s]	**dP/dt$_{max}$ AF-nHB [mmHg/s]**
465	592
960	1088
840	936
1178	1305
802	876
314	481
743	694
938	960
1116	1288
825	982
801	807
816,55(252,64)	**909,91(261,25)**

SR: sinus rhythm, AF-nHB: Anodal-first nonselective His Bundle pacing.

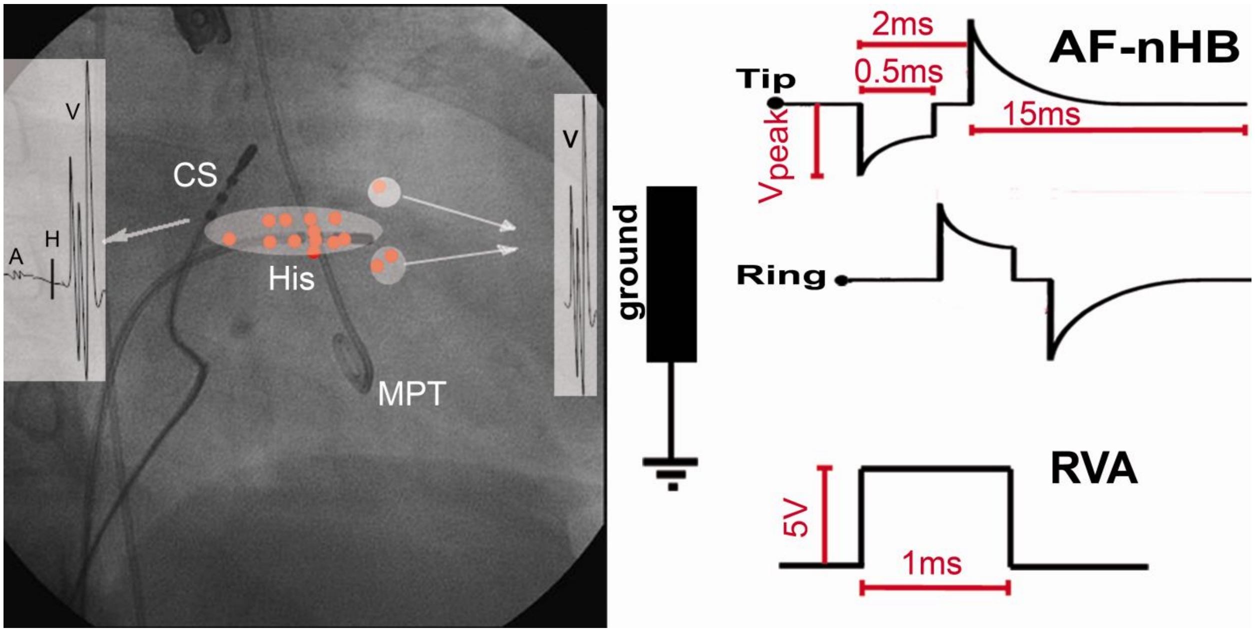

Figure 1: Left) Catheters positioning and stimulation sites. Left: Right anterior oblique 45º fluoroscopic image showing quadripolar stimulation catheter in His zone, decapolar catheter in coronary sinus (CS) and Millar pressure transducer in the left ventricle. Red circles mark stimulation site for every patient. 13 patients evidenced small atrial (A), mild His (H) and large ventricular (V) contributions in Blazer catheter (left insert) whereas 3 patients showed only V deflections (right insert). Right) Stimulation waveforms and connections. AF-nHB: Anodal-first Nonselective His Bundle pacing. Interphase delay (2ms), Recharge duration (15ms) and Pulse width (0.5ms) were fixed. Voltage amplitude (V_{peak}) varied symmetrically. RVA: Right ventricular apical pacing. Amplitude and pulsewidth were fixed at 5V and 1ms respectively. Both configurations utilized a ground pad beneath the patient.

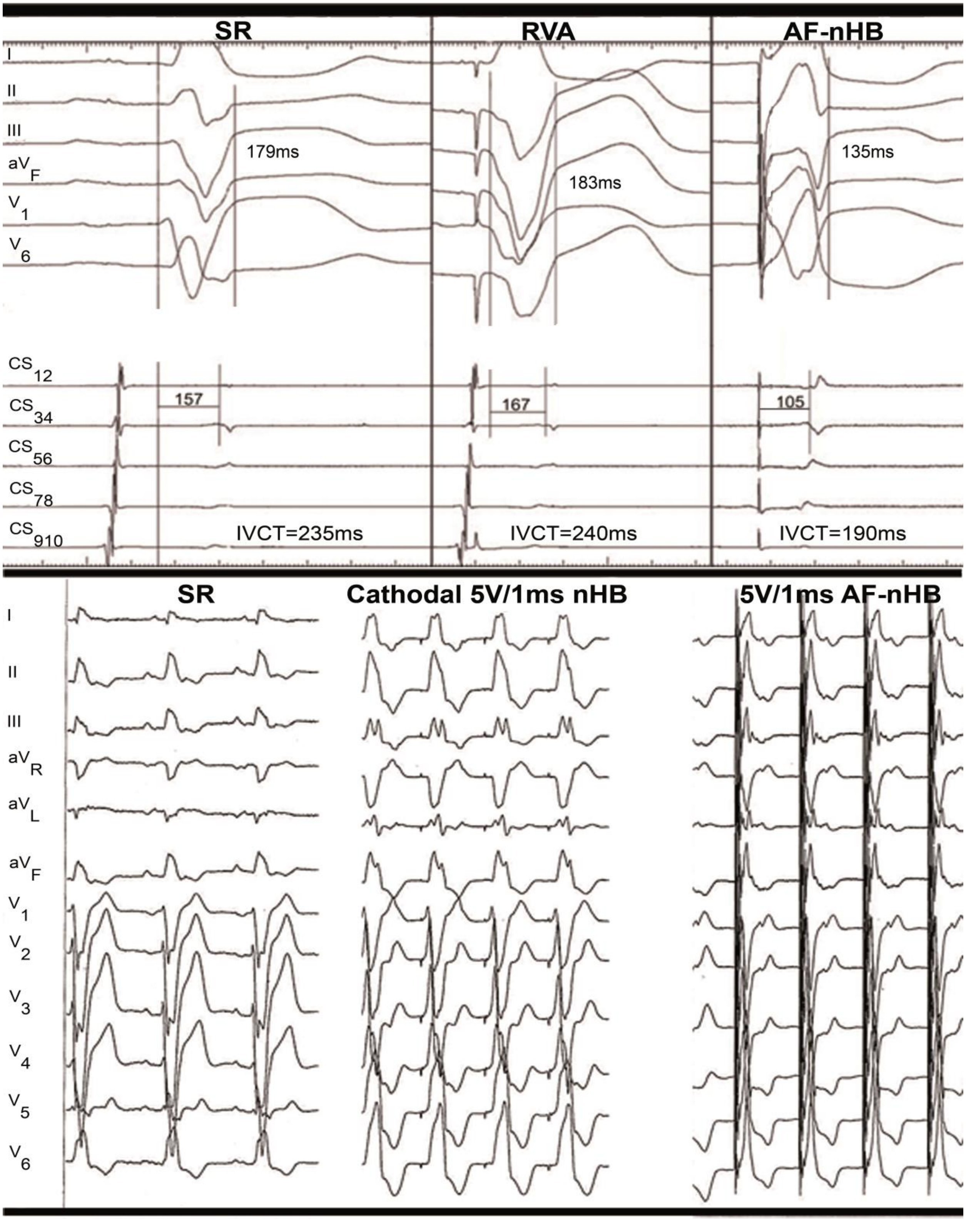

Figure 2: Top) Effect of RVA and AF-nHB on a LBBB patient. Paced beats are preceded by the stimulation spike. QRS durations are marked on top of aV_F/V_1 leads

and RLVT on top of CS_{3-4} channel. On top of CS_{9-10} channel, IVCT values are displayed for paced and sinusal beats. Notice the significant QRS narrowing and advance of RLVT and IVCT under AF-nHB. Bottom) Monophasic cathodal 5V/1ms pacing (middle) versus Anodal-first $5V_{peak-peak}$ 1ms pacing (right) for AF-nHB implementation in a LBBB patient (left). Notice that LBBB pattern remains under the cathodal and disappears under AF-nHB implementation.

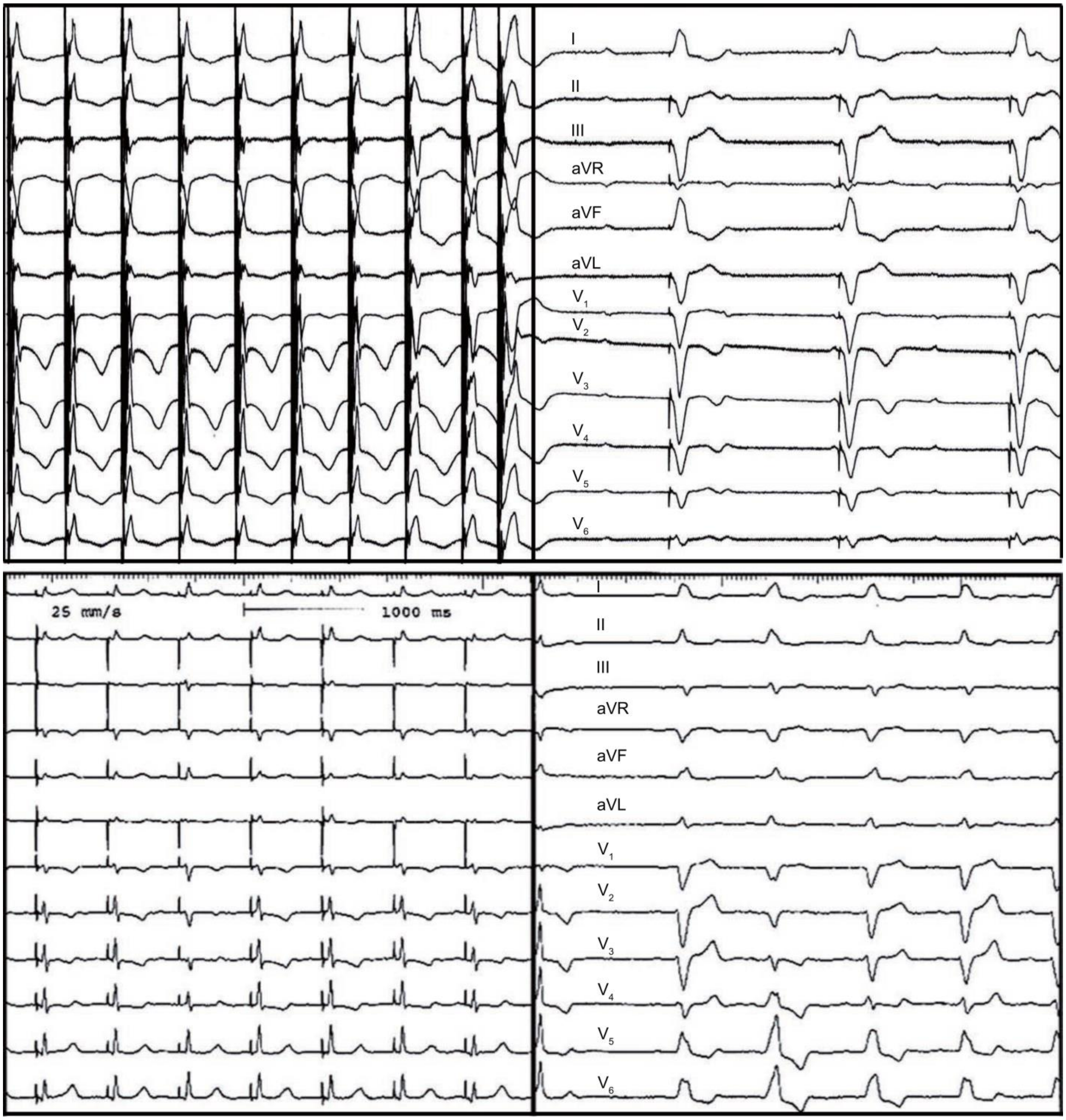

Figure 3: Representative 12-lead ECGs showing cardiac memory. Top) Patient undergoing AF-nHB (left) and RVA (right). Note how the AF-nHB T-waves on V1 to V6 follow the QRS polarity from the LBBB pattern induced by RVA. Bottom) LBBB patient under AF-nHB (left) vs SR (right). Notice the paced negative T-waves in lead V1-V2-V3, consistent with basal QRS polarity originated by the left bundle block.