

# Prevention of Ventricular Desynchronization by Permanent Para-Hisian Pacing After Atrioventricular Node Ablation in Chronic Atrial Fibrillation

## A Crossover, Blinded, Randomized Study Versus Apical Right Ventricular Pacing

Eraldo Occhetta, MD, Miriam Bortnik, MD, Andrea Magnani, MD, Gabriella Francalacci, MD, Cristina Piccinino, MD, Laura Plebani, PhD, Paolo Marino, MD, FESC  
*Novara, Italy*

<b>OBJECTIVES</b>	The aim of our study was to evaluate the feasibility, the safety, and hemodynamic improvements induced by permanent para-Hisian pacing in patients with chronic atrial fibrillation and narrow QRS who underwent atrioventricular (AV) node ablation.
<b>BACKGROUND</b>	Right ventricular apical pacing, inducing asynchronous ventricular contraction, may impair cardiac function; permanent para-Hisian pacing could preserve interventricular synchrony and improve left ventricular function.
<b>METHODS</b>	After AV node ablation, 16 patients were implanted with a dual-chamber pacemaker connected to a screw-in lead positioned in close proximity to the His bundle and to a right ventricular apical lead. Clinical and echocardiographic data were collected at baseline and after two randomized six-month periods (with para-Hisian and conventional pacing).
<b>RESULTS</b>	During para-Hisian pacing, the interventricular electromechanical delay improved as well ( $34 \pm 18$ ms) as during right apical pacing ( $47 \pm 19$ ms), $p < 0.05$ . Para-Hisian pacing allowed an improvement in New York Heart Association functional class ( $1.75 \pm 0.4$ vs. $2.33 \pm 0.6$ at baseline and $2.5 \pm 0.4$ during apical pacing, $p < 0.05$ for both), in quality-of-life score ( $16.2 \pm 8.7$ vs. $32.5 \pm 15.0$ at baseline, $p < 0.05$ ), and in the 6-min walk test ( $431 \pm 73$ m vs. $378 \pm 60$ m at baseline and $360 \pm 71$ m during apical pacing, $p < 0.5$ for both). Mitral and tricuspid regurgitation improved during para-Hisian pacing ( $1.22 \pm 0.8$ and $1.46 \pm 0.5$ index, respectively, vs. $1.68 \pm 0.6$ [ $p < 0.05$ ] and $1.62 \pm 0.7$ [ $p = \text{NS}$ ] index at baseline, respectively), with a slight worsening during apical pacing ( $1.93 \pm 1$ and $1.93 \pm 0.7$ index, respectively, $p < 0.05$ for both).
<b>CONCLUSIONS</b>	Permanent para-Hisian pacing is feasible and safe. Compared with conventional right apical pacing, it allows an improvement in functional and hemodynamic parameters over long-term follow-up. (J Am Coll Cardiol 2006;47:1938-45) © 2006 by the American College of Cardiology Foundation

In patients with atrial fibrillation (AF) refractory to drug therapy, radiofrequency (RF) ablation of the atrioventricular (AV) node and permanent pacing are effective in controlling the ventricular rate, and have been shown to be effective in alleviating symptoms and in improving the quality of life

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(QoL) (1). Conventional right ventricular apical pacing may result in asynchronous ventricular contraction with delayed left ventricular activation (2), interventricular motion abnormalities with negative inotropic effects (3), and worsening of functional mitral and tricuspidal regurgitation (4). Moreover, some randomized trials have reported negative effects of right conventional apical pacing such as increased mortality, worsening of left ventricular function, and AF recurrences (5-9).

Recently, the use of cardiac resynchronization has been proposed for "primary prevention" in patients with congestive heart failure that requires a high percentage of ventricular pacing (10). In subjects with preserved intraventricular conduction and AV block, physiologic cardiac stimulation could be achieved with biventricular pacing (11) as well as with permanent direct His-bundle or para-Hisian pacing (12,13).

The aims of our crossover, patient blind, randomized study, in a patient population with chronic AF undergoing AV node ablation, were: 1) to evaluate the feasibility and long-term safety of permanent para-Hisian pacing; and 2) to compare the effects of permanent para-Hisian pacing with those of conventional right apical stimulation on functional and hemodynamic parameters.

**Patient population.** From September 2000 to June 2003, 36 patients underwent AV node RF ablation for chronic AF in Novara, Italy. Patients were screened for enrollment if they had an indication for AV node ablation for chronic AF, and fast ventricular rate not controlled pharmacologically (digoxin, beta-blocker, or diltiazem, alone or in association),

From the Divisione Clinicizzata di Cardiologia, Facoltà di Medicina e Chirurgia di Novara, Università degli Studi del Piemonte Orientale, Novara, Italy.

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**Abbreviations and Acronyms**

- AF = atrial fibrillation
- AV = atrioventricular
- DDDR = dual-chamber rate-responsive pacing-sensing
- EF = ejection fraction
- ICD = implantable cardioverter-defibrillator
- NYHA = New York Heart Association
- PM = pacemaker
- QoL = quality of life
- RF = radiofrequency
- VVIR = ventricular rate-responsive pacing-sensing

concomitant heart disease, narrow QRS complexes even at high ventricular rates (during 24-h Holter monitoring). All patients gave their written informed consent.

Eighteen patients were excluded from the study: nine because they had already been implanted with a pacemaker (PM) or an implantable cardioverter-defibrillator (ICD); three due to the absence of escape rhythm after RF ablation; six because they were in poor clinical condition and not suitable for adequate clinical follow-up. In the end, 18 subjects (50%) (9 men, age  $71 \pm 5$  years) were enrolled in the study; their clinical characteristics are outlined in Table 1.

After the study of 18 patients, we considered that feasibility and safety end points had been reached, and decided to implant subsequent patients with a single para-Hisian pacing lead only, without the back-up right ventricular apical lead. We reasoned that the crossover intrapatient analysis in 18 patients comparing two randomized pacing sites had allowed detection of a 60-m difference in the 6-min walk test, with a power exceeding 90% at 5% level

(14). The study protocol was approved by the institutional ethics committee.

**METHODS**

Before the ablate and pace procedure, all patients enrolled underwent New York Heart Association (NYHA) functional class determination, assessment of QoL through the Minnesota Living with Heart Failure questionnaire (15), the 6-min walk test, and 24-h Holter electrocardiogram (ECG) monitoring.

Echocardiographic recordings were made using a phased-array echo-Doppler system (Sonos 5500, Philips, Andover, Massachusetts) equipped with a 3-MHz transducer. Complete standard echocardiography, including measurements of left ventricular ejection fraction (EF), internal left ventricular diastolic dimensions, end-systolic and end-diastolic volumes computed according to a biplane Simpson's method, was performed at baseline and was repeated at the 6- and 12-month follow-up examinations. The severity of mitral and tricuspid regurgitation was graded semiquantitatively from color-flow Doppler in the conventional parasternal long-axis and apical four-chamber images, according to the American Society of Echocardiography recommendations (semiquantitative analysis: 1 = mild, 2 = moderate, 3 = severe) (16). Systolic pulmonary pressure was estimated from the continuous-wave Doppler tricuspid regurgitation velocity. Pulsed-wave Doppler velocity signals were recorded from the right and left ventricular outflow tracts to measure the right and left electromechanical delay (time from the beginning of QRS to the start of pulmonary or aortic flow). The difference between pre-ejection times (interventricular mechanical delay) was used as an

**Table 1.** Clinical Features of the Study Population

Patient #	Age (yrs)	Gender	NYHA Functional Class	Cardiopathy	EF (%)	Min HR (beat/min)	Max HR (beats/min)
1	69	F	III	DCM	44	40	190
2	83	M	II	Hypertension	48	29	190
3	63	F	II	Valve disease	60	43	210
4	72	F	II	Valve disease	50	47	123
5	66	M	II	Valve disease	47	32	186
6*	75	M	II	Hypertension	51	25	163
7†	67	F	II	Valves replac.	40	47	160
8*	70	F	II	Hypertension	60	58	200
9	79	F	III	Hypertension	61	28	198
10†	70	M	III	DCM	64	50	145
11	78	M	III	CAD	28	25	182
12	72	F	II	Hypertension	56	50	210
13	78	M	III	CAD	63	25	160
14*	71	F	II	Hypertension	57	47	180
15*	75	M	III	CAD	50	36	127
16	72	M	II	CAD	52	32	164
17	65	F	III	CAD	45	28	172
18	61	M	III	Hypertension	59	45	209
Mean $\pm$ SD	$71.4 \pm 5.6$		$2.4 \pm 0.4$		$52.0 \pm 9.1$	$38.1 \pm 10.4$	$176.0 \pm 25.8$

\*Patients in whom true direct His bundle pacing was achieved; †Patients subsequently excluded from the study (see text for further explanation).

CAD = coronary artery disease; DCM = dilated cardiomyopathy; EF = ejection fraction; HR = heart rate; Min and Max HR = heart rates observed during previous 24-h Holter ECG monitoring during daily life; NYHA = New York Heart Association; Valves replac. = previous valve replacement.

indicator of synchronicity between right and left ventricular contraction.

**AV nodal RF ablation.** Atrioventricular junction ablation was performed positioning a standard electrode in the right ventricular apex for backup pacing, and an ablation 4-mm catheter at the AV junction where the His-bundle potential was barely visible and the atrial-to-ventricular electrogram amplitude ratio was  $\geq 2:1$ . Radiofrequency was then delivered ( $70^\circ$  for 60 s) in order to achieve a stable AV block with an escape rhythm of  $>30$  beats/min and narrow QRS, preceded by a Hisian potential. The ablation catheter was left to guide the following lead positioning for para-Hisian pacing.

**Pacemaker implant with para-Hisian and apical right ventricular pacing.** After RF ablation, a conventional bipolar (passive or active fixation) lead was positioned in the right ventricular apex, via the right cephalic or subclavian vein; the correct position was confirmed using standard parameters (pacing threshold, lead impedance, and R-wave sensing).

Through the same approach, another bipolar screw-in lead (1.5-mm retractable helix) was advanced and positioned, using a steerable stylet (Locator 4036, St. Jude, Sylmar, California) high in the interventricular septum, with distal pole of the screw-in lead located as close as possible to the mapping lead dipole (in right and left anterior oblique projections).

Phrenic nerve stimulation was excluded in all the patients for both the implanted leads with a transient high-energy stimulation (8 V).

Successful criteria for direct His-bundle pacing were defined as (13):

- 12-lead surface ECG equivalence between native and paced QRS
- His-ventricular interval of the spontaneous escape rhythm equal to the pace-ventricular interval (discrepancy of 20 ms was allowed)
- Pacing threshold  $>2$  V

Criteria for para-Hisian pacing were:

- Paced QRS at least 50 ms shorter than right apical paced QRS (always  $<130$  ms)
- Paced QRS axis concordant with the electrical axis of the native QRS (discrepancy not superior to  $20^\circ$  to  $30^\circ$ )
- Pacing threshold lower than 1 V, as also the muscular portion of the interventricular septum was captured

The correct position of the pacing lead positioned in the His area (high interventricular septum) was assessed using the following parameters:

- R-wave sensing (escape rhythm)  $>5$  mV
- Absence of atrial "far fields," due to a too-high lead position

- Paced QRS criteria concordant with the direct His or para-Hisian pacing

Ten minutes after both leads were positioned, their stability was checked, performing slight traction movements.

The high interventricular septum lead was then connected to the "atrial" port, while the conventional right ventricular apical lead was connected to the "ventricular" port of a dual-chamber rate-responsive PM, which was programmed in DDDR mode with a short AV delay (90 ms). In this way, if para-Hisian stimulation was effective, the following apical stimulus fell in the ventricular refractory period, whereas if para-Hisian stimulation failed due to lead dislodgement and/or pacing threshold increase, cardiac stimulation was guaranteed by the conventional apical lead. Pacemaker output was adjusted with a 100% voltage safety margin above the pacing threshold for both the leads.

**Clinical evaluation and follow-up.** All the pacing parameters were re-evaluated before hospital discharge; chest X-rays with anterior-posterior, right and left anterior oblique, and lateral projections were also taken. After one month, the proper functioning of the system (both for para-Hisian and apical pacing) and the lead position stability were checked using fluoroscopic images.

The enrolled patients were randomly assigned to a six-month period of "DDDR" pacing mode (para-Hisian stimulation with backup apical pacing), or to six months of apical ventricular ("VVIR") pacing mode. Periodic 24-h Holter monitoring tests were planned in order to confirm the efficacy of the previous AV node ablation and to assess constant ventricular capture with the programmed pacing mode. After completion of the first six-month period, patients crossed over for a six-month period of the alternative pacing modality.

Rate-responsive algorithm programming (with activity sensor activated) was the same in all patients and unchanged in both randomized study periods; the lower rate was 80 beats/min during the run-in period to minimize the risk of bradycardia-dependent ventricular arrhythmias, and 70 beats/min during the two randomized study periods; the upper rate was between 120 and 130 beats/min. Patients were blinded to the pacing mode assigned.

The run-in period and the subsequent balanced randomization of the sequence of pacing sites avoided the influence of heart rate stabilization on the evaluated clinical effects concerning the different pacing sites. At the end of each period, a complete assessment of QoL, functional class, and echocardiographic parameters was performed; the medical investigators who conducted the clinical and echocardiographic evaluation were also blinded to the pacing mode. Para-Hisian pacing effectiveness was determined by comparing the data obtained after six months with this pacing modality with the results achieved after six months of apical pacing.

At the end of the one-year follow-up study period, the PM was permanently programmed in the para-Hisian



pacing mode. The drug therapy administered after the run-in period was the same during the two crossover study periods in all patients (digoxin in 56% of patients, angiotensin-converting enzyme inhibitors-angiotensin receptor blockers in 75%, diuretics in 68%, beta-blockers in 31%, diltiazem in 19%, vasodilators in 37%, dicumarolics in 87%, acetylsalicylic acid in 12%).

**Statistical analysis.** All the data are expressed as mean  $\pm$  SD. The results were analyzed using paired two-tailed *t* tests.

Repeated-measures analysis of variance was used to assess the site-pacing-related changes in left ventricular volumes, with the value of the EF (median of baseline value 52%) as a between-patient factor.

A *p* value  $<0.05$  was considered statistically significant.

## RESULTS

**PM implantation data.** The implanted leads for apical pacing were conventional bipolar ventricular leads (active or passive fixation). The leads used for para-Hisian pacing were screw bipolar leads: Capsure Fix 4068 (six patients), 5068 (three patients), and 5076 (eight patients) (Medtronic Inc., Minneapolis, Minnesota). The pacing lead was always positioned in close proximity to the His-bundle potential mapping dipole (Fig. 1). All the patients were implanted with a dual-chamber PM Clarity DR 860, Vitatron (Arnhem, the Netherlands) (rate-responsive PM with a dual sensor: Activity + QT). Mean fluoroscopic exposure time for the para-Hisian lead implant was  $18 \pm 9$  min (range from 8 to 40 min).

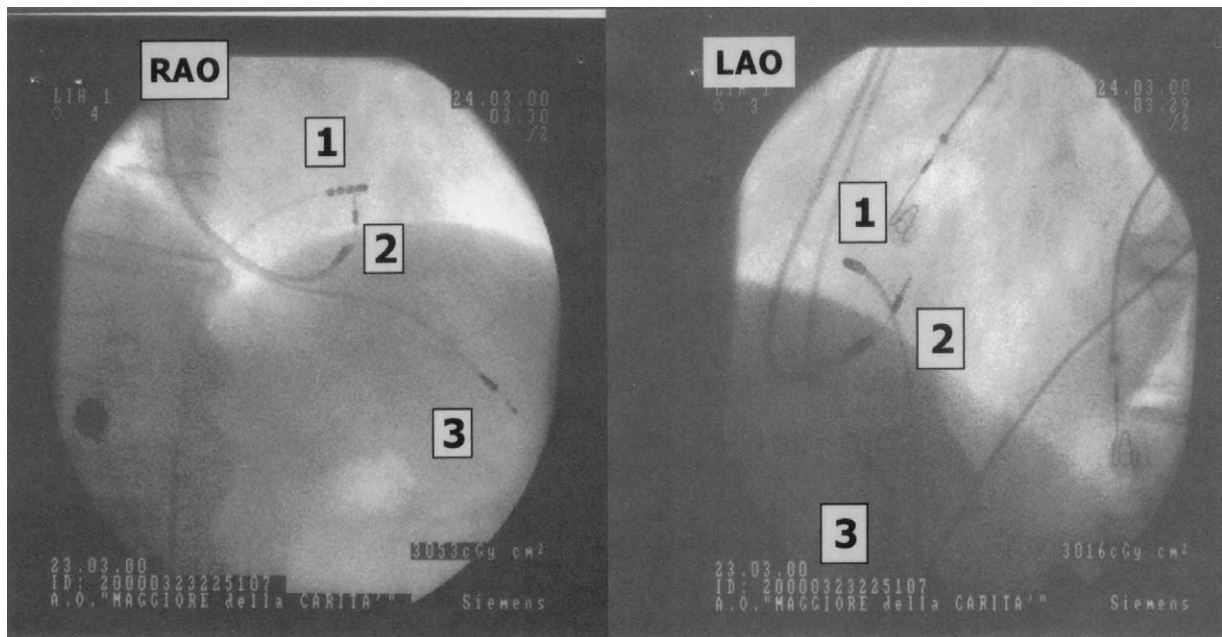
Acute pacing threshold ranged from 3.8 V (pulse width 0.5 ms) in case of direct His-bundle pacing to values always  $<1$  V in case of para-Hisian stimulation. The mean pacing

threshold was  $0.92 \pm 0.7$  V (0.5 ms); mean pacing impedance was  $614 \pm 177$  ohms; mean sensed potential (R-wave sensing) was  $6.9 \pm 3.4$  mV; atrial "far-field" potentials were never observed from para-Hisian pacing leads. Electrical measurements detected from the apical ventricular lead were within normal ranges (mean pacing threshold  $0.55 \pm 0.1$  V, at 0.5 ms).

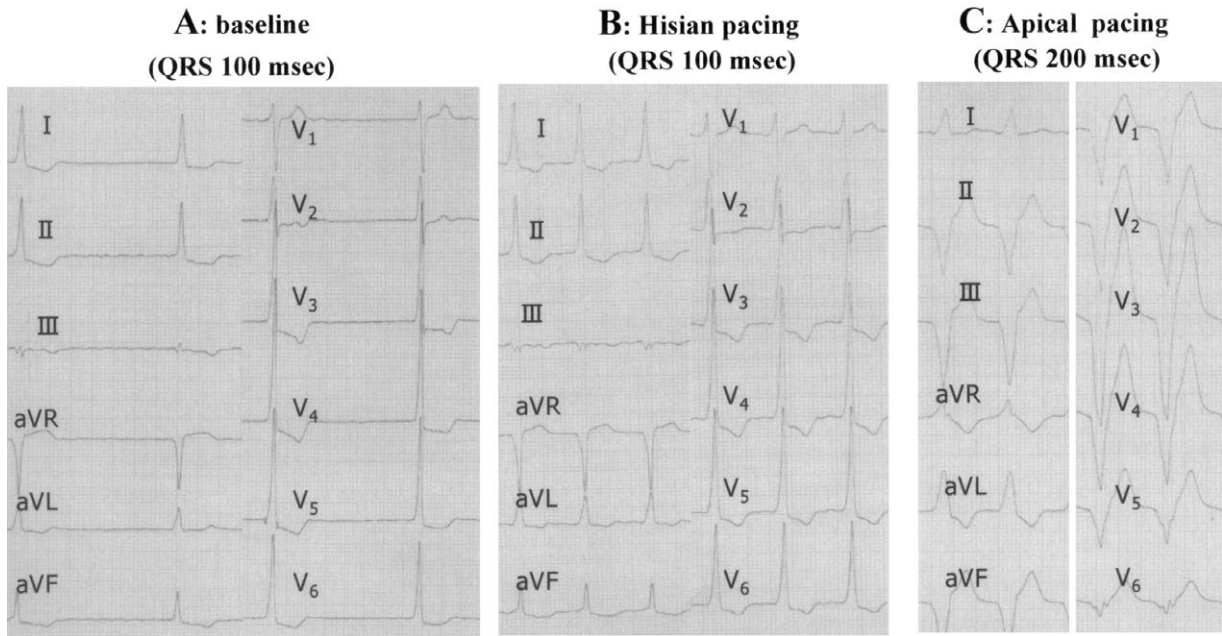
In one patient (#7), it was not possible to perform para-Hisian pacing because of lead instability, probably due to AV junction anatomical changes subsequent to previous mitral and aortic valve replacement. In another patient (#10), five days after the implant, the patient experienced an in-hospital cardiac arrest due to primary ventricular fibrillation; the system was then explanted, and a rate-responsive single-chamber cardioverter-defibrillator was implanted.

Implant and complete follow-up data were collected in 16 patients with permanent para-Hisian pacing and backup right ventricular apical stimulation. In 4 of 16 patients (25%), true direct His-bundle stimulation was achieved (Fig. 2), with a correct latency between spike and paced QRS onset, similar to the native H-V interval. In 12 of 16 patients (75%), all the criteria for para-Hisian pacing were met. Mean QRS duration was  $88.3 \pm 7.1$  ms at baseline,  $121.1 \pm 9.9$  ms during para-Hisian pacing,  $179.4 \pm 17.8$  ms during apical pacing ( $p < 0.001$  QRS width during para-Hisian vs. apical stimulation). Data collected in each patient (baseline QRS duration, QRS width during para-Hisian and apical pacing) are reported in Table 2.

**Follow-up data.** All 16 patients completed the one-year follow-up with two randomized periods of para-Hisian versus conventional pacing. In one patient, a slight para-Hisian lead dislodgement was observed one month after



**Figure 1.** Patient #6. Right anterior oblique (RAO) and left anterior oblique (LAO) fluoroscopic projections showing leads position during the "ablate and pace" procedure and Hisian pacing; 1 = quadripolar Hisian mapping catheter; 2 = screw-in bipolar lead positioned in close proximity to the His-bundle; 3 = bipolar passive fixation positioned in right ventricular apex.



**Figure 2.** Patient #6. 12-lead surface electrocardiogram: (A) after atrioventricular node radiofrequency ablation: chronic atrial fibrillation with nodal escape rhythm (QRS 100 ms); (B) during direct His-bundle pacing: paced QRS duration 100 ms, with morphology and electric axis equal to the native QRS; (C) during right apical ventricular pacing: paced QRS duration 160 ms, with extreme left-axis deviation and “left bundle branch block” morphology.

implantation; the lead remained in a stable position at 3 cm from the original position, with a paced QRS similar to the one detected at implantation. No late dislodgement was observed after the first month of follow-up.

At follow-up examinations after 1, 6, and 12 months, the QRS duration remained the same as that recorded at

**Table 2.** QRS Duration (ms) During Junctional Escape Rhythm With Nodal AV Block Post-RF Ablation (Basal), During Hisian and Para-Hisian Stimulation (Pacing His), and During Right Apical Conventional Stimulation (Pacing Apex)

Patient	Basal (QRS, ms)	Pacing His (QRS, ms)	Pacing Apex (QRS, ms)
1	80	120	170
2	80	130	190
3	90	120	170
4	90	120	170
5	80	130	210
6*	80	100	160
7†	90	NA	NA
8*	90	110	160
9	90	120	170
10†	90	130	190
11	80	130	210
12	90	120	170
13	100	130	200
14*	100	100	150
15*	100	120	180
16	80	130	200
17	90	120	170
18	90	130	180
Mean ± SD	88.3 ± 7.1	121.1 ± 9.9	179.4 ± 17.8

p < 0.05 Hisian/para-Hisian pacing vs. apical pacing. \*Patients in whom true direct His bundle pacing was achieved; †patients subsequently excluded from the study (see text for further explanation).

AV = atrioventricular; NA = not available; RF = radiofrequency.

implantation. Pacing thresholds remained within acceptable safety margins ( $1.0 \pm 0.8$  V; 0.5 ms vs.  $0.68 \pm 0.2$  V during apical stimulation; p = 0.13) after 12 months of follow-up; both for apical and para-Hisian pacing, <5 V (0.5 ms) were used, with conventional impact on the battery life.

**Hemodynamic and functional evaluation.** Data on hemodynamic and functional performances collected at the enrollment, after six months of para-Hisian pacing, and after six months of right ventricular apical pacing are reported in Table 3.

The NYHA functional class ( $2.33 \pm 0.6$  baseline) was unchanged during apical pacing ( $2.5 \pm 0.4$ ) and showed a significant improvement during para-Hisian stimulation ( $1.75 \pm 0.4$ ; p < 0.05 both vs. baseline and vs. apical

**Table 3.** Functional and Echocardiographic Data Regarding Baseline Conditions, Para-Hisian Stimulation, and Right Ventricular Apical Pacing of the 16 Patients in the Study

	Baseline	Hisian/Para-Hisian Pacing	Right Apical Pacing
NYHA functional class	2.33 ± 0.6	1.75 ± 0.4†	2.5 ± 0.4
6-min walk test (m)	378 ± 60	431 ± 73†	360 ± 71
QoL (score)	32.5 ± 15	16.2 ± 8.7*	20.6 ± 8.5
LV-EDV (ml)	98.8 ± 29.6	93.2 ± 26.6	99.4 ± 33.1
LV-ESV (ml)	49.3 ± 25.0	44.7 ± 17.6	50.9 ± 23.2
LVEF (%)	52.0 ± 9.1	53.4 ± 7.9	50.0 ± 7.9
MR degree	1.68 ± 0.6	1.22 ± 0.8†	1.93 ± 1
TR degree	1.62 ± 0.7	1.46 ± 0.5‡	1.93 ± 0.7
PAPs (mm Hg)	32.7 ± 5.6	32.9 ± 6.1	36.3 ± 7.8

\*p < 0.05 para-Hisian pacing vs. baseline; †p < 0.05 para-Hisian pacing vs. apical pacing and vs. baseline; ‡p < 0.05 para-Hisian pacing vs. apical pacing.

LV-EDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LV-ESV = left ventricular end-systolic volume; MR = mitral regurgitation; NYHA = New York Heart Association; PAP = systolic pulmonary pressure; QoL = quality of life; TR = tricuspid regurgitation.

ping). Exercise tolerance as assessed by the distance walked in 6 min ( $378 \pm 60$  m at enrollment) showed a slight worsening during apical stimulation, which was not statistically significant ( $360 \pm 71$  m), but significantly improved during para-Hisian pacing ( $431 \pm 73$  m;  $p < 0.05$  vs. baseline and apical pacing). The QoL score showed a positive trend, which was not statistically significant, from baseline (score  $32.5 \pm 15.0$ ) to apical conventional pacing (score  $20.6 \pm 8.5$ ), probably because the beneficial effect induced by heart rate regularization was counterbalanced by the negative hemodynamic effects related to ventricular desynchronization. Only during para-Hisian pacing was a significant improvement observed (score  $16.2 \pm 8.7$ ;  $p < 0.05$  vs. baseline conditions).

The left ventricular EF did not show significant differences, with a slight increase during para-Hisian pacing ( $53.4 \pm 7.9\%$ ) compared with apical pacing ( $50.0 \pm 7.9\%$ ). However, when patients were stratified according to the EF (median of baseline values  $\leq 52\%$  or  $> 52\%$ ), the site-pacing related changes in volumes differed between the two groups. In patients with EF  $\leq 52\%$  ( $n = 9$ ), baseline left ventricular volumes (diastolic  $118 \pm 30$  ml; systolic  $66 \pm 27$  ml) were larger than those of patients with EF  $> 52\%$  ( $n = 7$ ) (diastolic  $82 \pm 14$  ml,  $p < 0.04$ ; systolic  $31 \pm 5$  ml,  $p = 0.06$ ). Furthermore, there was a site-specific interaction between the two groups, which was of borderline significance ( $p = 0.076$ ), with a  $13 \pm 20\%$  (para-Hisian pacing) and  $5 \pm 21\%$  (apical pacing) cavity volume reduction in the group with low EF, and a  $26 \pm 66\%$  (para-Hisian pacing) and  $35 \pm 58\%$  (apical pacing) volume dilation in patients with good EF.

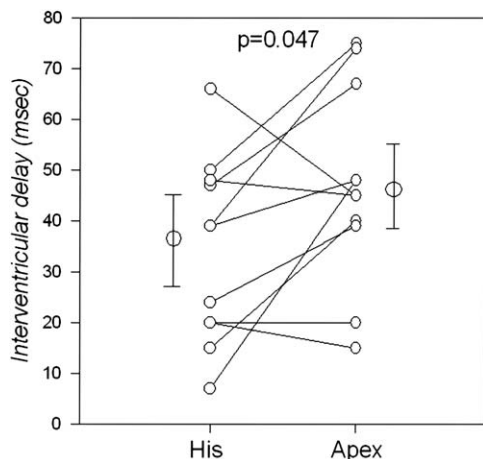
The degree of mitral and tricuspid regurgitation was significantly greater during apical pacing ( $1.93 \pm 1$  and  $1.93 \pm 0.7$  index at semiquantitative analysis, respectively) than during para-Hisian pacing ( $1.22 \pm 0.8$  and  $1.46 \pm 0.5$ ;  $p < 0.05$  for both). A significant relation between pacing site and the degree of mechanical dyssynchrony was observed as well: conventional pacing resulted in significant prolonga-

tion of interventricular mechanical delay ( $47 \pm 19$  ms), which was significantly higher than during para-Hisian pacing ( $34 \pm 18$  ms,  $p < 0.05$ ) (Fig. 3).

## DISCUSSION

One of the aims of permanent cardiac stimulation is to maintain an adequate heart rhythm, trying to restore the physiological sequence of heart activation. Over the last decades, great importance has been attributed to two elements considered essential for physiological cardiac stimulation: AV synchrony and rate-responsive function. Dual-chamber rate-responsive PMs, now widely used, were thus considered "physiological." More recently, clinical observations and large studies (5-9) comparing VVIR and DDDR pacing modes have demonstrated that the latter stimulation modality is not fully "physiological" either. The Canadian Trial Of Physiologic Pacing (CTOPP) (5) with VVI compared to DDD pacing, the Randomized Comparison of Atrial and Dual-Chamber Pacing in 177 Consecutive Patients With Sick Sinus Syndrome (DANISH) study (6) with AAI versus DDD pacing, the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial (7) with ICD-VVI mode (40 beats/min) compared with ICD-DDD mode (70 beats/min), the Mode Selection Trial (MOST) studies (8,9) with patients affected by sick sinus syndrome randomized to DDDR or VVIR pacing, and the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II patients with predominantly right ventricular pacing (17), all reported reduced left ventricular systolic function and a higher hospitalization rate for heart failure when the percentage of right ventricular pacing was high ( $> 40\%$ ). A truly physiological ventricular pacing modality, in fact, must ensure correct synchronization of the two ventricles. In case of spontaneous ventricular desynchronization, biventricular pacing is currently being widely recommended because its positive results on cardiac function and QoL have been confirmed by major controlled trials (18-21). Apart from well-established biventricular pacing, other alternative pacing sites have been proposed such as right ventricular outflow tract (22) and bifocal right ventricular stimulation (23), with uncertain and partial results. In the presence of preserved intraventricular conduction and AV nodal block, however, a preventive physiological mode of pacing should be chosen (10); apart from well-established biventricular pacing (11), permanent direct His-bundle pacing could be an optimal alternative (12,13), even if these two pacing techniques have never been compared.

Electrical stimulation of the His bundle has been used for diagnostic purposes since the 1970s, and recently too, by various researchers (24-27). In the 1990s, other researchers (28-30) introduced this approach for therapeutic purposes, as an experimental non-conventional pacing site. In 2000, Deshmukh et al. (12) presented, for the first time, a study population in which direct His-bundle pacing was achieved; they confirmed the reliability and the effectiveness of this



**Figure 3.** Interventricular mechanical delay (ms) during para-Hisian (His) and apical (Apex) pacing in 11 patients evaluated with Doppler echocardiography: comparison between pre-ejection aortic and pulmonary times.



modality of pacing in 12 of 18 patients (65%) with chronic AF, dilated cardiomyopathy (EF <40%), NYHA functional class III to IV, and spontaneous narrow QRS complexes. During a mean follow-up of 23 months, they observed a significant improvement in functional class and hemodynamic parameters; it was not clear if the documented benefit could be related, at least in part, to ventricular rate control rather than to pacing modality. Similarly encouraging results were also reported by Padeletti et al. (31) in 5 patients, and by Vazquez et al. (32) in 12 patients.

Recently, Deshmukh and Romanyshyn (13) confirmed the previously obtained results in a larger patient cohort, well defining the possible problems related to this pacing modality. In particular, he emphasized that the criteria for true direct His-bundle pacing are very rigorous and not easily met: they were fulfilled in 70% of patients. In our experience, direct His-bundle stimulation was achieved in 25% of patients. In the majority (75%) of the population, para-Hisian pacing was obtained: the muscular portion of the high interventricular septum was activated together with the His-bundle conduction system. This is proved by the relatively narrow paced QRS (always shorter than 130 ms) and, overall, the electrical axis that was always concordant with that of native QRS. The latter observation could mean that, despite a partial “pre-excitation” of the superior portion of the interventricular septum, the conduction in the His-Purkinje system allows the stimulus to be conducted to the ventricular myocardium simultaneously, activating both ventricles in a synchronous fashion. The hypothetical possibility of damaging the His bundle using the helix of the screw-in lead must be considered, however, even if it has not been reported in preliminary studies (28,30).

Patients with chronic AF in whom the “ablate and pace” procedure is performed are particularly suitable for comparing “non-physiological” right ventricular apical pacing with “physiological” para-Hisian stimulation. In these subjects, in fact, the absence of atrial contraction allows researchers to ascribe possible hemodynamic improvements only to ventricular resynchronization. In preliminary results reported by Deshmukh et al. (12), the benefits induced by Hisian pacing were determined by the comparison between the basal pre-ablation situation and this new mode of pacing; these positive results, however, could also have been related to the reversal of tachycardiomyopathy, which was achieved with AV node ablation. The clinical experience of our group, reported in previous preliminary abstracts (33,34) and in the present study, seems to confirm that, apart from the benefits induced by the regression of tachycardiomyopathy, which might have been achieved by ablation of the AV node, physiological para-Hisian stimulation also induces significant functional and hemodynamic improvements. They seem, to some extent, to be modulated by basal EF. Although there were no overall changes in ventricular volumes, when patients were stratified according to pump function (EF >52% vs. ≤52%), site-pacing related changes in volumes of borderline significance could be detected

between the two pacing sites in favor of the para-Hisian mode. Despite the limited number of depressed ventricles in our population, it is conceivable that differences in favor of para-Hisian pacing, according to our analysis, would be further amplified by recruiting patients with very low EF.

Furthermore, the amount of mitral and tricuspid regurgitation significantly decreased (Table 3) only with para-Hisian pacing, suggesting that the clinical and functional improvements with stimulation at this site are probably mediated by improvement of interventricular dyssynchrony, as evidenced by the decrease in the interventricular mechanical delay associated with QRS shortening.

In conclusion, the efficacy on functional and hemodynamic parameters and the long-term safety of para-Hisian pacing may allow a more widespread use of this technique, justifying this approach as the first choice in patients with left ventricular dysfunction and preserved intraventricular conduction who require permanent ventricular stimulation.

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**Reprint requests and correspondence:** Dr. Eraldo Occhetta, Divisione Clinicizzata di Cardiologia, Azienda Ospedaliera Maggiore della Carità Corso Mazzini 18, 28100 Novara, Italy. E-mail: occhetta@r-j.it.

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