Pacemaker-induced mitral regurgitation: prominent role of abnormal ventricular activation sequence versus altered atrioventricular synchrony

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Key words:
Doppler echocardiography; Mitral regurgitation; Pacemaker.

Background. **Functional mitral regurgitation is a hemodynamic adverse consequence of right ventricular apical pacing that profoundly modifies the contraction and relaxation of the left ventricle by inverting and delaying its activation sequence. The aim of this study was to analyze by Doppler echocardiography in the acute setting the true incidence and the mechanism responsible for the right ventricular apical pacing-induced mitral regurgitation.**

Methods. **We studied 27 consecutive patients submitted to pacemaker implantation (VVI n = 9; DDD n = 18) because of bradyarrhythmias. The exclusion criteria were structural cardiac disease and permanent atrioventricular block. Patients underwent Doppler echocardiographic examination during both spontaneous rhythm (pacemaker off) as well as during programmed pacing at a rate of 70 b/min. In case of a double chamber pacemaker, a non-optimized atrioventricular delay of 150 ms was chosen.**

Results. **Two groups were identified: 11 patients with (Group 1, mean age 71 ± 7 years) and 16 patients without (Group 2, mean age 71 ± 4 years) new-onset pacing-induced mitral regurgitation. The incidence of mitral regurgitation was found to be higher during DDD (33%) than during VVI (24%) pacing mode. The relationship between gender and the occurrence of pacing-induced mitral regurgitation was striking: 10/13 women (77%) presented with mitral regurgitation during acute right ventricular apical pacing while this complication occurred in only 1/14 men (7%). Moreover, analysis of variance (ANOVA) and *post-hoc* pairwise multiple comparison showed an increased size of the mitral apparatus, as defined by the enlargement of the annulus (long axis 28 ± 3 vs 23 ± 2 mm; short axis 25 ± 3 vs 20 ± 3 mm, p = 0.05) and the lengthening of the anterior mitral leaflet (23 ± 4 vs 18 ± 2 mm, p = 0.05) and chordae tendineae (16 ± 3 vs 13 ± 2 mm, p = 0.05). This was probably related to the high female prevalence (91%) in Group 1 as compared to the control group (50 healthy subjects; 17 men, 33 women; mean age 71 ± 8 years). No significant differences were observed between Group 2 and controls.**

Conclusions. **Our study confirmed that functional mitral regurgitation is a frequent consequence of right ventricular apical pacing. Despite the maintenance of normal atrioventricular synchrony, we found that the pathway for ventricular depolarization was the critical determinant of normal mitral valve function. Such data show the importance of the preservation of a normal ventricular activation sequence during permanent cardiac pacing where it is technically feasible. Female patients seemed to be exposed to a higher risk of pacing-induced mitral regurgitation due to an anatomic predisposing condition of the mitral apparatus and to the left ventricular dyssynchronous contraction secondary to right ventricular apical pacing.**

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Introduction

As early as in the 70's, Furman and Escher[1] emphasized the deleterious hemodynamic effects of mitral regurgitation (MR) occurring as a possible complication of asynchronous ventricular pacing. Such an adverse hemodynamic consequence was widely attributed to the loss of atrioventricular (AV) synchrony during ventricular demand pacing (VVI) and to the left ventricular dyssynchronous contraction due to the stimulation into the right ventricular apex that, by inverting and delaying the left ventricular activation, causes an altered depolarization pattern.

Investigators have been increasing their interest in the hemodynamic effects of right

ventricular pacing since the introduction of standard DDD pacing with a short AV delay and of biventricular pacing systems as therapeutic options for dilated cardiomyopathy, in view of the fact that both techniques provide at least one stimulation site in the right ventricle[2-5].

Right ventricular apical pacing leads to a left bundle branch block-like electrocardiographic pattern but, unlike the classic left bundle branch block, the hemodynamic effects are less clear. Classic left bundle branch block *per se* accounts for a high incidence of functional MR but, since the mechanical consequences are not exactly the same, data about the true incidence of right ventricular pacing-induced MR and about its role in causing deleterious hemodynamic effects are still scant and controversial[6-8].

The aim of the present study was to investigate by Doppler echocardiographic methods in the acute setting the role of right ventricular apical pacing in determining functional MR and to compare this role to that of the altered AV synchrony.

Methods

Patients. From January 1998 to June 2000, patients referred to our Center for bradyarrhythmias which needed definitive cardiac pacing were candidates for this study. Since the study protocol included a pre-implant Doppler echocardiographic evaluation during normal AV conduction, patients with permanent AV block were excluded. Thus, 27 subjects without any clinical or echocardiographically diagnosed structural cardiac abnormalities were recruited in the study.

Study protocol. Patients enrolled in the study underwent a standard Doppler echocardiographic examination immediately before pacemaker implantation; in those patients with paroxysmal AV block, the recordings were obtained only in case of persistent normal AV conduction. Before discharge, a Doppler echocardiographic examination was repeated to assess the presence or absence of MR during programmed pacing at a rate of 70 b/min or at rates exceeding the intrinsic heart rate by approximately 10 b/min, in order to ensure that cardiac stimulation was total. The programming was maintained for 5 min. An AV delay of 150 ms or the longest interval able to guarantee a complete ventricular capture without fusion beats on the surface ECG was chosen during DDD mode; such a non-optimized AV delay value lies within the usual range of individually optimized AV delays measured in other studies. In those patients with a DDD pacemaker in whom the AV synchronous pacing did not induce MR, a Doppler echocardiographic exam was repeated after reprogramming the pacemaker in VVI mode and maintaining the same rate and the same duration of stimulation.

Doppler echocardiographic assessment. An Acuson 128XP/5 machine (Acuson Corp., Mountain View, CA, USA) equipped with a 2.5-3.5 MHz transducer was used. Patients underwent standard M-mode and two-dimensional echocardiographic examination; all measures were calculated from the echocardiographic images according to the American Society of Echocardiography recommendations[9]. Rather than the ejection fraction, the left ventricular fractional shortening was calculated because it has been shown that the asymmetry of ventricular depolarization induced by right ventricular apical pacing may lead to significant errors in the estimation of the left ventricular ejection fraction[10]. Additionally the dimensions of each mitral valve connective tissue element were calculated by two-dimensional echograms as follows: the end-diastolic (at the onset of the QRS complex) diameters of the annulus were obtained in the 4-chamber and 2-chamber apical views; in the left parasternal long-axis view we measured the end-diastolic length of the leaflets and the end-systolic length of the chordae tendineae, the latter being measured from the tip of the postero-medial papillary muscle to the leaflets' coaptation point. The presence and semi-quantification of MR was established using mapping criteria by color Doppler based on the depth and width of systolic flow disturbances; the severity of MR was evaluated by planimetry in the view that showed the largest jet area and expressed as a percentage of the left atrial area as follows: mild (< 20%), moderate (20-40%) and severe (> 40%)[11]. Trivial and inconstant MR were considered as variants of normal. Fifty subjects without cardiac disease (17 men, 33 women, mean age 71 ± 8 years) represented the control group for the echocardiographic findings.

Statistical analysis. Data are reported as mean ± SD; means of the two groups were compared by the Student's t-test, whereas means of the three groups were compared by one-way analysis of variance (ANOVA). When significant differences were detected, the data were analyzed by the *post-hoc* pairwise multiple comparison procedure of Bonferroni in order to identify which mean differed from another. The χ^2 test with the Yate's continuity correction and the binomial test were used to assess the significance of difference between two percentages. The non-parametric Mann-Whitney U-test was used when it was necessary.

A p value ≤ 0.05 was considered statistically significant. All statistical procedures were performed using the SPSS 9.0 (SPSS Inc., Chicago, IL, USA) statistical software.

Results

Patients characteristics (Tables I and II). Twenty-seven patients (13 women and 14 men) fulfilled the inclusion criteria; the mean age was 71 ± 4 years. Indications for definitive pacing included sinus node dysfunction in 18 patients, paroxysmal AV block in 4, low-rate chron-

Table I. Characteristics of the 27 patients with bradyarrhythmias in whom a permanent pacemaker was implanted.

Patient	Age (years)	Sex	Body surface area (m^2)	Indication for implant	Pacemaker	IVCD	Retrograde VA conduction	Pacemaker dependent
1	86	F	1.72	SND	VVI	LAFB	N	N
2	77	F	1.69	SND	VVI	–	Y	N
3	78	M	1.85	SND	VVI	–	NE	N
4	75	M	1.74	SND	DDD	–	N	Y
5	68	F	1.84	SND	DDD	–	N	N
6	72	F	1.73	SND	DDD	–	N	N
7	70	F	1.74	SND	DDD	–	N	N
8	70	M	1.85	SND	DDD	–	N	N
9	74	M	1.90	SND	DDD	LAFB	NE	N
10	71	M	1.74	SND	DDD	–	Y	N
11	67	M	1.86	SND	DDD	RBBB	N	N
12	57	F	1.69	VVS	DDD	–	N	N
13	70	M	1.80	SND	DDD	–	N	N
14	68	M	1.74	SND	DDD	–	N	N
15	67	M	1.97	SND	DDD	–	N	N
16	77	M	1.91	SND	DDD	–	N	N
17	76	F	1.73	AF	VVI	–	NE	Y
18	68	F	1.69	AVB	DDD	–	Y	N
19	69	F	1.68	AVB	DDD	–	N	N
20	72	M	1.84	AF	VVI	–	NE	Y
21	70	F	1.71	SND	DDD	–	N	N
22	70	M	1.83	SND	VVI	–	Y	N
23	69	M	1.77	AVB	DDD	–	N	N
24	75	M	1.92	SND	VVI	–	N	N
25	74	F	1.76	AF	VVI	–	NE	N
26	61	F	1.79	AVB	DDD	–	N	N
27	70	F	1.85	AF	VVI	–	NE	Y

AF = atrial fibrillation; AVB = atrioventricular block; IVCD = intraventricular conduction defect; LAFB = left anterior fascicular block; RBBB = right bundle branch block; SND = sinus node dysfunction; VVS = vasovagal syncope. Retrograde VA (ventriculo-atrial) conduction: N = absence; NE = non evaluated; Y = presence. Pacemaker dependent: N = predominantly non-paced rhythm; Y = predominantly paced rhythm.

ic atrial fibrillation in 4, and vasovagal syncope with bradycardia in 1 patient.

The following devices were implanted: 9 VVI (Regency SCX, St. Jude Medical, St. Paul, MN, USA) and 18 DDD/R (10 Trilogy DC/DR+ and 2 Affinity DR, St. Jude Medical; 4 Actros DR, Biotronik, Berlin, Germany; 2 Thera DR, Medtronic, Minneapolis, MN, USA). In all patients, the right ventricle was paced by a passive-fixed lead into the apex. Two VVI patients and 2 DDD patients were pacemaker-dependent. Three patients presented with an intraventricular conduction defect: a left anterior fascicular block in 2 patients and a right bundle branch block in 1 patient. Among the 23 patients with sinus rhythm, retrograde ventriculo-atrial conduction was assessed in 4 patients. Both the programmed AV delay and the pacing rate necessary to achieve complete ventricular capture were significantly different from the basal values.

Doppler echocardiographic studies. New-onset MR during the programmed pacing of the right ventricular apex occurred in 10 patients. Two of them had a history of chronic atrial fibrillation (Fig. 1). Pacing-related MR developed in 4/9 VVI patients and in 6/18 DDD patients. In accordance with the study protocol, 12 DDD patients without MR during AV synchrony pacing underwent a subsequent Doppler evaluation after reprogramming the pacemaker in the VVI mode; however, when the pacing modality was switched from DDD to VVI, only 1 patient, with a history of vasovagal syncope, displayed a mild degree new-onset MR. Finally, the population of subjects tested during the VVI and DDD pacing modes consisted of 21 and 18 patients respectively. The incidence of pacing-induced MR associated with the DDD pacing mode (33%) was higher than that observed for the VVI (24%) pacing mode. There were no statistical differences between the number of patients with and without MR induced using the DDD pacing mode ($p = 0.44$) whereas the difference was statistically significant when VVI pacing-mode was employed ($p = 0.02$) (Fig 2). In summary, two groups were identified: 11 patients with MR (Group 1, mean age 71 ± 7 years) and 16 without MR (Group 2, mean age 71 ± 4 years) during programmed cardiac pacing. The MR was considered as functional because its development was reversible and strictly related to the activation of right ventricular pacing in patients with normal hearts. The degree of MR was estimated mild and moderate in 9 and

Table II. Pacemaker-induced mitral regurgitation (MR) features in patients with and without preserved normal atrioventricular synchrony.

Patient	Degree of MR	Pacing mode responsible for MR	Heart rate (b/min)		AV delay (ms)	
			Spontaneous rhythm	Programmed pacing	Baseline value	Programmed pacing
1	1+	V-P	50	70	155	*
2	1+	V-P	60	70	160	*
3	0	V-P	58	70	155	*
4	0	AV-P	45	70	130	108
5	2+	AV-P	65	75	180	150
6	1+	AV-P	65	75	170	150
7	2+	AV-P	57	70	200	150
8	0	AV-P	46	70	200	150
9	0	AV-P	62	70	165	125
10	0	AV-P	59	70	190	150
11	0	AV-P	56	70	210	150
12	1+	V-P	61	70	140	*
13	0	AV-P	58	70	205	150
14	0	AV-P	60	70	180	150
15	0	AV-P	70	85	145	125
16	0	AV-P	65	75	180	150
17	1+	V-P	38	70	**	*
18	1+	AV-P	70	80	165	125
19	1+	AV-P	65	75	200	150
20	1+	V-P	42	70	**	*
21	1+	AV-P	50	70	170	150
22	0	V-P	61	70	155	*
23	0	AV-P	68	80	200	150
24	0	V-P	56	70	180	*
25	0	V-P	53	70	**	*
26	0	AV-P	58	70	155	125
27	0	V-P	39	70	**	*
Mean ± SD			57 ± 9§	72 ± 4	177 ± 24§	141 ± 14

AV= atrioventricular; AV-P = atrioventricular synchronous pacing; V-P = asynchronous ventricular pacing; 1+ = mild; 2+ = moderate.
* AV delay not available in patients paced in the VVI mode; ** AV delay not available in patients with atrial fibrillation; § $p < 0.001$.

2 patients respectively. Moreover, using the non-parametric Mann-Whitney U-test, no significant differences ($p = 0.378$) were found between Group 1 and Group 2 with regard to the different programmed AV delays needed to completely capture the ventricular rhythm; thus a cut-off value of the AV delay, considered as "protective" against the pacemaker-induced functional mitral insufficiency, was not identified.

Gender was strongly related to the presence or absence of pacing-induced MR: 10/13 women (77%) compared to 1/14 men (7%) developed MR during acute right ventricular apical pacing ($p < 0.0001$) (Fig. 3). Consequently the patient population in Group 1 consisted almost exclusively of women (91%) while females constituted only 19% of the patient population in Group 2.

The echocardiographic characteristics of the patients at baseline are shown in table III. One-way analysis of variance revealed no significant difference among the three groups with regard to the left ventricular size and to the fractional shortening; only the left atrial size was significantly increased in Group 1. However, even for this group values were within the normal range. Group 1, represented almost exclusively by women, had a smaller mean body surface area compared with Group 2 (1.73 ± 0.06 vs 1.83 ± 0.07 m^2, $p = 0.05$). At *post-hoc* analysis, a tendency towards increased dimensions of the mitral apparatus was found in Group 1. In particular, compared to Group 2 and to controls, patients in this group presented with a significant enlargement of the annulus and with an increased length of the anterior mitral leaflet and chordae tendineae.

Discussion

Although ventricular pacing-induced MR has been described since the 1960s as a contributory mechanism of the "pacemaker syndrome", our knowledge on this phenomenon is based only on anecdotal cases. Data about its prevalence and regarding its etiologic role in the development of deleterious hemodynamic effects are scant and controversial. In 1984 an experimental study by Maurer et al.[12] demonstrated the frequent occurrence of right ventricular pacing-related MR. In our study the incidence of MR paralleled the experimental data of Maurer et al. and occurred, in direct relation to the pacing of the right ventricular apex, in about one third of the patients. First, in 1974 Haas and Strait[13] documented a clinical case of an overt correlation between heart failure and MR, caused by endocardial pacing in the apex of the right

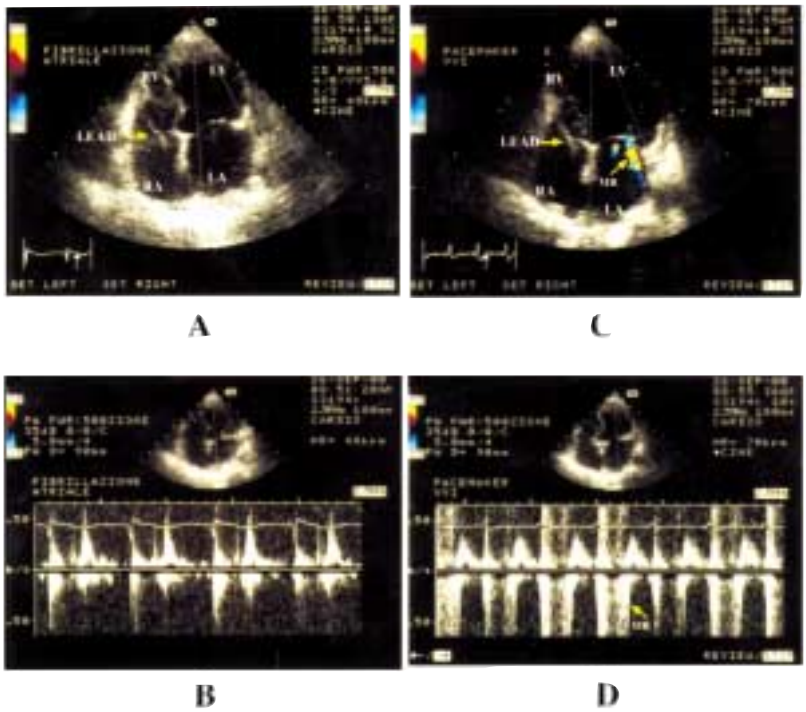

Figure 1. *Example of a two-dimensional echocardiographic image in the 4-chamber apical view in a patient suffering from atrial fibrillation with complete atrioventricular block and a substitutive narrow QRS complex rhythm. The* upper panels *show mitral flow color Doppler mapping while the* lower panels *show pulsed-wave Doppler mapping. During a normal ventricular activation sequence at a rate of 48 b/min (*A *and* B*) no systolic mitral regurgitation (MR) was observed whereas mild MR appears during ventricular pacing at a rate of 70 b/min (*C *and* D*). In this example, since this patient presented with atrial fibrillation, functional mitral insufficiency is clearly related to the left ventricular dyssynchrony due to right ventricular apical pacing and not to the loss of atrioventricular synchrony due to the VVI pacing. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.*

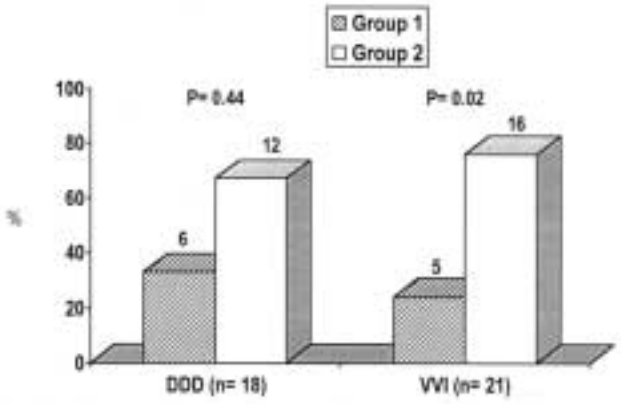

Figure 2. *Relationship between the occurrence of functional mitral regurgitation and different cardiac pacing modalities. Compared to ventricular asynchronous pacing (VVI), atrioventricular synchronous pacing (DDD) did not provide any added benefit in the prevention of pacing-induced mitral regurgitation.*

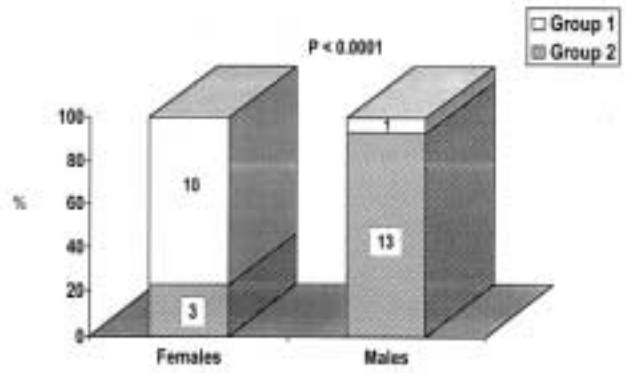

Figure 3. *Relationship between pacing-induced mitral regurgitation and gender. The female gender was strongly related to the induction of new-onset mitral regurgitation during programmed cardiac pacing as demonstrated by the gender distribution in subjects with (Group 1) and without (Group 2) pacing-induced mitral regurgitation.*

ventricle, that required the discontinuation of the asynchronous ventricular pacing.

In these reports, it was postulated that the loss of AV synchrony during VVI pacing was a major mechanism leading to MR; consequently, it was assumed that synchronous AV pacing, such as that achieved using the DDD mode, would have prevented this phenomenon.

Afterwards, other authors showed that the maintenance of normal AV synchrony by a DDD pacemaker failed to prevent the occurrence of MR[14-16].

Mark and Chetham[15] reported a case of hypotension consequent to replacement of atrial demand pacing (AAI) by AV synchronous pacing which resulted in an abrupt worsening of the preexistent MR and hemodynamically significant consequences.

Le Tourneau et al.[16] described 2 cases of mitral valve replacement in patients with pacing-induced MR after radiofrequency ablation of the AV junction. In these 2 cases both VVI and DDD pacing caused severe worsening of MR. In accordance with such data, in our pa-

Table III. Baseline echocardiographic characteristics in patients with (Group 1) and without (Group 2) pacing-induced mitral regurgitation compared with the control group.

Parameter	Group 1 (n=11)	Group 2 (n=16)	Controls (n=50)	p
Body surface area (m^2)	1.73 ± 0.06	1.83 ± 0.07§	1.74 ± 0.07	0.0001
Left cardiac cavity size				
LV end-diastolic diameter (mm)	49 ± 2	49 ± 2	49 ± 9	0.621
LV end-systolic diameter (mm)	34 ± 2	34 ± 2	33 ± 2	0.11
LV fractional shortening (%)	30 ± 3	30 ± 2	30 ± 3	0.581
LA dimensions (mm)	34 ± 4*	33 ± 4	31 ± 3	0.013
Mitral apparatus				
Annular long axis (mm)	28 ± 3**	23 ± 2	23 ± 2	0.0001
Annular short axis (mm)	25 ± 3**	18 ± 2	20 ± 3	0.0001
Chordae tendineae (mm)	16 ± 3**	13 ± 2	13 ± 2	0.011
Anterior leaflet (mm)	23 ± 4**	18 ± 2	18 ± 2	0.0001
Posterior leaflet (mm)	10 ± 2	9 ± 1	9 ± 1	0.083

LA = left atrial; LV = left ventricular. * p = 0.05 vs controls; ** p = 0.05 vs Group 2 and controls; § p = 0.05 vs Group 1 and controls.

tients MR was observed to occur less frequently in the VVI than in the DDD pacing mode, although this difference did not reach statistical significance; besides, the extent of the transmitral regurgitation jets as assessed by color Doppler was similar in both pacing modalities. Thus, despite the maintenance of AV synchronous pacing, the pathway for ventricular depolarization related to the ventricular pacing site turned out to be a critical determinant of normal mitral valve function.

The same conclusion was reached by Cannan et al.[17] who reported a case of a patient with chronic atrial fibrillation in whom severe ventricular pacing-induced MR necessitated that the programmed stimulation rate be decreased in order to attain a low frequency cardiac pacing[17]. Similarly, our 2 VVI patients with chronic atrial fibrillation, in whom MR did not occur during native conduction to the left ventricle, developed MR following right ventricular apical pacing. This result excludes the role of the loss of AV synchrony in the pathogenesis of MR, while conferring a major role to the dyssynchronous left ventricular contraction which, in turn, is attributable to the right ventricular pacing site. Recent clinical studies showed that adverse hemodynamic consequences related to conventional physiologic DDD pacing with right ventricular apical stimulation may occur even in patients in good clinical conditions[18,19].

Since a worsening of left ventricular hemodynamics as well as the degree of MR due to asynchronous contraction are more pronounced in case of left ventricular dysfunction, this may explain the reason why we induced, in the vast majority of patients, only mild MR during right ventricular apical pacing, as all our patients had preserved left ventricular function[20,21]. The only 2 patients who showed mild-to-moderate pacing-induced MR did not significantly differ in terms of baseline clinical and echocardiographic characteristics from the remaining 9 patients with inducible MR. Both patients were implanted with a DDD, confirming that AV synchronous pacing is unlikely to prevent the occurrence and to reduce the severity of MR when compared to ventricular asynchronous pacing. A possible explanation is that any benefit of a synchronous AV contraction is counterbalanced by the left ventricular dyssynchronous contraction caused by the right ventricular apical pacing that represents the standard pacing site in both DDD and VVI. Nevertheless, despite the widely reported impairment on left ventricular hemodynamics related to apical pacing, recent data on alternative choices of lead placement in the right ventricle, such as the outflow tract or the His bundle, are still controversial and inconclusive[22-27].

Analysis of the clinical characteristics of our population suggests that gender may have a critical role in the development of pacing-induced MR. In fact, the incidence of the latter was significantly higher in women than in men. In the group of patients with pacing-induced MR, gender distribution was significantly different with a prevalence of females (91%). These findings are similar to those observed in studies on mitral valve prolapse in which a higher prevalence of MR in females is reported. The authors held that the phenotypic characteristics of patients with functional prolapse-related MR included female gender[28-31]. Moreover, it has been observed that in healthy women, redundancy of the mitral apparatus as related to the left ventricular size, occurs more frequently than in healthy men. Our echocardiographic data confirmed these findings. In fact, the group of patients with pacing-induced MR, consisting almost exclusively of women, showed, despite a smaller body surface area, a significant annular enlargement and lengthening of the anterior mitral leaflet which were both more pronounced than those observed in the group of patients without pacing-induced MR and to controls.

We speculate that gender-related differences in mitral valve structure may account for the higher tenden-

cy of women to develop functional MR in the presence of a predisposing factor such as dyssynchronous left ventricular contractions. Thus, as postulated by other authors, left ventricular regional dyskinesia and alterations in the timing of papillary muscle contractions due to the initiation of the contraction in the right ventricular apex might play an important role in the development of MR. A contributory mechanism is likely to be represented by anatomic predisposing factors such as primary (i.e. gender-related) or secondary (i.e. cardiac disease-related) mitral size disproportion relative to the dimensions of the left ventricle[12,32-35].

Limitations of the study. We only evaluated the acute effects of right ventricular apical pacing on mitral function. However, this does not take into account the effects of long-term pacing that, by remodeling the cardiac chambers, might lead to a predisposing condition for late-onset structural MR.

The heart rate and the AV delay programmed during pacing were different from the basal values. This was necessary in order to achieve complete ventricular capture; however the mean programmed values (heart rate 72 b/min and AV delay 141 ms) lie within the usual range of optimal values in healthy hearts; in addition only 1 patient, in whom MR was not inducible, needed an AV delay as short as 108 ms.

Conclusions. Our clinical study demonstrated the frequent occurrence of functional MR directly related to right ventricular apical pacing. Despite the maintenance of normal AV synchrony with DDD pacing, the pathway for ventricular depolarization was found to be the critical determinant for normal mitral valve function. This confirms the importance of preservation of a normal ventricular activation sequence during permanent cardiac pacing in all patients in whom it is technically feasible.

Female gender seems to play a critical role in the development of pacing-induced MR. This might be due to the overlapping of two predisposing conditions such as the primary relative redundancy of the mitral valve apparatus and the altered timing of the papillary muscle contraction due to the pacing in the apex of the right ventricle.

Further studies are needed to investigate the long-term effects of chronic pacing on mitral valve function and its possible hemodynamic consequences in patients with and without left ventricular dysfunction.

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