

## Original Research

## Indications for Permanent Pacing and Pacing Mode Prescription from 1989 to 2006. Experience of a Single Academic Centre in Northern Greece

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**Introduction:** Indications for pacing and pacing mode prescription have changed in the past decades following advances in pacemaker technology. The aim of the present study was to evaluate changes in indications for pacing and pacing modes during the years 1989-2006 in a single academic pacemaker centre in Northern Greece.

**Methods:** Archives of permanent pacemaker implantation procedures were studied retrospectively and data from all implants, first or replacements, were retrieved.

**Results:** Data from 2078 procedures were found, 78.7% of which were first implantations. Patients were 54% male with mean age 72.5 years. Main indications for pacing were atrioventricular block (AVB, 45.7%), sick sinus syndrome (SSS, 32.8%), and atrial fibrillation (12.1%). Almost half (48.9%) of the AVB cases were complete AVB, while the most common types of SSS were tachy-brady syndrome (44.1%) and asystole (27.1%). Rare indications for pacing were carotid sinus syndrome (5.0%), heart failure (3.3%) and hypertrophic obstructive cardiomyopathy (1.0%). The two most frequently used pacing modes were VVI (38.5%) and DDD (25.8%). However, pacing modes have changed greatly over the years, with a marked increase in dual-chamber pacing after 1997 and a preference for rate responsive units after 2002. Biventricular systems were also used in selected patients with heart failure from 2002 on.

**Conclusions:** Indications for pacing and pacing mode prescription in our centre are similar to other pacemaker registries and reflect the global trend in pacing for mimicking the physiological activity of the heart and for addressing problems other than symptomatic bradycardia.

**P**ermanent pacemakers were first developed in the late 50s to prevent mortality from complete heart block.<sup>1</sup> Over the subsequent decades, there was impressive progress in pacing technology and permanent pacing became the standard treatment for symptomatic bradycardia. The early primitive pacing devices, which allowed only fixed rate asynchronous pacing in the right ventricle, soon evolved into more complicated systems capable of responding to the patient's heart rate, as well as pacing both the right ventricle and the right atrium.

These advances allowed pacemaker therapy to progress from simply preventing mortality to restoring normal atrioventricular activation, improving haemodynamic function and thus improving quality of life.<sup>2</sup>

In parallel with the evolution of pacing technology, the choice of pacing mode has changed over the years and the indications for pacing have extended to conditions other than symptomatic bradycardia.<sup>3,4</sup> Scientific societies have revised the indications for pacing and issued recommendations and guidelines.<sup>5</sup> The choice of

best pacing mode, though, seems to be strongly affected by many factors, which involve both the patient and the doctor as well as socioeconomic indices.<sup>6</sup>

Given the geographic differences within Europe and the alterations in pacing modes and indications over the past years,<sup>7</sup> we found it interesting to look through the archives of the permanent pacemaker implantations in a single academic pacemaker centre in northern Greece: the 1st University Cardiology Department of AHEPA University Hospital in Thessaloniki.

## Methods

### Data

Data were retrieved retrospectively from the clinic's archive and were transferred to an electronic database using SPSS 12 for windows. The study protocol included all the implantations, first or replacements, of permanent pacemakers that took place in the clinic from January 1989 until June 2006. For some analyses two separate periods were studied: period A, from 1989 until 1997; and period B, from 1998 until 2006. Implantations with many missing data were excluded from the study (102 cases, 4.6% of all implantations).

### Statistical analysis

Statistical analysis was carried out using SPSS 12 for windows. For continuous variables mean value, median value, variance and standard deviation were computed. Dichotomous variables were expressed as rates and percentages. Continuous variables were tested for normal distribution and appropriate statistical tests were applied. Means were compared using Student's t-test for the normally distributed variables, or the Mann-Whitney test otherwise. A p-value <0.05 was considered statistically significant. Means of more than two groups were compared using analysis of variance (ANOVA) for the normally distributed variables, or the Kruskal-Wallis test otherwise. Differences between groups were sought using the Mann-Whitney test with a level of statistical significance,  $p < 0.05/n$ , where n is the number of groups according to the Bonferroni correction.

## Results

### Patient characteristics

From 1989 until June 2006 there were 2180 pacemaker implantations registered, 102 (4.6%) of which had ma-

ny missing data and were excluded from any analysis. Statistical analysis was performed on the remaining 2078 cases, 1635 (78.7%) of which were first implants whereas 443 (21.3%) were replacements. The patients' mean age was  $72.5 \pm 10$ ; 54% were men and 46% women. Patients came from the Prefecture of Thessaloniki (43.5%) and from all other Prefectures of Northern Greece (Larissa 10.8%, Kozani 6.1%, Pieria 4.8%, Pella 4.3%, Kilkis 3.9%, Chalkidiki 3.9%, Magnisia 3.5% Serres 3.5%, Imathia 2.8%, Trikala 2.7%, Kavala 2.6%, Grevena 1.8%, Drama 1.1%, Florina 1.0%). The remaining 3.7% of patients came from Evros, Kastoria, Rodopi, Xanthi, Attica, Dodekanisos, Limnos, Evoia, Karditsa, Kerkyra, Fthiotida, and the Agion Oros).

### First implant procedures

From 1989 until June 2006 there were 1635 first implant procedures. The patients' mean age at first implant was  $72.4 \pm 10.1$  years. Mean age at first implant did not change significantly over the years ( $p=0.361$ ). Fifty-five percent (55%) of the patients were men and 45% women. The mean age of male patients at first implant was 72.5 years and did not differ significantly from that of female patients (71.8 years;  $p=0.127$ ).

Patients' symptoms at first implant were dizzy spells (51.4%), syncope (35.8%), dyspnoea (5%), palpitations (4.2%), vague symptoms (2.9%), while 0.7% were asymptomatic (preventive pacemaker implantation).

Aetiologies for pacing were fibrosis of the conductive system (56%), ischaemic (25.9%), valve diseases (6.8%), heart surgery (2%), heart failure (3.3%), cardiomyopathy (1%), congenital (1%), and other or unknown (4%).

### Indications for pacing at first implant

The most common indications for pacing were atrioventricular block (45.7%), sick sinus syndrome (32.8%), and atrial fibrillation (12.1%). In a small percentage there were pacemaker implants for carotid sinus syndrome (5.0%), heart failure (3.3%) and hypertrophic obstructive cardiomyopathy (1.0%) (Table 1).

Indications for first implantation have changed over the years. At first and until 1993 there were only three indications: atrioventricular block, sick sinus syndrome, and atrial fibrillation. In 1994 permanent pacing indications expanded to the treatment of carotid sinus syndrome. In 1997 and the following years some cases of hypertrophic obstructive cardiomyopathy were

**Table 1:** Indications for pacing at first implant.

Indication	%		
Atrioventricular block (AVB)	45.70	AVB type:	% of AVB
		Complete AVB (% of AVB)	48.9
		Second degree AVB	37.7
		Trifascicular AVB	7.5
		Bifascicular AVB	5.7
		Congenital AVB	0.2
Sick sinus syndrome (SSS)	32.8	SSS type:	% of SSS
		Tachy-brady syndrome (SSS)	44.1
		Asystole	27.1
		Sino-atrial block	15.7
		Sinus bradycardia	13.1
Atrial fibrillation	12.1		
Carotid sinus syndrome	5.0		
Heart Failure	3.3		
Hypertrophic obstructive cardiomyopathy	1.0		

paced (13 cases) and finally, starting in 1997, cardiac pacing was used in the treatment of heart failure. In 2005 the observed percentage of pacing for heart failure was unexpectedly large. This was due to the fact that the overall pacemaker implantations in that year were very few, for a number of non-scientific reasons. This percentage is therefore unsubstantiated and it by no means represents a true fivefold increase in pacing for heart failure as compared to the previous year (Table 2).

### Pacing mode

The pacing modes that were most frequently used in the overall population were VVI mode (651 cases, 38.5%) and the DDD mode (437 cases, 25.8%). Pacing modes have, however, changed a great deal over the years (Table 3).

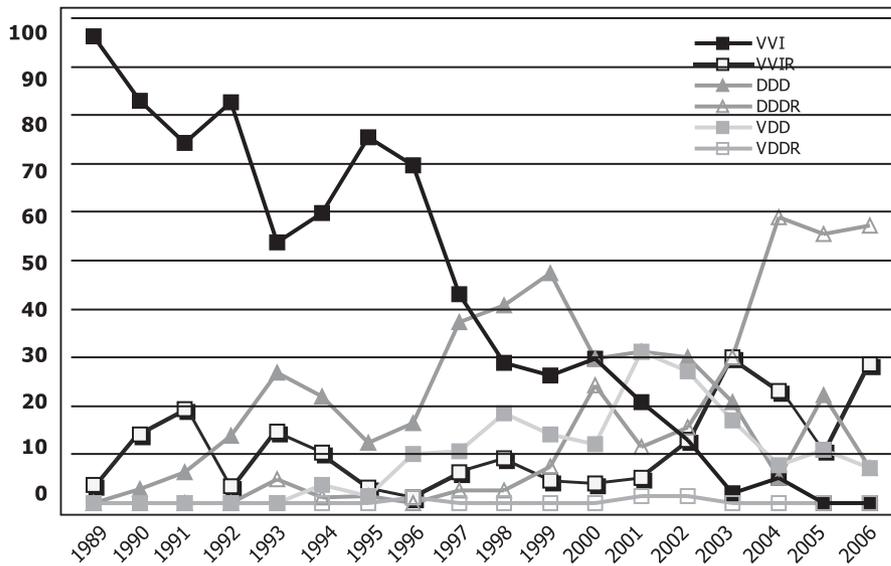
Atrial pacing (AAI and AAIR) was used in a small minority of cases and only during the years 1994-1996. Ventricular pacing (VVI and VVIR) was the first pacing mode that is still used, although there has been an

**Table 2.** Indication for pacing at first implant (1989-2006).

	AV Block	SSS	AF	CSS	HOCM	HF
1989	53.8	40.4	5.8	-	-	-
1990	58.8	32.4	8.8	-	-	-
1991	57.1	42.9	-	-	-	-
1992	46.7	46.7	6.7	-	-	-
1993	42.3	60.9	-	-	-	-
1994	38.2	47.6	11.9	2.4	-	-
1995	47.6	50.8	-	1.6	-	-
1996	50	43.3	1.1	5.6	-	-
1997	56.5	27.9	10.9	3.6	0.7 (2)	0.4 (1)
1998	42.6	32.1	16.7	6.8	0.6 (1)	1.2 (2)
1999	32.6	34.7	20.1	8.3	3.5 (5)	0.7 (1)
2000	42.7	26.7	20	9.3	1.3 (1)	-
2001	47.4	37.2	9.0	2.6	3.8 (3)	-
2002	46.2	21.8	15.4	6.4	1.3 (1)	9.0 (7)
2003	41.1	19.6	23.2	5.4	-	10.7 (6)
2004	36.2	14.9	21.3	10.6	-	17.0 (8)
2005	18.8	18.8	3.1	15.6	-	43.8 (14)
2006	42.1	15.8	15.8	-	-	26.3 (5)

Values are expressed as percentages. Values in parentheses are numbers of cases.

AF – atrial fibrillation; AV – atrioventricular; CSS – carotid sinus syndrome; HF – Heart failure; HOCM – hypertrophic obstructive cardiomyopathy; SSS – sick sinus syndrome.



**Figure 1.** Pacing mode at first implant (%).

expected decrease over the years in favor of dual-chamber pacing. There has also been a progressive increase in the use of rate responsive systems (VVIR), which was especially evident after 2002. Dual-chamber (atrioventricular) units were first used in 1990 with DDD mode, in 1993 with DDDR mode, and in 1994 with VDD mode. The initially low rates of dual pacing modes at first implantations have progressively increased over the years, and since 1997 dual pacing has been more frequently used than ventricular

pacing. From 2003 and on rate-responsive dual pacing systems also became more popular (Figure 1). Overall, atrioventricular pacing has increased, becoming more frequent than ventricular pacing after 1997, and finally in the last six years constituting around 70-80% of pacing modes at first implant (Table 3). Biventricular pacing systems have been employed since 2002, when they were first introduced, and their rate of implantation has increased until the present day.

**Table 3.** Pacing mode at first implant (1989-2006).

	AAI	AAIR	VVI	VVIR	DDD	DDDR	VDD	VDDR
1989	-	-	96.2	3.8	-	-	-	-
1990	-	-	82.9	14.3	2.9 (1)	-	-	-
1991	-	-	74.2	19.4	6.5	-	-	-
1992	-	-	82.8	3.4	13.8	-	-	-
1993	-	-	53.7	14.6	26.8	4.9 (2)	-	-
1994	2.6	-	59.7	10.4	22.1	1.3	3.9	-
1995	4.6	1.5	75.4	3.1	12.3	1.5	1.5	-
1996	1.3	-	69.6	1.3	16.5	-	10.1	1.3
1997	-	-	43	6.3	37.3	2.5	10.8	-
1998	-	-	29	9.3	40.7	2.5	18.5	-
1999	-	-	26.4	4.7	47.3	7.4	14.2	-
2000	-	-	29.7	4.1	29.7	24.3	12.2	-
2001	-	-	20.8	5.2	31.2	11.7	31.2	-
2002	-	-	12.9	12.9	30	15.7	27.1	1.4
2003	-	-	1.9	30.2	20.8	30.2	17	-
2004	-	-	5.1	23.1	5.1	59	7.7	-
2005	-	-	-	11.1	22.2	55.6	11.1	-
2006	-	-	-	28.6	7.1	57.1	7.1	-

Values are expressed as percentages. Values in parentheses are numbers of cases.

**Pacing mode according to indication**

In period A (1989-1997) atrioventricular block was most frequently paced with a VVI pacemaker (57.3%), whereas in period B (1998-2006) dual-chamber pacing prevailed (DDD 29.6%, DDDR 19.9% and VDD 11.4%) (Table 4).

In period A sick sinus syndrome was treated mainly with ventricular pacing (71.7% VVI and 6.6% VVIR). In period B, however, dual-chamber systems were widely used (51.5% DDD and 13.9% DDDR).

Slow atrial fibrillation was treated with ventricular pacing in both periods, with a marked increase in rate response systems in period B (40.5% VVIR).

Carotid sinus syndrome has been treated with pacing since 1994. In period A VVI pacing was used in 61% of cases and DDD pacing in 33.3%. In period B carotid sinus syndrome was paced almost exclusively with dual-chamber systems (54% DDD and 40% DDDR).

There were 13 cases of hypertrophic cardiomyopathy with left ventricular outflow tract obstruction that were treated with DDD or DDDR pacing.

There were 44 cases of pacing for heart failure in New York Heart Association (NYHA) stages III-IV due to dilated or ischaemic cardiomyopathy. During the years 1997-1999 there were 4 cases of heart failure treated with dual-chamber pacing. Since 2002, when the first biventricular system was implanted, heart failure has been treated with biventricular pacing.

**Biventricular pacing or cardiac resynchronisation therapy**

Forty-five (45) biventricular system procedures have been recorded since 2002, 37 of which were successful

(success rate 82.2%). Left ventricular lead placement failed in 6 cases because of anatomical variations in the origin of the coronary sinus, in 1 because of dissection of the coronary sinus, and in 1 because of severe tortuosity of the target vein. In 3 of these cases an epicardial lead was surgically placed. Indications for cardiac resynchronisation therapy were ischaemic (63.3%) or non-ischaemic (36.7%) cardiomyopathy, with symptomatic heart failure in NYHA stage III (81.7%) or IV (18.3%), and ejection fraction 30-35% (8.2%), 25-30% (37.5%), 20-25% (35.2%), and 15-20% (19.1%).

**Replacement operations**

From 1989 until June 2006 there were 443 pacemaker replacement operations. The most common reason for replacement was battery failure (351 cases, 85%). Among the rarer reasons for pacemaker replacement were infection/erosion (5.7%), dysfunction (5.5%), and indication for different pacing mode (3.3%). There was one case of replacement because the patient had undergone a magnetic resonance imaging scan and one case of prophylactic replacement according to the recommendations of the manufacturer.

The mean time to replacement was 7 years (7.07  $\pm$  2.9), with a maximum of 18 years and a minimum of less than 1 year. Replacement time according to reason of replacement was 7.6  $\pm$  2.5 years for battery failure, 3.1  $\pm$  1.9 years for dysfunction, 3.2  $\pm$  2.2 years for different pacing mode indication and 2.7  $\pm$  1.5 years for infection-erosion of the pacemaker pocket.

Battery duration was statistically significantly longer in VVI mode as compared to VVIR ( $p=0.001$ ), DDD ( $p<0.001$ ), DDDR ( $p<0.001$ ) and VDD ( $p=0.003$ )

**Table 4.** Pacing mode according to indication in period A (1989-1997) and in period B (1998-2006).

AV block	VVI	VVIR	DDD	DDDR	VDD	VDDR		
1989-1997	57.3	3.6	6.8	0.9	11.4	-		
1998-2006	8.7	1.7	29.6	19.9	39.7	0.3		
Sick sinus syndrome	VVI	VVIR	DDD	DDDR	VDD	VDDR	AAI	AAIR
1989-1997	71.7	6.6	16.3	1.2	-	-	1.7	0.3
1998-2006	23.7	9.8	51.5	13.9	1.0	-	-	-
Atrial fibrillation	VVI	VVIR	DDD	DDDR	VDD			
1989-1997	81.8	18.2	-	-	-			
1998-2006	55.2	40.5	-	3.4	0.9			
Carotid sinus syndrome	VVI	VVIR	DDD	DDDR				
1989-1997	61.1	-	33.3	-				
1998-2006	4.0	2.0	54.0	40.0				

Values are expressed as percentages.

modes. ( $p < 0.0083$  was considered statistically significant according to the Bonferroni correction).

In 24.4% of all replacements a pacing mode different to the original was used. The most common change was adding the rate-response characteristic (12.5% of the replacements). Upgrading to atrioventricular pacing was observed in 2.2% of the replacements.

## Discussion

Mean age at first implantation was  $72.4 \pm 10.1$  and has not significantly changed over the years, in contrast to the UK registry where mean age at first implantation was 72.07 in 1989 and increased progressively to 74.59 in 2002.<sup>8</sup> Nevertheless, when implantations for cardiac resynchronisation therapy were excluded from the analysis, mean age showed a trend to increase, especially in the two last years, when mean age at first implantation was higher ( $75.62 \pm 8.9$ ) than in the previous years, although not statistically significantly so.

Indications for pacing were in accordance with other European registries.<sup>8,9</sup> In the year 2002, for example, SSS accounted for 26.7% and AF for 20% of first implantations in our centre. In the same year pacing for SSS and AF in the UK accounted for 26.7% and 19.1%, respectively, while in Germany SSS accounted for 38.8% and AF for 18.5%. Pacing for atrioventricular block in 2002 was 46.2% in our centre, 45.5% in the UK and 33.1% in Germany.<sup>8,9</sup>

The pacing modes that were most frequently used in our centre were VVI (38.5%) and DDD (25.8%). Ventricular pacing (VVI/R) was the only pacing mode that was used initially, accounting for 100% and 97.2% of first implantations in years 1989 and 1990, respectively. In the same years ventricular pacing in the UK registry was lower, namely 80.8% and 76.8%, respectively, because of an already significant usage of dual pacing systems. Nevertheless, in year 2002 ventricular pacing in our centre dropped to 25.8% while in the UK it was 37%.<sup>8</sup> Our data concerning pacing modes are in accordance with unpublished data from the panhellenic registry of pacemakers also relating to 2006 (DDD/DDDR 3.48/58.47% in the panhellenic registry, 7.1/57.1% in ours).<sup>10</sup> In general, our centre seems to have followed the trend towards “physiologic” pacing (atrial or atrioventricular pacing which preserves normal atrioventricular conduction, in contrast to ventricular pacing). This was motivated by large trials published in the last decade, starting with An-

dersen et al in 1997<sup>11</sup> and followed by many others,<sup>12-14</sup> all of which showed a significant benefit of “physiologic” pacing in reducing the risk of atrial fibrillation, while some of them also showed an additional benefit in reducing hospitalisation for heart failure and improving quality of life. However, chronic right ventricular apical pacing can lead to an adverse clinical outcome, since it produces a rather non-physiologic excitation of the ventricles, which is associated with left ventricular dyssynchrony, deterioration of left ventricular ejection fraction,<sup>15</sup> and even a moderate worsening of diastolic left ventricular function, possibly triggering higher left ventricular filling pressures.<sup>16</sup>

### Pacing for sick sinus syndrome

Sick sinus syndrome was paced with VVI/R systems in 80.2% of cases during period A and in 33.6% during period B, while there was a marked increase in dual-chamber pacing. Atrial pacing is considered to be the ideal pacing mode for some types of sick sinus syndrome, especially tachy-brady syndrome with intact atrioventricular conduction.<sup>17,18</sup> The low rate of atrial pacing in our centre could be attributed to the difficulties in ensuring intact atrioventricular conduction at the time of implantation as well as in maintaining it, given the negative impact of many drugs and pathological conditions on atrioventricular conduction.

However, conventional dual-chamber pacing results in a high rate of ventricular pacing, which causes ventricular desynchronisation and has been linked to an increased risk of atrial fibrillation in patients with sinus node disease. To address this problem newer pacing algorithms that minimise ventricular pacing are being tested for the treatment of sick sinus syndrome.<sup>19</sup> In addition, alternate sites for permanent pacing, such as the interatrial septum and the ostium of the coronary sinus for atrial pacing, and the right ventricular outflow tract for ventricular pacing, have been used with favourable results, in order to eliminate atrial fibrillation and the harmful effect of right ventricular apical pacing.<sup>20,21</sup>

### Pacing for atrioventricular block

Atrioventricular block was paced with ventricular systems in 57.3% of cases during period A, while in period B dual-chamber systems were used in 60.9%. This increase in favor of atrioventricular pacing is in accordance with other registries.<sup>8,9</sup> DDD/R and VDD/R are the recommended pacing modes for complete or

second degree atrioventricular block, since they allow a normal sinus node to serve as the physiologic marker for appropriate heart rate, based upon metabolic requirements, while at the same time they maintain normal atrioventricular synchrony.<sup>22</sup>

### ***Pacing for hypertrophic obstructive cardiomyopathy (HOCM)***

Dual-chamber pacemakers with an optimal atrioventricular delay have been shown to improve symptoms and haemodynamics in patients with severe HOCM and left ventricular outflow tract obstruction who do not respond to drug therapy.<sup>23,24</sup> Randomised clinical trials, however, failed to show a long-term benefit from pacing this group of patients.<sup>25</sup> Selected high risk HOCM patients may benefit from a dual-chamber implantable cardioverter-defibrillator.<sup>26,27</sup> According to clinical data and recent guidelines, the patients with HOCM who may benefit from dual-chamber pacing are those who do not tolerate or do not respond to drug therapy, those at high risk for surgical treatment, and those who have other indications for pacing.<sup>5</sup> There were 13 cases of DDD/R pacing in cardiomyopathy patients in our centre, which account for 1.0% of the indications at first implantation.

### ***Pacing for heart failure***

Permanent pacing in heart failure has been used to address the problem of mechanical asynchrony of the ventricles.<sup>28</sup> Dual-chamber pacemakers were initially used and proved to achieve clinical improvement in some patients.<sup>29</sup> In our centre DDD/R pacing in heart failure was applied in some patients in years 1997-1999, even though the clinical benefits of dual-chamber pacing in heart failure patients had already been known for some years.<sup>30</sup> However, the revolution in pacing heart failure patients came with biventricular systems, also known as cardiac resynchronisation therapy (CRT) devices, which improve haemodynamic and functional status,<sup>31</sup> reduce hospitalisation due to heart failure, and reduce all cause mortality in selected patients.<sup>32-34</sup> Since 2002, in our centre, biventricular pacing has been used as an adjunctive therapy for patients with heart failure and ventricular conduction delays.

### ***Replacement operations***

The apparently large percentage of infection-erosion

(5.7%) does not coincide with the percentage of erosion as a complication following pacemaker implantation in our population, which is estimated to be much smaller. It refers to the incidence of infection-erosion among the patients who came for reoperation (24 cases) in our centre, which is a reference centre for the whole of northern Greece and attracts complicated cases. In general, reasons for pacemaker replacement as well as their frequency are in accordance with the UK registry.<sup>8</sup>

### ***Limitations of the study***

We acknowledge that, for the population studied, no sufficient follow-up data are available for publication. A better organised follow-up program, strictly adhering to the international scientific guidelines for pacemaker follow-up, is necessary in order to improve the healthcare services we provide to the pacemaker patients.<sup>35</sup>

### ***Conclusions***

Changes in pacing modes from 1989 to 2006 in our centre reflect a global attempt at approaching normal myocardial excitation. Ventricular pacing was followed by dual-chamber pacing in order to maintain atrioventricular synchrony, while, at the same time, rate-responsive systems were used in order to offer an adjunctive benefit to chronotropically incompetent patients. Finally, since 2002 cardiac resynchronisation therapy has been used, following the discussion about inter- and intraventricular synchrony that began in the mid 90s.

In addition, evolution in pacemaker technology has led to the expansion of indications for pacing from atrioventricular block and sick sinus syndrome to carotid sinus syndrome and heart failure. Study of data from the 1st Cardiology Department of AHEPA University Hospital archive has shown that pacing indications and pacing modes are in accordance with the results of large randomised pacing trials, as well as with other European pacemaker registries.

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