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Circulation. 2005;111:1100-1105; originally published online February 21, 2005;
doi: 10.1161/01.CIR.0000157153.30978.67

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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World Wide Web at:

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Worldwide Survey on the Methods, Efficacy, and Safety of Catheter Ablation for Human Atrial Fibrillation

Riccardo Cappato, MD; Hugh Calkins, MD; Shih-Ann Chen, MD; Wyn Davies, MD; Yoshito Iesaka, MD; Jonathan Kalman, MD; You-Ho Kim, MD; George Klein, MD; Douglas Packer, MD; Allan Skanes, MD

Background—The purpose of this study was to conduct a worldwide survey investigating the methods, efficacy, and safety of catheter ablation (CA) of atrial fibrillation (AF).

Methods and Results—A detailed questionnaire was sent to 777 centers worldwide. Data relevant to the study purpose were collected from 181 centers, of which 100 had ongoing programs on CA of AF between 1995 and 2002. The number of patients undergoing this procedure increased from 18 in 1995 to 5050 in 2002. The median number of procedures per center was 37.5 (range, 1 to 600). Paroxysmal AF, persistent AF, and permanent AF were the indicated arrhythmias in 100.0%, 53.0%, and 20.0% of responding centers, respectively. The most commonly used techniques were right atrial compartmentalization between 1995 and 1997, ablation of the triggering focus in 1998 and 1999, and electrical disconnection of multiple pulmonary veins between 2000 and 2002. Of 8745 patients completing the CA protocol in 90 centers, of whom 2389 (27.3%) required >1 procedure, 4550 (52.0%; range among centers, 14.5% to 76.5%) became asymptomatic without drugs and another 2094 (23.9%; range among centers, 8.8% to 50.3%) became asymptomatic in the presence of formerly ineffective antiarrhythmic drugs over an 11.6 ± 7.7 -month follow-up period. At least 1 major complication was reported in 524 patients (6.0%).

Conclusions—The findings of this survey provide a picture of the variable and evolving methods, efficacy, and safety of CA for AF as practiced in a large number of centers worldwide and may serve as a guide to clinicians considering therapeutic options in patients suffering from this arrhythmia. (*Circulation*. 2005;111:1100-1105.)

Key Words: fibrillation ■ catheter ablation ■ antiarrhythmia agents ■ follow-up studies

Since its introduction into clinical practice,^{1,2} catheter ablation (CA) aimed at cure of atrial fibrillation (AF) has become increasingly prevalent. Different techniques have been proposed and are currently under investigation in various electrophysiology (EP) laboratories,³⁻⁷ with increasing knowledge of the pathophysiology of human AF⁸ and critical assessment of clinical outcome after the curative procedure.^{2,3-5} The favorable results reported in different studies have fueled enthusiasm for CA of AF, with the number of ablation procedures increasing from 1994 to the present time. These studies, however, involved relatively small numbers of patients and different techniques. The follow-up periods were relatively short, and data represented the experience of only single institutions.

The purpose of the present study was to provide a survey on the methods, safety, and efficacy of curative CA of AF over a broader spectrum of EP laboratories. To this aim, a

questionnaire was circulated to 777 EP laboratories worldwide. The present article reports the result of this survey.

Methods

Study Design

In February 2002, 10 EP investigators from different continents joined to form an independent Steering Committee with the responsibility of developing a detailed questionnaire, identify all EP centers officially accredited by national or international cardiology or arrhythmia scientific societies, and review the analyses. The questionnaire was sent to 777 EP centers worldwide. Centers were selected from the following sources: the North American Society of Pacing and Electrophysiology (NASPE) member list, the European Society of Cardiology (ESC) member list, and official lists of national working groups on arrhythmias in the different countries of Europe; Asia; North, Central, and South America; Africa; and Oceania. The selected institutions were contacted by facsimile, and contact was reinforced by e-mail in all cases. For centers not responding after the first contact, a second contact was attempted 1

Received March 10, 2004; revision received December 13, 2004; accepted December 21, 2004.

From the Arrhythmias and Electrophysiology Center (R.C.), Policlinico San Donato, Milan, Italy; Johns Hopkins University School of Medicine (H.C.), Baltimore, Md; Veterans General Hospital (S.-A.C.), Taipei, Taiwan; St. Mary's Hospital (W.D.), London, UK; Cardiovascular Center (Y.I.), Tsuchiura Kyodo Hospital, Tsuchiura Ibaraki, Japan; Royal Melbourne Hospital (J.K.), Parkville, VIC, Australia; Cardiology Department (Y.-H.K.), Asan Medical Center, Seoul, South Korea; Department of Cardiology (G.K., A.S.), University Hospital, London ON, Canada; and Division of Cardiology (D.P.), Mayo Foundation—St. Mary Hospital, Rochester, Minn.

The online-only Data Supplement, which contains two appendices, can be found with this article at <http://www.circulationaha.org>.

Correspondence to Riccardo Cappato, MD, Arrhythmia and Electrophysiology Center, Policlinico San Donato, Via Morandi 30, 20097 San Donato Milanese, Milan, Italy. E-mail rcappato@libero.it

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000157153.30978.67

month later by the same modalities. A total of 181 responded to the invitation.

The questionnaire comprised 43 questions (see Data Supplement Appendix 1 for details) addressing the following issues: year of start of a CA program; number of catheter procedures performed each year; whether a CA program attempting curative treatment of AF had been started and year of start; the different techniques used, and if so, the year each was started; patient entry criteria and characteristics; anticoagulation techniques used before, during, and after the ablation procedure; the success rate free of antiarrhythmic drugs (AADs) and with AADs, as administered according to common clinical practice; number of procedures per patient to obtain the reported success rates; and the incidence for each of a preselected list of complications. Centers were required to collect data from existing databases. The deadline for final collection of all fully filled documents was the end of August 2003.

All completed questionnaires were collected and sent to an independent statistical center (Bioepidemiology Center of the University of Pavia, Italy) for analysis. All data were entered into a database using Access 2000, and statistical analysis was performed with STATA software 7.0 (Stata Corp).

Outcomes

The questionnaire was conceived to examine the following outcome parameters: freedom from recurrent AF in the absence of AADs; freedom from recurrent AF in the presence of formerly ineffective AADs; overall freedom from recurrent AF (ie, both in the absence and presence of orally administered AADs); and development of major complications. The mean follow-up was calculated as the mean of mean follow-up from single centers, whereas the range was extracted from the minimum and maximum of all ranges from the different centers. Major complications were defined as those that were likely to result in permanent injury, prolongation of hospitalization, requirement of intervention for treatment, or death.⁹

Statistical Analysis

The validity of the survey inclusive of assessment of the least acceptable response rate was fixed, requiring that the sampling fraction would not affect the precision of the estimates of >20% (confidence coefficient, gaussian deviate $z=1.28$).¹⁰ Descriptive analysis was performed by using mean \pm SD for continuous variables and percentage values for discrete variables. Discrete variables were compared with χ^2 or Fisher exact test ($\alpha=0.05$). Success rates with and without AADs and failure rates were described in relation to the number of procedures per center and follow-up duration, divided by groups. The association among these variables was investigated by Spearman correlation.

Results

One hundred eighty-one (23.3%) responded to the questionnaire. The quality standards of participating centers were deemed representative of today's good clinical practice in interventional EP by all members of the Steering Committee. This hypothesis was substantiated by the following observations: (1) All participating centers are members of at least 1 national or international scientific society, and (2) responding centers are uniformly distributed (1 of every 4 contacted centers) in all continents. Moreover, the Italian centers ($n=52$) contacted in this survey reported in the official registry of the Italian Association on Cardiac Arrhythmias a similar number of total procedures performed between 1995 and 2002 in a subgroup of 18 responding centers (298 ± 208) and 34 nonresponding centers (287 ± 234 , $P=NS$). A detailed list of all participating centers is presented in Data Supplement Appendix 2. Between January 1995 and December 2002, 100 (55.9%) of 181 centers had started a program of CA of AF. Altogether, data were made available from 9370

TABLE 1. Distribution of Preferred Ablation Technique According to Date Between 1995 and 2002

Year	RAC	LAC	CA-TF	PV-Dis	Other	Total
1995	13	2	0	0	3	18
1996	38	4	1	0	5	48
1997	67	32	23	0	0	122
1998	109	57	158	49	22	395
1999	142	89	332	88	28	679
2000	135	110	383	569	42	1239
2001	179	230	274	1534	31	2248
2002	169	556	355	4360	10	5450
Total	852	1080	1526	6600	141	10 199

RAC indicates right atrial compartmentalization; LAC, left atrial compartmentalization; CA-TF, catheter ablation of the triggering focus; PV-Dis, electrical disconnection of pulmonary veins. Boldface type indicates the numbers of patients treated by the most prevalent technique during the pertinent year of analysis, although 1563 more procedures were performed with a combination of 2 or more techniques.

patients undergoing 11 762 CA procedures (median per center, 37.5; range, 1 to 600). Among entry criteria were the following: drug refractoriness in 93.0%, paroxysmal AF in 100.0%, persistent AF in 53%, and permanent AF in 20% of centers. Exclusion criteria included an upper limit of left atrial size (between 55 and 60 mm of maximal transverse diameter) reported in 46%, a lower limit of left ventricular ejection fraction (between 30% and 35%) in 65%, and prior heart surgery in 64% of centers.

Ablation Strategy

Five different strategies for CA of AF were reported, including right atrial compartmentalization in 852 patients, left atrial compartmentalization in 1080 patients, ablation of the triggering focus in 1526 patients, pulmonary vein (PV) electrical disconnection in 6600 patients, and a combination of 2 or more strategies in the same individual in 490 patients; other nonspecified strategies were reported in 141 patients. Altogether, 12 830 transeptal punctures were performed in 8745 patients, with 2389 patients undergoing >1 procedure. Table 1 outlines the distribution of the strategies used between 1995 and 2002. The number of patients undergoing CA of AF almost doubled each successive year between 1995 and 2002. Among patients undergoing electrical disconnection of PVs, achievement of the target end point was aimed for in all PVs in 46 (58.2%) and in 3 PVs in 24 (30.4%) of 79 centers reporting use of this technique. Electrical disconnection of the superior vena cava, of the Marshall vein, and of the coronary sinus was aimed for in 34 (40.0%), 18 (22.8%), and 18 (22.8%) centers, respectively.

Techniques for mapping and ablation included the use of Carto in 1846 patients in 43% of centers, Lasso in 3385 patients in 77% of centers, En Site in 141 patients in 12% of centers, and basket-shaped electrode catheters in 317 patients in 21% of centers. Complete data with regard to the source of energy used were available for 4918 patients: Of them, 4127 received radiofrequency current ablation; 220, cryotherapy ablation; 115, ultrasound ablation; 94, laser ablation; and 93, other forms of energy.

TABLE 2. Success Rates Relative to Number of Procedures Performed per Center

No. of Procedures per Center	No. of Centers	No. of Patients	Success Without AADs			Success With AADs			Overall Success	
			n	Rate, %	(Range), %	n	Rate, %	(Range), %	n	Rate, %
1–30	35	547	163	29.8	(14.5–43.6)	165	30.1	(18.7–46.5)	328	59.9
31–60	15	639	214	33.5	(20.8–46.6)	217	34.0	(20.4–48.1)	431	67.5
61–90	12	923	341	36.9	(18.3–51.2)	311	33.7	(16.7–50.3)	652	70.6
91–120	7	728	258	35.4	(24.1–48.7)	221	30.4	(22.8–39.0)	594	81.6
121–150	4	556	187	33.6	(22.6–46.5)	160	28.8	(20.9–37.1)	347	62.4
151–180	4	671	297	44.3	(32.8–51.9)	199	29.7	(23.1–37.8)	496	74.0
181–230	3	607	320	52.7	(42.1–63.0)	138	22.7	(18.3–25.9)	458	75.4
231–300	3	830	519	62.5	(55.7–70.4)	236	28.4	(22.3–35.6)	755	91.0
>300	7	3244	2069	63.8	(50.3–76.5)	514	15.8	(8.8–24.5)	2583	87.9
Total	90	8745	4550	52.0	(14.5–76.5)	2094	23.9	(8.8–50.3)	6644	75.9

Clinical Outcome

Of 6 possible definitions of success (see Data Supplement Appendix 1, question 18), all responding centers reported definition (c) (ie, number of patients free of AF with or without drugs [a] or without drugs [b]) as the only definition used to evaluate the success of ablation therapy. Complete data for assessment of efficacy over 11.6 ± 7.7 (median, 12; range, 1 to 98) months of follow-up were available for 8745 patients (age range, 16 to 86 years; male sex, 63.8%) completing the ablation protocol in 90 centers. Of them, 4550 (52.0%; range among centers, 14.5% to 76.5%) became asymptomatic in the absence of any AAD, whereas another 2094 (23.9%; range among centers, 8.8% to 50.3%) became asymptomatic with continued use of formerly ineffective AADs. Therefore, 6644 patients (75.9%; range among centers, 22.3% to 91.0%) obtained resolution of symptoms after completion of any of the ablation protocols used. To achieve the reported success rate, 2122 patients (24.3%) required 2 and 267 patients (3.1%) required 3 procedures. The success rate free of AADs was 52.7% in 65 centers, including patients with paroxysmal AF only, 48.5% in 17 centers including patients with paroxysmal or persistent AF, and 57.3% in 8 centers including patients with all forms of AF.

The success rate free of AADs ($P < 0.001$) and the overall success rate ($P < 0.05$) significantly increased as the number of procedures performed per center increased; in these groups, the success rates in the presence of AADs were inversely related to the success rate free of AADs ($P < 0.05$)

(Table 2). In centers with follow-up between 7 and 18 months, the success rate free of AADs and the overall success rates were higher than in centers with shorter or longer follow-up ($P < 0.05$); also in these groups, the success rates in the presence of AADs were inversely related to the success rates in the absence of AADs ($P < 0.001$) (Table 3).

Anticoagulation Strategies

Preablation, subcutaneous (37.6%), low-molecular-weight (43.5%), or intravenous heparin (18.9%) was used, regardless of whether patients were taking long-term oral anticoagulants. A transesophageal echocardiogram was required before the ablation procedure in 72.0% of centers. During the ablation procedure, all 73 centers providing full disclosure of their anticoagulation protocol reported intravenous administration of heparin. Of them, 57 (78.1%) used activated clotting time (ACT)-guided administration (minimum ACT range, 230 to 350 seconds), whereas 16 (21.9%) did not use ACT guidance. After ablation, 83.0% of centers reported the use of oral anticoagulants, whereas aspirin was administered in the remaining 17.0% of centers over a follow-up of 1 to 6 months.

Complications

A major complication occurred in 524 patients (6.0%). A detailed list of the different complications reported with their relative incidence is outlined in Table 4. The most significant complications included 4 early deaths (massive cerebral

TABLE 3. Success Rates Relative to Different Ranges of Follow-Up Duration

Range of Follow-Up Duration, mo	No. of Centers	No. of Patients	Success Without AADs			Success With AADs			Overall Success	
			n	Rate, %	(Range), %	n	Rate, %	(Range), %	n	Rate, %
0–3	4	179	39	21.8	(15.6–48.9)	83	46.4	(32.6–57.8)	122	68.2
4–6	16	906	312	34.4	(23.5–58.6)	303	33.4	(21.9–46.3)	615	67.8
7–9	14	1271	661	52.0	(34.6–78.1)	278	21.9	(10.1–32.8)	939	73.9
10–12	15	1537	1009	65.6	(37.5–87.3)	374	24.3	(11.8–38.5)	1383	89.9
13–18	17	2607	1616	62.0	(41.2–84.3)	419	16.1	(5.2–29.4)	2035	78.1
19–24	8	467	179	38.3	(16.4–55.9)	147	31.5	(17.0–42.1)	326	69.8
>24	6	1619	688	42.5	(21.7–58.5)	437	27.0	(18.5–35.7)	1125	69.5

TABLE 4. Major Complications

Complication Type	No. of Patients	% of Patients
For all types of procedures (n=8745 patients)		
Periprocedural death	4	0.05
Tamponade	107	1.22
Sepsis, abscesses, or endocarditis	1	0.01
Pneumothorax	2	0.02
Hemothorax	14	0.16
Permanent diaphragmatic paralysis	10	0.11
Femoral pseudoaneurysm	47	0.53
Arterovenous fistulae	37	0.42
Valve damage	1	0.01
Aortic dissection	3	0.03
For procedures involving left atrial ablation (n=7154 patients)		
Stroke	20	0.28
Transient ischemic attack	47	0.66
PV stenosis		
No. with >50% stenosis		
Acute	23	0.32
Chronic	94	1.31
No. with closure		
Acute	2	0.03
Chronic	15	0.21
Patients with symptoms		
Acute	3	0.04
Chronic	41	0.57
Patients undergoing intervention		
Percutaneous	51	0.71
Surgical	2	0.03
Grand total	524	5.9

thromboembolism in 2, extrapericardial PV perforation in 1, and unknown in 1), 20 strokes, 47 transient ischemic attacks, and 107 episodes of tamponade. Altogether, 117 PVs sustained significant (>50%) stenosis (assessed by means of pre- and postablation PV angiography in 67.0% and magnetic resonance in 23.0% of centers), which resulted in the need for corrective intervention in 53 patients (0.7% of 7154 patients undergoing ablation in the left atrium). Of 41 patients with chronic symptomatic PV stenosis, 25 were diagnosed within 3 months of follow-up, 5 between 3 and 6 months, and 5 between 6 and 12 months, whereas no information about the time of diagnosis was reported in the remaining 6 patients. Atypical atrial flutter of new onset (iatrogenic) was reported in 340 patients (3.9%) and was significantly ($P<0.001$) more frequently observed in centers only using exclusively 3D-guided compartmentalization strategies (8.4%) than in centers exclusively performing ablation of the triggering substrate or PV electrical disconnection (0.8%).

Discussion

This is the first study reporting on the methods, efficacy, and safety of CA aimed at curative treatment of AF based on the

results of a survey investigating clinical practices over a large number of centers around the world. The survey demonstrates that this strategy is largely and increasingly practiced worldwide. Between the years 1995 and 2002, the number of patients undergoing CA of AF in the centers participating in this survey has increased from 18 to 5050. However, 44.1% of all centers responding to the questionnaire had not started a program of CA of AF as of 2002.

Methods

During the period surveyed, changes in the selection of techniques used reflected the evolution reported in the literature,¹⁻⁸ with the most frequently used techniques being right atrial compartmentalization between 1995 and 1997, ablation of the triggering focus between 1998 and 1999, and electrical disconnection of multiple veins draining into the atria between the years 2000 and 2002. Of note, only 26.0% of centers adhered to the same technique throughout the period surveyed.

Outcomes

In a large and heterogenous population, with different techniques, and with variable and growing investigator's experience, CA proved curative in 52.0% of patients in the absence of any AAD and in an additional 23.9% of patients with the use of formerly ineffective AADs. A large variability of efficacy was reported in the responding centers (Table 2). These results were achieved with 24.3% of patients requiring a second and 3.1% of patients requiring a third ablation procedure. Success rates did not appear to be dependent on the type of AF being treated. PV electrical disconnection contributed to about two thirds of these outcome figures (Table 1).

Not unexpectedly, the success rate free of AADs and the overall success rate were higher in higher-volume compared with lower-volume centers (Table 2). When analyzed in relation to the duration of follow-up, a peak AAD-free and overall success rate was observed from centers reporting a follow-up interval of between 7 and 18 months, whereas lower success rates were reported from centers with <7 or >18 months of follow-up. A larger relative benefit from AADs during the first months of follow-up may be related to the prophylactic use of these agents early after completion of the ablation protocol in some centers. In patients with the longest follow-up, it is possible that cumulative success rates are lower than in patients with intermediate follow-up because of the limited experience and reduced efficacy of ablation techniques applied in the very early phase of CA for AF. It may also reflect adverse evolution of the atrial substrate with time.

Overall, centers and techniques with lower success rates free of AADs derived a relatively greater benefit from AADs (Table 2). Similarly, the lower AAD-free success rates in centers with the longest follow-up were, at least in part, compensated for by increased benefits from AADs (Table 3).

Complications

The overall incidence of major complications was 6.0%. This rate is not trivial and should influence the process of selecting

and approving a patient for CA of AF. All 4 reported deaths occurred intraoperatively or perioperatively and were caused by massive cerebral thromboembolism in 2 cases. A rate of tamponade of 1.2% is somewhat higher than commonly observed during CA of other arrhythmogenic substrates⁹ and is likely to be related to the combined influence of catheter manipulation in the left atrium and the need for continuous intravenous anticoagulation during the procedure.

Significant PV stenosis and stroke occurred in 1.3% and 0.2% of patients, respectively. Importantly, about half of the PV stenoses required interventional treatment, a strategy that does not necessarily abolish symptoms.¹¹ The occurrence of atypical atrial flutter of new onset was reported in 3.7% of patients, of whom the majority had received 3D-guided compartmentalization techniques. The occurrence of this arrhythmia late after ablation may be associated with very symptomatic palpitations and represent a difficult challenge for curative treatment.¹²

Comparison With Prior Reports

The crude success rate in this survey appears lower than those reported in the literature by pioneering centers. This difference may, at least in part, reflect the "learning curve" involved with the specific ablation procedures in many centers, as well as the heterogeneity of the patients treated and the techniques used. Previous studies on catheter ablation with right atrial compartmentalization, left atrial compartmentalization, ablation of the triggering focus, and PV electrical disconnection reported crude success rates ranging between 8% and 12%,^{2,5,13} 15% and 88%,^{4,5,14–17} 27% and 86%,^{3,6,7,18} and 62% and 88%,^{7,19–22} respectively, and were improved to a varying degree by the use of AADs. Comparison of efficacy among the different types of AF is difficult because of the uneven distribution of patient subgroups. An interesting observation from the present survey is that a greater benefit after ablation from formerly ineffective AADs was seen when a lower crude success rate had been achieved. Finally, the overall incidence of major complications in the present survey appears higher than that reported in single-center reports,^{3–8,14–22} a finding that, again, may reflect the learning curve involved with the specific ablation procedures.

Clinical Implications

An AAD-free success rate of 52.0% in the present survey and the wide variability of efficacy among centers (between 14.5% and 76.5%) outline the relative inadequacy of CA for the curative treatment of AF that appears to be independent of the technique used and the type of AF. This conclusion is further supported by the careful patient selection used by most centers. The additional 23.9% success rate (range among centers, 8.8% to 50.3%) observed in the presence of AADs suggests that the changes in cardiac and PV tissue caused by ablation may, in some cases, be insufficient to eradicate the substrate for triggering and perpetuation of AF but enough to enable control by formerly ineffective AADs. Still, it remains to be established whether the inefficacy of CA is related to the inadequacy of the ablation design or the inability of an otherwise adequate ablation design to be acutely or chronically effective.

This survey suggests that relapses of AF may occur months after completion of the ablation protocol²² and questions the maintenance of acute ablation effects or a possible and independent evolution of the target substrate. In agreement with this observation, a recent report focusing on PV electrical disconnection has shown that up to 80% of disconnected PVs may have reconnected some months after the first procedure and that prospectively designed, multiple-step ablation strategies may overcome this limitation and be associated with crude success rates in the range of 90%.²² The current evaluation of extended ablation designs and the use of alternative ablation techniques or energy sources will likely contribute to our understanding of these questions. Further advances in the understanding of AF mechanisms, particularly in the evolution from paroxysmal to persistent AF and the interaction between triggers, perpetuators, and substrate, will lead to further improvements in ablation design.

Study Limitations

The present survey reflects the experience of those centers (24.0%) that elected to respond to our request and does not correspond to the experience of all contacted centers. Therefore, it is possible that better results than those reported here are observed in clinical practice. However, because of the level of compliance in this study introducing a one-fourth sampling fraction bias, inflation in the variances of the estimates did not amount to >20%, thus rendering the bias on the estimates practically negligible. In addition, the large variation in efficacy reported by responding centers provides a credible picture in the distribution of the mean success rate obtained in responding as well as nonresponding centers. Finally, the present survey represents the largest published series of the methods, efficacy, and safety of CA of AF recorded in centers deemed representative on geographic and quality-standards grounds and may serve as a guide to clinicians considering therapeutic options for their patients with AF.

CA of AF is a rapidly evolving technique, and data collected between 1995 and 2002 may be out of date in 2004; however, much of the information currently available relative to techniques, results, and complications of CA of AF^{3–8,14–22} was drawn from data collected between 1995 and 2002. Therefore, a survey obtained from a large number of EP centers during this same time frame offers a reasonable model to investigate the impact and outcome that techniques proposed by centers of excellence have achieved in widespread clinical practice. In the present study, success rates are expressed as cumulative data throughout the investigated period. As a result, it is not possible to evaluate the influence that time and experience may have had on the most recent outcome data. Finally, criteria guiding data collection in this series do not allow direct comparison of success and complication rates among subgroups of interest, such as those based on the type of AF (paroxysmal versus persistent versus permanent AF) and the use of the different catheter techniques, ablation tools, or energy sources. This was due to the fact that the majority of centers reported variable and evolving criteria for patient inclusion and preferred strategy.

Acknowledgments

We are grateful to Adriana Carolei, PhD, Antonella Bitetto, MD, PhD, and Alberto Morabito, PhD, for the statistical analyses and to Marcella Manca for secretarial assistance in the preparation of the manuscript.

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