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Decennial follow-up in patients with recurrent tachycardia originating from the right ventricular outflow tract: electrophysiologic characteristics and response to treatment

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Aims In the setting of right ventricular outflow tract-tachycardia (RVOT-T), data about long-term follow-up (FU) with respect to the therapeutic strategies are missing. All patients (pts) referred to our institution during the last 20 years for the treatment of RVOT-T were studied in a retrospective analysis to assess mortality and efficacy of treatment.
Methods and results One hundred and thirty-three patients (77 female; 39 ± 13 years) with sustained RVOT-T were included in this study. At the time of first presentation, diagnosis of RVOT-T was made by complete invasive and non-invasive diagnostic assessment, including electrophysiology study and two-dimensional echocardiography. After 135 ± 68 months (median 136, range 29–248), patients were invited to undergo clinical assessment. Of the 133 pts, 127 (95%) survived and six (5%) died from non-cardiac disease. Anti-arrhythmic (AA) drugs were given to 62 of the 133 pts (47%); of them 32 (52%) had recurrences during follow-up. The mean time to recurrence was 10.02 years (95% CI 7.46–12.59). The other 71 study patients (53%) underwent catheter ablation. The procedure was successful in 58 pts (82%). During follow-up, 30 (52%) of the 58 successfully treated patients had recurrences of RVOT-T. The mean time to recurrence was 6.28 years (95% CI 4.96–7.6). RVOT-T recurrences were similar in morphology to those treated previously in 33% and different in 67% of cases.
Conclusions Long-term follow-up in patients with RVOT-T is favourable. Catheter ablation is effective in this setting. However, late recurrences with similar or different morphology may arise in half of the patients after initially successful treatment. AA drug therapy is a valid initial therapeutic option, since it is effective in about half of the patients.

Introduction

The most common idiopathic ventricular tachycardia originates from the right ventricular outflow tract (RVOT-T) and is associated with inferior axis morphology and left bundle branch block (LBBB) pattern.[1,2]

Mostly, RVOT-T presents repetitive or sustained and discomforts can be invaliding, often requiring hospitalization. In addition, RVOT-T can rarely result in tachycardia-induced cardiomyopathy.[3]

Catheter ablation has become an early therapeutic option for RVOT-T, because of high success and low complication rates.[4–10] However, catheter ablation is limited when the arrhythmogenic site is located epicardially or when tachycardia is not inducible at the electrophysiology (EPS) study.

Even in the era of interventional treatment, drug therapy still represents a valid, initial therapeutic option in a high number of symptomatic patients.[1,2] However, little information is available on long-term success rate of both, catheter ablation and drug therapy for the treatment of RVOT-T.

Purpose of this study was to assess the long-term follow-up in patients with suspected RVOT-T with regard to clinical efficacy and mortality. Thus, in a retrospectively designed study, all patients presenting at our institution with RVOT-T during the last 20 years were investigated.

Methods

Study patients

All patients referred to our institution for the treatment of idiopathic RVOT-T between February 1983 and July 2003 were included.

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Patients with evidence of structural heart disease and patients with previous heart surgery were excluded from this analysis.

The diagnosis of RVOT-T was based on the documentation of 12-lead ECG, showing ventricular tachycardia with inferior axis and LBBB configuration and sinus rhythm with normal QRS morphology and QT interval. Patients presenting with only isolated ventricular ectopic beats or couplets were not considered for this analysis. In contrast, one documented episode of sustained or non-sustained RVOT-T was assumed to be sufficient for enrolment in the study. According to the proposed ECG criteria, only patients suspected to have RVOT-T were enclosed in the study.[11] Thus, the presence of S wave in lead I, R wave duration index in V1 and V2 $\geq$0.5, and R/S wave amplitude index in V1 and V2 $\geq$0.3 were assumed as exclusion criterion.

Non-sustained RVOT-T was defined as three or more consecutive ventricular beats lasting $<$30 s. Sustained RVOT-T were those lasting more than 30 s or requiring an intervention for termination due to haemodynamic instability. Incessant RVOT-T was either the continuous presence of sustained tachycardia or runs of non-sustained tachycardia interrupted by one or two sinus beats.[12,13]

For enrolment in the study, the files of 247 (125 female, 41 $\pm$ 13 years) subjects were evaluated between January and June 2004.

Data collection

At the time of the first presentation at our institution, each patient underwent standardized diagnostic assessment consisting of detailed medical history, physical examination, laboratory analysis, chest X-ray, 12-lead ECG, 24 h Holter monitoring, transthoracic two-dimensional echocardiography, EPS and, if required, selective coronary angiography.

Non-invasive diagnostics

Clinical patient files were carefully reviewed. Twelve-lead surface ECG during sinus rhythm and two-dimensional echocardiography were evaluated in all patients. Analysis of Holter recordings was systematically performed. Coupling intervals between each sinus beat and the following RVOT ectopic beat were evaluated for the entire ECG documentation.

Electrophysiology study and radiofrequency catheter ablation

EPS was performed in a fasting, non-sedated state after informed consent was obtained. All anti-arrhythmic (AA) drugs were discontinued for at least five half-lives before testing. In all patients programmed stimulation was performed at RVA and RVOT with two different basic cycle lengths (510 and 440 ms) and up to three extrastimuli with a minimal coupling interval of 180 ms. Incremental atrial and ventricular pacing was performed in all cases following the programmed stimulation. In the setting of non-inducibility, the stimulation protocol was repeated during intravenous orciprenaline infusion (5 mg/500 mL NaCl 0.9%) with at least 20% increment of heart rate, if no spontaneous ventricular arrhythmias were observed during pharmacological provocation. The morphology of the arrhythmia was considered as dominant if it lasted for $\geq$10 times longer than other morphologies. The site of catheter ablation was chosen as the site of the best pace mapping defined by the location where stimulation matched the QRS-morphology of arrhythmia on the 12-lead surface ECG. In addition, the site of earliest endocardial activation during tachycardia was regularly considered for choosing the ablation site. RFC delivery was performed in a temperature-controlled mode using a standard generator (HAT 300 smart, Sulzer-Osypka, Grenzach, Germany) with a maximal power output of 40 W, a pre-selected temperature of 70°C, and 60 s of pre-selected pulse duration. Impedance, temperature, power output, and catheter stability were monitored during each single RFC pulse. RFC application was interrupted immediately in cases of impedance rise ($>$25 ohms) or catheter displacement. After RFC ablation, induction of RVOT-T was checked with the same stimulation protocol as before ablation and a post-ablation waiting time of 30 min was always applied in order to exclude early recurrences. A 24 h monitoring period followed the ablation procedure in all patients. Immediate success of RFC ablation was defined as complete abolition of the RVOT-T.

Basically, all patients presenting in our institution with RVOT-T between February 1983 and March 1990 were treated medically, whereas RFC catheter ablation was offered to patients presenting after April 1990. The decision for RFC ablation was taken individually based on the clinical situation, induction of RVOT-T, and patient preferences. EPS was reviewed in all study patients.

Follow-up evaluation

Follow-up assessment was performed between July 2004 and December 2005. All study patients were contacted over telephone and asked about the entire clinical history. When a patient was not reachable or died, relations or family physicians were inquired. All survivors were invited to undergo a follow-up screening in our outpatient clinic including complete physical examination, 12-lead ECG, laboratory analysis, 24 h Holter recording, exercise testing, and transthoracic two-dimensional echocardiography. The follow-up assessment was aimed to compare parameters obtained at the time of the first diagnosis of RVOT-T and that of long-term follow-up. Before evaluation, informed consent was obtained for all subjects. Patients, who could not be successfully invited to visit our institution, were encouraged to undergo a similar follow-up screening in another institution and to send to us the medical reports. Thereafter, we contacted referring cardiologists in order to collect eventually lacking data.

Statistical analysis

Continuous data are presented as mean $\pm$ SD or as median and range. Mean time to recurrence and 95% confidence interval (CI) were calculated using Kaplan–Meier survival analysis. Owing to the crossing of the recurrence curves, a Breslow test was performed that emphasizes early events. Raw event rates are given for flow-chart diagrams. Comparisons of patient groups following successful and unsuccessful ablation were performed using Fisher's exact test for cross-tabulations and the Mann–Whitney *U* test for continuous data. All tests were calculated two-tailed and a *P*-value smaller than 0.05 was considered statistically significant. Data were analysed exploratory. No adjustment was made for multiple testing. Analysis was performed using SPSS version 14 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

One hundred and thirty three (54%, 77 female, 39 $\pm$ 13 years) patients could be included in the study. Another 114 patients did not meet the inclusion criteria (*Table 1*). Fifty-nine (24%) of these patients presented only with RVOT-VES, in 25 (10%) structural heart disease was diagnosed, eight (3%) had a history of heart surgery, in nine (4%) only incomplete clinical documentation was available, and in 13 (5%) no clear ECG signs indicating an RVOT origin of tachycardia were present.

In all 133 included subjects, 12-lead ECG documented RVOT arrhythmias. At least one episode of sustained RVOT-T was documented in each patient. All 133 study patients complained about palpitations which were disabling in 125 (94%) of them. Palpitations were associated with dizziness in 51 (41%), syncope or pre-syncope in 36 (29%), exercise-induced dyspnoea in 43 (34%), chest pain in 34

Table 1 Patient baseline characteristics

Total patients scheduled	247
Patients included, *n* (%)[a]	133 (54)
Age (years)	39 ± 13
Female, *n* (%)	77 (58)
Symptoms, *n* (%)	133 (100)
Disabling	125 (94)
At rest	69 (52)
During or after exercise	47 (35)
Both situations	17 (13)
Impaired LVEF/RVEF, *n* (%)	0
RV enlargement	11 (8)
LV enlargement	5 (4)
Holter recording, *n* (%)	129 (97)
Arrhythmias	122 (94)
VES	39 (30)
VES and nsVT	42 (32)
VES, nsVT, and VT	41 (32)
VES/24 h (mean ± SD)	899 ± 814
Exercise testing, *n* (%)	122 (92)
Arrhythmias	103 (84)
Increase of arrhythmias while exercise	83 (80)
Decrease of arrhythmias while exercise	7 (7)
No changes while exercise	13 (13)
EPS performed, *n* (%)	133
RVOT arrhythmias at baseline	45 (34)
Orciprenaline provocation	88 (66)
RVOT arrhythmias induced	69 (78)
Total patients with RVOT arrhythmias	114 (86)
VES	56 (49)
VES and nsVT	27 (24)
VES, nsVT, and VT	31 (27)
>1 VT morphology	19 (17)
First presentation AA drugs, *n* (%)[b]	62 (47)
Flecainide	34 (55)
Sotalol	15 (24)
Metoprolol	2 (3)
Propafenone	3 (5)
Amiodarone	1 (2)
Prajimaline	1 (2)
Combination of drugs	6 (10)
Total AA drugs, median (range)[c]	4 (1–6)

LVEF/RVEF, left and right ventricular ejection fraction; VES, ventricular extrasystole; nsVT, non-sustained ventricular tachycardia; VT, ventricular tachycardia; EPS, electrophysiology study.

[a]Number and percentage.

[b]Anti-arrhythmic (AA) drugs given by us at the time of first presentation.

[c]Total number of anti-arrhythmic drugs taken before and during the study.

(27%), and with other discomforts in 39 (31%) of the 125 patients.

Between symptom-onset and presentation at our institution 36 months (range 0–388) elapsed. During this time interval, 78 (59%) of the 133 study patients received AA drugs: class I agents ($n = 36$; 46%), sotalol ($n = 24$; 31%), beta-blockers ($n = 11$; 14%), calcium-channel blockers ($n = 4$; 5%), and others ($n = 5$; 6%). In all these patients drugs were ineffective. However, at the time of the first presentation, 39 (55%) subjects received an insufficient dose that was below the manufacturer-recommended minimal dosage.

Initial visit

In the 133 study patients, physical examination, laboratory tests, 12-lead ECG, and chest X-ray did not show any significant alterations.

Echocardiography

Two-dimensional echocardiography was performed in all patients. In 11 (8%) patients, a slight enlargement (30 ± 3 mm) of the right ventricle was diagnosed; none had impaired right ventricular (RV) function. Left ventricle (LV) dilatation (63 ± 2 mm) was present in five (4%) subjects. No severe heart valve regurgitation or stenosis was detected.

Holter recording

Holter recording was performed in 129 (97%) of the 133 study patients. The mean duration was 23 ± 2 h. Sustained and non-sustained RVOT-T were detected in 41 (32%) of the 129 subjects, exclusively non-sustained RVOT-T in 42 (32%), only RVOT-VES in 39 (30%), and no ventricular arrhythmias in the remaining seven (5%) patients. In all 129 patients, the mean number of RVOT-VES during 24 h was 899 ± 814.

Exercise testing

Exercise testing was performed in 122 (92%) subjects. During exercise, RVOT arrhythmias were observed in 103 (84%) patients. Of them, 78 (76%) patients showed one morphology, 22 (21%) two, and three (3%) more than two morphologies on ECG. A dominant morphology of RVOT arrhythmia was detected in all cases.

Echocardiographic evaluation of coupling intervals

Evaluating the complete ECG documentation in all patients, the mean coupling interval between sinus beat, and the following RVOT-VES or RVOT-T was 408 ± 101 ms (median 400, range 220–900).

Coronary angiography

Coronary angiography was performed in 38 (28.5%) of the 133 study patients. No patient had significant coronary artery disease.

Electrophysiology study and ablation

All 133 study patients underwent an EPS. At baseline, 45 (34%) of them had RVOT arrhythmias, whereas the remaining 88 (66%) showed only sinus rhythm. Of these 45 subjects, 31 (69%) had isolated RVOT-VES, 11 (24%) non-sustained RVOT-T, and three (7%) sustained RVOT-T. Pharmacological provocation with intravenous orciprenaline was performed in all 88 subjects without RVOT arrhythmias at baseline. During orciprenaline infusion, 19 (22%) of them continued to have no arrhythmias, whereas 25 (28%) developed RVOT-VES, 16 (18%) non-sustained, and 28 (32%) sustained RVOT-T. Thus, RVOT arrhythmias were observed in 114 (86%) of the 133 subjects undergoing EPS. Induced RVOT arrhythmias showed one morphology in 95 (83%) patients, two morphologies in 14 (12%), and more than two morphologies in the remaining five (4%) patients. In all cases of multiple morphologies, one dominant form of RVOT arrhythmia was recognizable. No polymorphic tachycardia was observed. Catheter ablation was performed in 71 (62%) of the 114 patients in whom RVOT arrhythmias were observed or induced at EPS.

For these patients, the decision to perform catheter ablation was based on the patients' preferences. Thus, the remaining 43 (38%) patients did not undergo catheter ablation, since they did not consent to this procedure (14 subjects) or were seen between 1983 and 1989 (29 subjects; *Figure 1*).

Catheter ablation was acutely successful in 58 (82%) patients and unsuccessful in the other 13 (18%; *Figure 2*, *Table 2*). In all cases of successful ablation, pharmacological provocation with intravenous orciprenaline was performed after ablation in order to check its efficacy. A waiting time of 30 min was always applied after successful ablation to exclude early recurrences.

In 11 (19%) cases of successful ablation, one rare isolated RVOT-VES (<1 VES/5 min.) with different morphology was observed during the waiting time under pharmacological provocation with orciprenaline. Because of their low frequency of appearance, these RVOT-VES were considered clinically non-relevant and were not targeted.

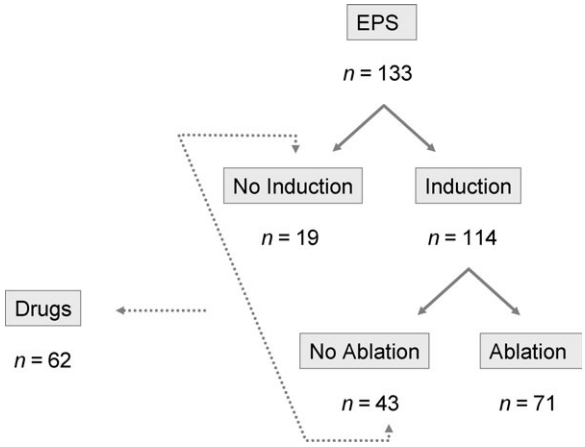

Figure 1 Flowchart showing recruitment of patients for primary drug therapy or catheter ablation.

In two (2%) of the 133 study patients, pericardial effusion was observed immediately after the procedure.

After successful ablation AA drugs were discontinued in all but two patients who continued to take metoprolol because of arterial hypertension.

Drug therapy

Of the 133 study patients, 62 (47%) were treated with AA drugs (*Figure 3*). In this group, 34 (55%) patients received flecainide (186 ± 34, median 200 mg daily), 15 (24%) sotalol (262 ± 52, median 240 mg daily), two (3%) metoprolol (120 ± 40, median 100 mg daily), three (5%) propafenone (450 ± 0, median 450 mg daily), one (2%) amiodarone (200 mg daily), one (2%) prajmaline (40 mg daily), and the remaining six (10%) patients received a drug combination ($n = 3$: flecainide and sotalol; $n = 3$: flecainide and metoprolol).

Follow-up evaluation

Follow-up data could be obtained for all 133 study patients. In 82% of cases, patients were investigated in our outpatient clinic, whereas general practitioners, who send the complete clinical documentation to our institution, evaluated 18% of patients.

From the first presentation at our institution, the mean follow-up duration was 135 ± 68 (median 136, range 29–248) months. Since patients presented 61 ± 67 (median 36, range 0–388) months after the onset of symptoms, the mean follow-up duration from the first manifestation of arrhythmias was 197 ± 94 (median 188, range 35–473) months. During follow-up, six (4.5%) subjects died from exclusively non-cardiac cause.

A 12-lead ECG was obtained in all 127 survival patients, of them 124 having (98%) sinus rhythm, one (1%) paced rhythm, and two (1.5%) atrial fibrillation. The mean heart rate and QTc interval was 75 ± 12.5 b.p.m. and 400 ± 20 ms,

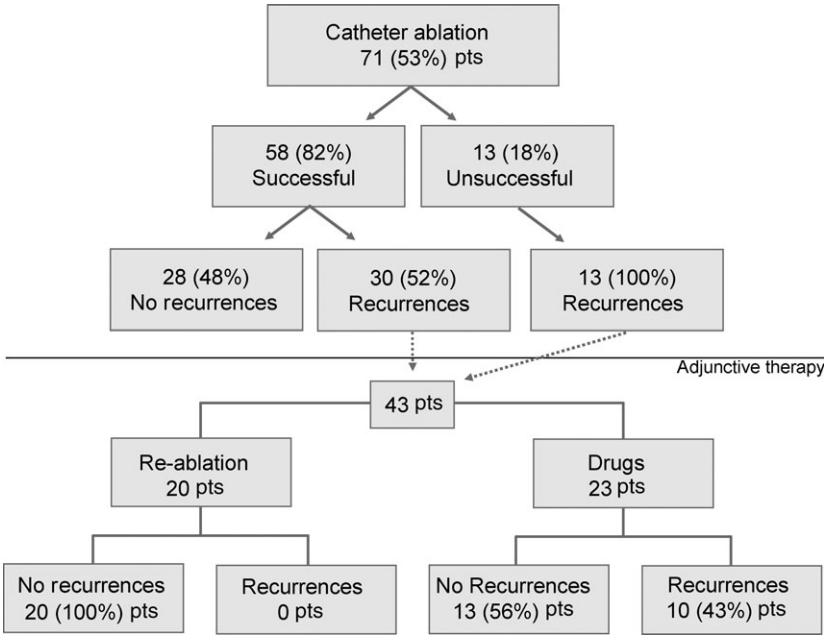

Figure 2 Flowchart showing acute success rate of catheter ablation and follow-up results. As adjunctive therapy, a second therapeutic strategy and follow-up data in patients having recurrences of right ventricular outflow tract arrhythmias after catheter ablation are shown.

respectively. No epsilon waves and no significant alterations were detected in all ECG.[14]

Patients undergoing catheter ablation

In the ablation group, 43 of the 71 patients (61%) showed recurrences of RVOT-arrhythmia after a mean time of 5.13 years (95% CI 3.91–6.35) (*Figure 4*). After successful ablation, 30 (52%) of the 58 patients presented recurrences of RVOT arrhythmias that were documented by 12-lead ECG in all cases (*Table 2*, *Figure 2*). The mean time to recurrence was 6.28 years (95% CI 4.96–7.6). In 10 (33%) patients, recurrent arrhythmias showed the same morphology as those treated previously, whereas in the other 20 (67%) cases, RVOT arrhythmias had a different morphology. However, detailed 12-lead ECG analysis revealed that in 13 (65%) of the 20 patients, RVOT-T morphology was completely different to that targeted for ablation suggesting the emergence of another arrhythmogenic focus, whereas in the other seven (35%) patients the difference in morphology between RVOT-T recurrence and ablated arrhythmias was only discrete. In these cases, a remodelling of the arrhythmogenic site promoted by ablation could be hypothesized.

In addition, in nine (45%) of these 20 subjects, morphology of arrhythmias was similar to a rare isolated RVOT-VES arising after successful ablation and considered clinically non-significant because of the low frequency of its appearance, as described above. Among those patients treated successfully by catheter ablation, there were six subjects having multiple RVOT arrhythmias and 52 with single morphology (*Table 2*). During follow-up, recurrences of RVOT arrhythmias arose in four (67%) of the six patients with multiple morphologies and in 26 (50%) of the 52 subjects with single morphology.

In 30 patients with recurrences, symptoms arose 21 ± 9 (median 20, range 3–42) months after successful catheter ablation. However, 22 (73%) patients reported a considerable improvement of symptoms. The other eight (27%) subjects continued to have the same discomforts as before ablation.

Table 2 Comparison of baseline characteristics and biophysical parameters in patients undergoing successful and unsuccessful catheter ablation

	Acute success	Acute unsuccess	*P*
Patients, *n* (%)[a]	58 (82%)	13 (18%)	n/a[b]
RCF pulses (*n*)[c]	5 ± 4	10 ± 4	<0.01
Rx time (min)	21 ± 14	33 ± 17	0.02
Rx dose (cGy cm^2)	1690 ± 902	2016 ± 1419	0.47
VES, *n* (%)	31 (53)	7 (54)	1.0
nsVT, *n* (%)	11 (19)	1 (8)	0.44
VT, *n* (%)	16 (27.5)	5 (38)	0.51
One morphology (*n*)	52 (90%)	8 (61.5%)	0.02
Multiple morphologies (*n*)	6 (10%)	5 (38%)	0.02
Recurrences during follow-up, *n* (%)	30 (52)	13 (100)	<0.01
Mean time to recurrence (months and 95% CI)	75.3 (8.1–59.5)	0.15 (0.02–0.28)	<0.01

[a]Number and percentage.
[b]Not applicable.
[c]Radiofrequency current.

Adjunctive therapy after ablation

In all 43 patients with unsuccessful ablation or recurrences of RVOT arrhythmias, a further therapeutic option was offered until follow-up assessment visit in our institution (*Figure 2*). In the 30 patients experiencing RVOT-T recurrences after successful catheter ablation, Holter recording and exercise testing were conducted, respectively, in 11 and eight subjects, during the time between onset of recurrences and beginning of the second therapy. Results of Holter recording and exercise testing before and after

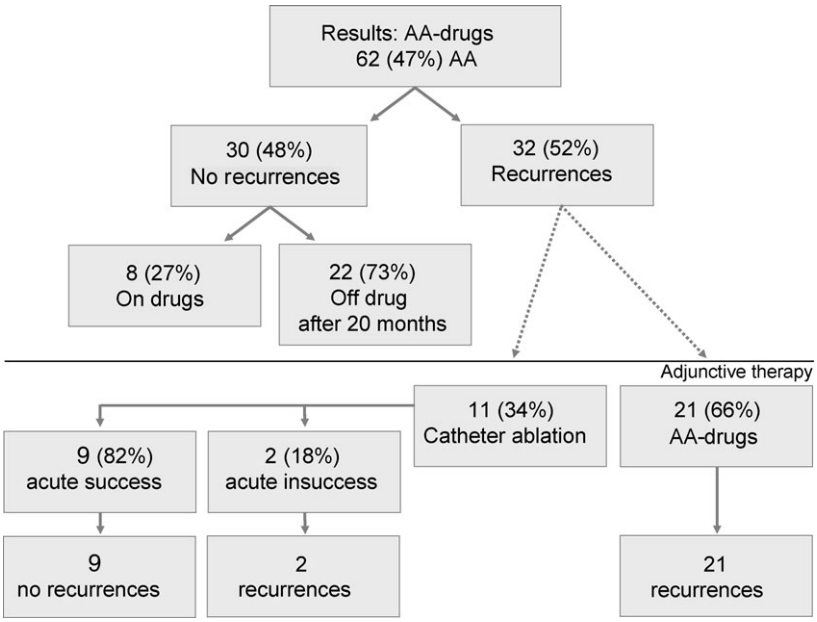

Figure 3 Flowchart showing results of drug therapy. Because of spontaneous remission, the majority of responders discontinued drug therapy after a median of 20 months. As adjunctive therapy, a second therapeutic strategy and follow-up data in patients with recurrences of RVOT arrhythmias on drug are shown.

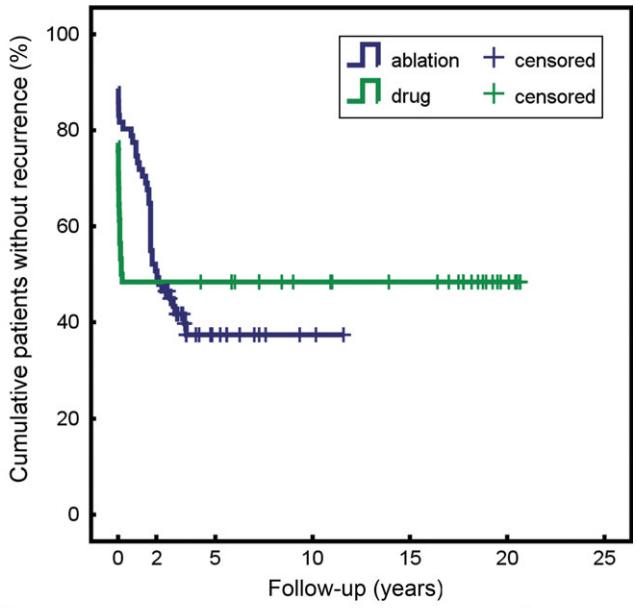

Figure 4 Kaplan–Meier plot of the recurrences of right ventricular outflow tract tachycardia for the drug and ablation therapy groups. Mean time to recurrence was 10.02 (95% CI 7.46–12.59) and 5.13 (3.91–6.35) years for the drug and ablation group, respectively (Breslow test $P = 0.47$).

successful catheter ablation were similar in patients who experienced recurrences of RVOT-T. However, all subjects reported an improvement of symptoms after catheter ablation.

Thus, at the time of the follow-up visit, 28 (86%) of the 71 patients undergoing catheter ablation had no recurrences of RVOT arrhythmias. Holter recording (performed in all patients) and exercise testing (performed in 59 patients) confirmed the absence of RVOT arrhythmias in all cases. The other 10 (14%) continued to have RVOT arrhythmias until their follow-up visit but all were less symptomatic.

Patients undergoing medical therapy

In the group of the 62 (47%) patients treated with AA drugs, 34 (55%) subjects received 186 ± 34 mg (median 200, range 100–200 mg) flecainide daily, 15 (24%) 262 ± 52 mg (median 240, range 160–320 mg) sotalol daily, two (3%) 120 ± 40 mg (median 100, range 100–200 mg) metoprolol daily, three (5%) 450 mg propafenone daily, one (2%) 200 mg amiodarone daily, one (2%) 40 mg prajmaline daily, and six patients received a drug combination (167 ± 47 mg flecainide plus 213 ± 38 mg sotalol daily and 167 ± 47 mg flecainide plus 100 mg metoprolol daily).

On medical therapy, 32 (52%) of the 62 patients continued to have RVOT arrhythmias with a mean time to recurrence of 10.02 years (95% CI 7.46–12.59). The other 30 (48%) remained free of recurrences (*Figures 3* and *4*). Distribution of different drugs and doses was similar in patients with and without recurrences. Of the 30 subjects without recurrences of RVOT arrhythmias, eight were on treatment at the time of the follow-up visit, whereas the other 22 patients suspended medication during follow-up. These 22 patients had no discomforts on drug treatment. Therefore, they interrupted therapy 20 ± 4 (median 20) months after its beginning and continued to feel well during further 159 ± 58 (median 177) months of follow-up. Holter recording and exercise testing at the follow-up visit showed no ventricular arrhythmia in these patients. Thus, they developed a spontaneous remission of the disease.

On treatment, the other eight subjects remained free of recurrences and asymptomatic during 186 ± 60 (median 217) months of follow-up. Holter recording and exercise testing showed no RVOT arrhythmias in six of them, whereas rare ventricular premature beats (<15 of 24 h) were observed in the other two patients. No statistical differences regarding baseline data and results of the clinical evaluation were detected between medically treated patients who had spontaneous disease remission ($n = 22$, all drug responders), and patients who did not ($n = 8$ drug responders and $n = 32$ non-responders).

Adjunctive therapy after initial drug therapy

Of the 32 patients with recurrences of RVOT arrhythmias during follow-up, 11 (34%) underwent catheter ablation, which was performed 70 ± 39 (median 64) months after beginning of the drug therapy and was successful in nine (82%), and unsuccessful in two (8%) cases. During 69 ± 40 months (median 102) of follow-up, no recurrences were observed in the nine cases after successful ablation, whereas in the other two patients RVOT-T resumed. In one patient undergoing successful ablation of RVOT arrhythmia, multiple RV and LV tachycardia were induced by programmed stimulation. This subject received an implantable cardioverter defibrillator and arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) was diagnosed. At the follow-up visit, in the nine patients undergoing successful ablation, Holter recording, and exercise testing revealed the absence of RVOT arrhythmias. The other 21 patients and the two subjects undergoing unsuccessful ablation continued to take AA drugs and experienced further recurrences (*Figure 3*). However, all patients reported an improvement of symptoms. In these patients, comparing results of Holter recording and exercise testing before and after beginning of the drug treatment, no differences in terms of arrhythmia incidence could be detected.

As reported in *Table 1*, all patients treated medically received 4 ± 1 (median 4, range 1–6) different AA drugs during the entire clinical history; experiencing non-responders 4 ± 1 drug regimens, and responders 3 ± 1. Patients with and without spontaneous remission of RVOT arrhythmias had the same total number of AA drugs (3 ± 1).

Echocardiography

At the follow-up visit, two-dimensional echocardiography was performed in all 127 study patients who survived. In 10 (8%) of them, enlargement (31 ± 4 mm) of the RV was detected and one of these 10 subjects had impaired RV function. LV presented dilated (63 ± 2 mm) in five (4%) of the 127 study patients and in four of these, LV function was reduced (slightly in three and marked in one). No severe heart valve alteration was detected in all patients.

In summary, overt cardiomyopathy (ARVD/C) was detected in one (1%) patient.

Discussion

Main results

This long-term retrospective analysis demonstrated that patients with RVOT-T have a favourable long-term prognosis.

Catheter ablation could be demonstrated to be safe and effective for the treatment of RVOT-T, confirming outcomes of previous publications.[4–9] However, long-term outcome with regard to arrhythmia suppression after a single procedure was moderate.

Even medical therapy revealed to be safe and efficacious in preventing RVOT-T. Finally, a marked discrepancy between symptoms and ECG outcome was observed in this study.

Generally, patients with RVOT-T are assumed to have a favourable prognosis. However, some cases of sudden death were identified in these patients.[12,15–19] In our retrospective analysis, no patient died from cardiac cause and only one patient developed to manifest a cardiomyopathy (ARVD/C) during long-term follow-up.

This case can be assumed as a case of RV dysplasia showing RVOT-T as initial clinical sign. However, progression from idiopathic RVOT-T to dysplastic cardiomyopathy cannot be excluded.

Recently, Haissaguerre *et al*. reported 27 cases of recurrent idiopathic ventricular fibrillation caused by ventricular premature beats.[20] In four of these patients, premature beats originated from the RVOT and the mean coupling interval initiating malignant arrhythmias was 355 ± 30 ms. This mechanism may explain previously reported cases of sudden deaths.[12,15–19]

However, of the 133 patients included in our study, none died suddenly. On the other hand, the mean coupling interval between sinus rhythm and RVOT arrhythmias was longer than that indicated by Haissaguerre *et al.*, supporting the favourable character of the disease in our study. Based on these observations, particular attention should be given to this aspect, since coupling intervals allow recognizing subjects at increased risk for sudden death.

Catheter ablation of RVOT-T has emerged as a treatment option in patients with RVOT-T resistant to AA drugs or in patients who do not tolerate medical treatment.[4–10] Acute success rate was reported as varying between 82 and 100%; in our series reaching 82%.[9] Our modest success rate is probably due to the limited experience with ablation procedures of RVOT arrhythmias in the early 1990s. In addition, three-dimensional mapping systems were not employed for the localization of the arrhythmogenic sources. Furthermore, novel ablation technology such as cooled tip ablation may have improved the ablation outcome but was not used in this population. Between patients undergoing successful ablation, 52% had recurrences of RVOT-T during follow-up. Recurrences arose after a median of 20 months. Interestingly, almost all these patients reported a marked improvement of symptoms and a considerable part of them were clinically not limited or thought to have other discomforts than those suffered in the past. This discrepancy between arrhythmia documentation and perception is comparable to a placebo effect and may be responsible for an underestimation of late recurrences in the setting of solely symptom-based follow-up. Especially, studies with telephonic follow-up or visits limited to the first months after ablation might fail recognizing late recurrences.[4,8] However, in our study, no systematic assessment of quality of life or quantitative symptom evaluation was performed.

In addition, 67% of patients with RVOT-T recurrences showed a different VT morphology than that treated previously, suggesting the emergence of a new arrhythmogenic focus or the remodelling of the original ablation site, may be due to a non-transmural ablation lesion. Previous studies demonstrated the efficacy of AA drugs for prevention of RVOT-T, establishing this as valid therapeutic alternative to catheter ablation.[1,2,13,21] However, available data on AA therapy for the treatment of RVOT-T are limited. In addition, a prospective, randomized trial comparing medical and ablative strategy in this setting has never been performed.

In our analysis, primary medical therapy was initiated in 62 of the 133 patients and during follow-up no electrocardiographic recurrences of RVOT arrhythmias were observed in 48% patients. No significant differences with regard to efficacy were detected between different classes of AA drugs. This is concordant to similar results reported previously by Gill *et al*.[21] Noteworthy is that 73% of patients who responded to drug therapy, continued to have no recurrences of RVOT-T after discontinuation of therapy. Thus, the majority of drug responders, which amount to more than one-third of patients, treated medically, experienced spontaneous remission of the arrhythmia. This phenomenon was previously described in other studies; however, the frequency of its occurrence was difficult to establish due to the low patient number.[1,16] Analysing patient baseline characteristics and electrophysiological properties of arrhythmias, no strong predictive factors could be identified for spontaneous remission. Thus, future prospective studies are required to investigate the need for catheter ablation as the first line therapy for RVOT-T in comparison with medical treatment, especially taking into account the possibility of spontaneous arrhythmia remission.

Study limitations

No three-dimensional mapping system was employed to facilitate localization of the arrhythmic source. Therefore, it cannot be excluded that the results may have been improved by the introduction of such mapping tools.

The objective evaluation of treatment efficacy was based on the Holter recording and exercise testing results which have low reproducibility in the setting of RVOT arrhythmias. Thus, diagnosis of recurrence could have been underestimated in some cases. However, during follow-up, many patients were seen several times by the familial cardiologist due to different reasons and related data were available at the time of the follow-up visit. Therefore, the rate of unnoticed recurrences should be limited.

At the time of follow-up visits, some patients had already experienced sequential therapeutic options such as medical therapy and subsequently catheter ablation for drug inefficacy.

Assessment of medical treatment efficacy was based exclusively on the efficacy of drugs given by us at the time of first presentation. Thus, no sequential therapy was evaluated in this study, which may have caused different results.

Conclusions

Patients with idiopathic RVOT-T have a favourable long-term prognosis. Catheter ablation is effective for the treatment

of RVOT-T. However, late recurrences with similar or different morphology may occur in a substantial number of patients, preferably those with persistent premature beats after ablation. AA drugs represent a valid initial therapeutic alternative, since they are efficacious in about half of the patients. In addition, in more than one-third of the medically treated patients, drugs can be discontinued because of spontaneous remission.

Conflict of interest: none declared.

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