Adenosine Sensitivity is Associated with Ablation Success Rate and Recurrence Rate with Nonirrigated Catheters in Patients with Ventricular Premature Contractions/Tachycardia from the Ventricular Outflow Tract

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Background: A high ablation success rate for ventricular arrhythmia (VA) from outflow tract has been achieved, but some of them cannot be eliminated from endocardium. We investigated the association between adenosine sensitivity and ablation success/recurrence rates with a nonirrigated or an irrigated catheter.

Methods: According to adenosine test, all patients were divided into a sensitive group (S group) or an insensitive group (I group). The patients of each group were randomized into a nonirrigated catheter (NA) subgroup or an irrigated catheter (IA) subgroup with a 2:1 ratio.

Results: In S group of 122 patients (84 in NA subgroup), the ablation success rate was similar between two subgroups (94.7% vs. 90.5%, P > 0.05), but in I group of 94 patients (60 in NA subgroup), it was higher in IA subgroup (94.1%) than that in NA subgroup (73.3%, P < 0.05). The success rate using nonirrigated catheter was significantly higher in S group (90.5%) than that in I group (73.3%, P < 0.01), and the recurrence rate was lower in S group than that in I group (1.3%, vs. 13.6%, P < 0.05). On the contrary, the success rate and the recurrence rate using irrigated catheter were similar between S group and I group (94.7%, 94.1%, P > 0.05, vs. 2.8%, 6.3%, P > 0.05).

Conclusions: Adenosine insensitivity is associated with a lower success rate and a higher recurrence rate for VA patients undergoing nonirrigated catheter ablation. Thus, irrigated catheters should be the first choice for VA ablation in adenosine insensitive patients.

Key words: Ablation; Adenosine; Catheter; Ventricular Tachycardia; Premature Ventricular Contractions

INTRODUCTION

Premature ventricular contractions (PVCs) originating from the ventricular outflow tract (OT) are types of idiopathic ventricular arrhythmia (VA).[1] They can occur in patients without structural heart disease and might be provoked by exertion, emotion, or dietary stimulants.[2] The clinical presentation of these subjects is heterogeneous.[3,4] Usually, these VAs can be eliminated by radiofrequency catheter ablation (RFCA) directly at the OT endocardium,[5] at the aortic sinus of valsalva[6,7] or at the great cardiac vein of the coronary venous system (CVS).[8]

A nonirrigated ablation catheter has been used for treatment of these types of arrhythmias,[5] and the success rate has been reported to be between 80% and 92%,[9,10] the recurrence rate is high (10%–24%) during follow-up.[10,11] The underlying reasons for failed ablation are not yet fully clarified, but one reason might be unpredictable power delivery because of variations in endocardial contact.[12] Intramyocardial or epicardial surface origin of monomorphic PVCs may also be responsible for the reported failure of RFCA with nonirrigated ablation catheters.[11] Irrigated-tip catheters are usually used for failed ablation with nonirrigated catheters.[6,7] Success rates for irrigated-tip catheter ablation have been reported to be high (ranging from 85% to 97%).[11] Irrigated-tip catheters are not routinely used for mapping and ablation of VAs in most electrophysiology centers due to the complex procedures involved, the higher cost of the procedure, and the risk for creating larger ablation lesions.[5,13]

Previous studies showed that intravenous adenosine is often effective in terminating ventricular tachycardia (VT) originating from the OT. Wilber demonstrated that intravenous adenosine reproducibly terminated VT

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originating from the right ventricular OT (RVOT) in a large proportion of patients with structurally normal hearts.\textsuperscript{[16]} Takahashi et al.\textsuperscript{[6]} showed that VT originating from the LVOT transiently disappeared after the adenosine triphosphate infusion. In another report, however, OT-VA was not terminated by intravenous adenosine.\textsuperscript{[17]} We hypothesized that the adenosine sensitivity predicts the success rate of RFCA using nonirrigated ablation catheters for patients with OT-VA. In this study, we confirmed an association between the adenosine sensitivity and ablation success and recurrence rates with nonirrigated catheters for patients with OT-VA.

**METHODS**

**Study population**

Two hundred and seventy-eight consecutive patients (143 males) with repetitive idiopathic VA referred for RFCA from April 2005 to July 2010 in our department were included in this prospective randomized study. Surface electrocardiogram (ECG) showed that idiopathic VA had a characteristic left/right bundle branch block morphology with a dominant R wave in the inferior leads. For patients with polymorphism of PVCs, only patients with the most PVCs from OT were included in this study. Patients with structural heart diseases, no spontaneous or inducible VA during electrophysiological study (EPS) were excluded. Structure heart disease was defined as the presence of coronary artery disease, a left ventricular (LV) ejection fraction < 40%, moderate or severe valvular heart disease\textsuperscript{[15]} or cardiomyopathy. The remaining consecutive patients were divided into a sensitive group (S group) or an insensitive group (I group) according to the adenosine test. The patients of each group were randomized into a nonirrigated catheter (NA) subgroup or an irrigated catheter (IA) subgroup with a 2:1 ratio of enrollment through a randomly generated number table.

**Study procedure**

All patients completed baseline questionnaires for eligibility screening and baseline characteristics were gathered. Routine 12-lead surface ECG and ambulatory ECG monitoring for 24 hours were obtained to determine the arrhythmia burden. Physical examinations, transthoracic echocardiography and coronary computed tomography angiography were performed at baseline and again at 3 months post ablation. EPS and the adenosine test were performed first followed by mapping and ablation. Patients were sent questionnaires to update their medical and lifestyle information at 3 months post ablation. The study was reviewed and approved by the Medical Ethics Board of the Hospital, and all patients provided written informed consent before enrollment.

**Electrophysiological study**

Electrophysiological study was performed after all antiarrhythmic drugs had been discontinued for at least five half-lives prior to the study. Catheters were inserted through the right femoral vein into the high right atrium and right ventricle under fluoroscopic guidance. LV mapping was performed through the retrograde aortic approach. An initial 3000-unit bolus of heparin was administered intravenously, followed by 1000 units/h throughout the procedure.

Programmed stimulation was performed at twice the diastolic threshold with a pulse width of 2 ms using a programmable stimulator (MicroPace EPS320 Cardiac Stimulator, USA). If VA did not occur spontaneously and were not induced during the baseline state, intravenous isoproterenol infusion (2–5 µg/min) was administered to provoke clinical arrhythmia\textsuperscript{[16]} and programmed stimulation was repeated. Ventricular programmed stimulation was performed with up to three extra stimuli at two basic drive cycle lengths (500 and 400 ms) and incremental burst pacing at a cycle length up to 250 ms, starting at RV apex, then at the RVOT at baseline and repeated after infusion of isoproterenol.

**Adenosine test**

During EPS, adenosine was administered as a bolus (18 mg)\textsuperscript{[7]} via a peripheral vein during frequent PVCs or short-burst VT. Adenosine action was defined as suppression or termination of VA, sinus node suppression, or atrial-ventricular block occurring within 60 s of adenosine administration. The starting-point of adenosine action was defined as the time at P-R or R-R interval prolongation by 30% or more above baseline level and the end-point was defined as the time when the P-R or R-R interval decreased by 30% or more of baseline level. Adenosine action interval was calculated as the difference between the starting-point time and the end-point time. The time interval between adenosine infusion and the starting-point of adenosine action was defined as the adenosine onset time. The response of the arrhythmia to adenosine was defined as follows: Adenosine sensitive when VT, which had persisted for at least 1 min before adenosine injection was terminated within 30 s of administration of adenosine\textsuperscript{[15]} or there were no PVCs or short-burst VTs of same morphology as spontaneous VA during the adenosine action interval [Figure 1]; adenosine insensitive when VT was not terminated or PVCs were not abolished during the adenosine action interval [Figure 2].

![Figure 1: A representative case of adenosine sensitive response of premature ventricular contractions (PVCs). PVCs were suppressed completely with development of A-V Block/Brady arrhythmias during the adenosine action interval.](image-url)
Mapping and radiofrequency catheter ablation

After EPS and adenosine test, an ablation catheter was placed at the RVOT, the LVOT and in the CVS to map PVCs or VT. For patients in NA subgroup, ablation was performed with a 4-mm-tip nonirrigated catheter (Biosense Webster). If this procedure was ineffective after 5 energy applications, a 3.5-mm-tip irrigated catheter (Thermocool, Biosense Webster) was used for ablation. For patients in IA subgroup, ablation was made only using an irrigated tip catheter. A three-dimensional activation map (3D map) was reconstructed with a 3D mapping system (CARTO, Biosense Webster) in all patients. A suitable target site for ablation was selected based on the earliest endocardial activation time (preceding the QRS by at least 20 ms) during arrhythmia and ideal pace mapping. The ideal pace mapping is an identical QRS pattern in at least 10 surface ECG leads (≥10/12 match) with a pace map score ≥90% between the clinical arrhythmia and the paced QRS morphology. Unmodulated radiofrequency current was delivered in a unipolar fashion from a generator (Stockert Epshuttle™, Germany). RFCA applications were delivered at a power of 30–35 W with a temperature limit of 65° for patients in NA subgroup. If VA disappeared within 30 seconds, energy was delivered continuously for 180 seconds. If radiofrequency current application failed to terminate the tachycardia or PVCs within 30 seconds, the catheter was moved to a different site. Five periods of RF application were applied to eliminate VT or PVCs. In NA subgroup, if ablation was unsuccessful after five periods of energy delivery, it was ineffective and repeated with the irrigated catheter. RFCA applications in IA subgroup were delivered at a power of 30 W with temperature limit of 43°, and the same procedure sequences (five applications) were performed as in the NA subgroup.

The ablation endpoint was defined as complete elimination of spontaneous VA for at least 30 minutes after the last application of energy, and VT or PVCs did not occur or could not be induced by ventricular stimulation or isoproterenol infusion. If VA appeared or was still inducible, the catheter was moved to another site, and the mapping was repeated. If the ablation endpoint was achieved, we considered it an effective ablation, and the ablation site was defined as the effective site.

Coronary artery angiography was performed prior to RFCA at the CVS or aortic sinus to confirm the distance from the ablation catheter tip to the coronary artery. Furthermore, a safe separation (above 0.5 cm) between the ablation target and the orifice of the coronary artery was maintained.

Follow-up

After RFCA, all patients received ECG monitoring for 24 h. Ambulatory ECGs were made within 1 week after the procedure. Subsequently, the patients received examinations on an outpatient basis, and clinical data were obtained. Holter recording (24 hours) was performed at 1, 3, 6 and 12 months after the procedure and every 6 months thereafter. Ablation was defined as successful with ≥ 80% reduction of PVC burden,[17] or ≤1500 PVCs or no VT episodes during the follow-up period. Otherwise, the case was defined as recurrence. All antiarrhythmic drugs were withheld after the ablation procedure. Repeat ablation was performed after 3 months from the time of the procedure for recurrent VA.

Statistical analysis

Data are presented as mean ± SD for continuous variables, median and 10%–90% confidence interval (CI) for ordinal variables and percentage for categorical data. Fisher’s exact test or Chi-square test was used to compare differences for categorical data between the two groups depending on sample size. Student’s t-test or nonparametric test (Mann–Whitney U-test) was used to compare differences for continuous variables between the two groups as indicated. A P < 0.05 was regarded as statistically significant.

RESULTS

Clinical characteristics

Of the 278 patients enrolled in the study, 38 (13.7%) patients were excluded because of structural heart diseases and 24 (8.6%) were excluded for missing VA, leaving 216 patients (S group, n = 122 and I group, n = 94) available for analysis. All patients failed to respond to at least one antiarrhythmic drug.

Patients’ clinical characteristics were similar between the two groups [Table 1]. Ambulatory ECGs demonstrated 725 ± 914 episodes of nonsustained VT/24 h and 3648 ± 554 episodes of PVCs/24 h in 38 patients with nonsustained VT prior to the procedure. PVCs were 18755 ± 10372/24 h in the remaining 178 patients.

Electrophysiological studies and adenosine test

At baseline, VT/PVCs were absent in 63 patients during the procedure. Among them, VT/PVCs were inducible by isoproterenol in 39 patients (21 patients were sensitive to adenosine, 18 patients were insensitive, P = 0.714). Sustained VT could not be induced in all patients with either ventricular pacing or isoproterenol infusion. According to the
adenosine test, 122 patients were sensitive, and 94 patients were insensitive. During the test, atrial tachycardia and asthma were induced in one patient respectively. The duration of the QRS complex (QRS-D), the coupling interval, the adenosine onset time, and the adenosine action interval of VA are summarized in Table 2. These parameters were similar between two groups or subgroups in each group (all \( P > 0.05 \)).

In S group, nonirrigated catheter was used in 84 patients and irrigated catheter was in the rest of 38 patients, the ablation success rate was similar between two subgroups (76/84, 90.5% vs. 36/38, 94.7%, \( P > 0.05 \)). In I group, nonirrigated catheter was in 60 and irrigated catheter was in the rest of 34, the ablation success rate was significantly higher in IA subgroup (32/34, 94.1%) than that in NA subgroup (44/60, 73.3%, \( P < 0.05 \)) [Table 3].

The ablation success rate using nonirrigated catheter was significantly higher in S group (76/84, 90.5%, 95% CI: 0.86–0.95) than that in I group (44/60, 73.3%, 95% CI: 0.66–0.81, \( P < 0.01 \)). By replacing with an irrigated catheter, ablation was repeated in patients that failed nonirrigated catheter ablation \((n = 24, 8\) in S group, 16 in I group) and was successful in 21 patients (87.5%). The ablation success rate using irrigated catheter was similar between S group (36/38, 94.7%, 95% CI: 0.9–1.0) and I group (32/34, 94.1%, 95% CI: 0.89–1.0, \( P > 0.05 \)). The patients that failed irrigated catheter ablation \((n = 3\) were treated with drugs thereafter [Table 4].

### Table 1: Clinical characteristics of patients with OT-VA \((n=216)\)

| Items                  | S group \((n = 122)\) | I group \((n = 94)\) | \(P^*\) |
|------------------------|------------------------|-----------------------|---------|
| Female, \(n\) (%)      | 62 (50.8)              | 50 (53.2)             | 0.729   |
| Age, years, mean ± SD  | 51.9 ± 14.3            | 54.5 ± 15.6           | 0.23    |
| LVEF, %, mean ± SD     | 57.4 ± 7.8             | 59.2 ± 9.6            | 0.41    |
| Nonsustained VT, %     | 24 (19.7)              | 17 (18.1)             | 0.768   |
| PVCs only, %           | 98 (80.3)              | 77 (81.9)             | 0.768   |
| Hypertension, %        | 50 (41.0)              | 40 (42.6)             | 0.817   |
| Diabetes, %            | 24 (19.7)              | 19 (20.2)             | 0.921   |
| \(\beta\)-blocker, %   | 70 (57.4)              | 56 (59.6)             | 0.745   |
| Amiodarone, %          | 79 (64.8)              | 58 (61.7)             | 0.644   |
| Mexitilene, %          | 41 (33.6)              | 29 (30.9)             | 0.668   |
| Propafenone, %         | 20 (16.4)              | 17 (18.1)             | 0.744   |
| Moracizine, %          | 28 (23.0)              | 23 (24.5)             | 0.795   |
| Spontaneously VA at baseline, % | 101 (57.1) | 76 (42.9) | 0.714 |
| Inducible VA by isoproterenol, % | 21 (53.8) | 18 (46.2) | 0.714 |

*For comparison between S group and I group, there were no significant difference in any comparison between two groups \((P > 0.05)\). LVEF: Left ventricular ejection fraction; OT: Outflow tract; VA: Ventricular arrhythmia; PVCs: Premature ventricular contractions; VT: Ventricular tachycardia.

### Table 2: Electrophysiological characteristics of patients with OT-VA \((n = 216)\)

| Group | Catheter type | VAT (ms) ± SD | QRS-D (ms) ± SD | Coupling-interval (ms) ± SD | Adenosine onset-time (s) ± SD | Adenosine action-interval (s) ± SD |
|-------|---------------|--------------|-----------------|-----------------------------|-------------------------------|----------------------------------|
| S \((n = 122)\) | NA \((n = 84)\) | 83.13 ± 21.91 | 140.88 ± 19.87 | 463.68 ± 90.10 | 15.57 ± 12.04 | 14.77 ± 10.32 |
|       | IA \((n = 38)\) | 83.00 ± 25.37 | 156.42 ± 23.10 | 450.00 ± 67.06 | 13.09 ± 3.38 | 22.93 ± 15.50 |
| I \((n = 94)\) | NA \((n = 60)\) | 96.95 ± 20.52 | 153.45 ± 16.32 | 470.32 ± 75.67 | 30.36 ± 46.77 | 12.88 ± 6.32 |
|       | IA \((n = 34)\) | 83.88 ± 27.62 | 140.88 ± 18.23 | 467.21 ± 90.44 | 19.84 ± 13.44 | 15.22 ± 5.74 |

There were no significant difference in any comparison between two groups or subgroups \((P > 0.05)\). S: Sensitive; I: Insensitive; NA: Nonirrigated ablation catheter; IA: Irrigated ablation catheter; QRS-D: Duration of QRS complex of PVC/VT; VAT: Left ventricular activation time of PVC/VT; OT: Outflow tract; VA: Ventricular arrhythmia; SD: Standard deviation.

### Table 3: The ablated target sites and the success rate on various sites \((n = 216)\)

| Group \((n = 216)\) | Target sites (effective sites) \((n = 118)\) | Intragroup \(P\) |
|---------------------|-----------------------------------------------|------------------|
| S \((n = 122)\)     | NA 76 (90.5)                                  | 0.263            |
|                     | IA 36 (94.7)                                  |                  |
| I \((n = 94)\)      | NA 60 (73.3)                                  | 0.263            |
|                     | IA 34 (94.1)                                  |                  |

There were no significant difference in ablation success rate among various target sites \((P > 0.05)\). S: Sensitive; I: Insensitive; NA: Nonirrigated ablation catheter; IA: Irrigated ablation catheter; RVOT: Right ventricular outflow tract; LVOT: Left ventricular outflow tract; CVS: Coronary venous system; Epi: Epicardium; AS: Aortic sinus.
The recurrent rate was similar in adenosine sensitive and insensitive patients using nonirrigated catheter and irrigated catheter among the various target sites (all *P* > 0.05, Table 3).

For patients with energy delivery at the aortic sinus, coronary angiography showed normal vasculature and blood flow after ablation. The successful ablation sites were located at a distance 0.8–1.1 cm from the coronary artery. Small pericardial effusion appeared in two patients using irrigated catheter in CVS during the perioperative period, and patients recovered without sequelae.

**Follow-up**

During a mean follow-up period of 11.4 ± 3.4 months, VA occurred in 2 patients (2/122, 1.6%) in S group and 8 patients (8/94, 8.5%) in I group (P < 0.05) [Table 4]. In patients using nonirrigated catheter, the recurrence rate was significantly lower in S group than that in I group (1/76, 1.3%, vs. 6/44, 13.6%, *P* < 0.05). But in patients using irrigated catheter, the recurrent rates were similar between two groups (1/36, 2.8% vs. 2/32, 6.3%, *P* > 0.05). By replacing with an irrigated catheter in two NA subgroups, VA disappeared in 21 patients but recurred in 3 patients (1 in S group, 2 in I group). The recurrent rates were similar between before and after catheter exchange (all *P* > 0.05). Among 10 recurrent patients, 2 patients were lost to follow-up after the first ablation procedure, 1 patient declined a second ablation, seven patients subsequently underwent a second RFCA with the irrigated catheter and ablation was successful in 6 patients.

During follow-up, repeat 24 h Holter monitoring demonstrated a significant reduction in the PVCs burden from 15700 ± 11498 beats/24 h to 1570 ± 5902 beats/24 h (*P* = 0.007). There was also a significant improvement in symptoms with a symptom-free rate of 81% during follow-up.

**Discussion**

The major finding of this study is that the initial success rate for OT-VA ablation using a nonirrigated catheter was significantly higher in adenosine sensitive patients than that in adenosine insensitive patients; while using an irrigated catheter, it is similar between sensitive and insensitive patients. Interestingly, a lower recurrent rate was observed in the adenosine sensitive patients compared with the adenosine insensitive patients after nonirrigated catheter ablation.

**Mechanism of ventricular arrhythmia sensitivity to adenosine**

In addition to reentry and automaticity mechanisms, cAMP-mediated triggered activity has been reported as a third mechanism responsible for VA.[18] Therefore, adenosine could terminate VA by means of the A1 receptor activation of the inhibitory G-protein G-bi. This would then inhibit cAMP generation by adenyl cyclase and block the triggered release of calcium from the sarcoplasmic reticulum even in the presence of normal calcium storage.[19] Thus, termination of VA by adenosine suggests cAMP-triggered activity. In the case of adenosine sensitive RVOT VT,[20] focal ablation at the earliest ventricular activation site resulted in long-term abolition of VT in the endocardium.[14] Diker found that the origin of adenosine sensitive left VT was located near to the anterior fascicle, that is, the focus was from the endocardium and suitable for nonirrigated catheter ablation.[21]

The fact that adenosine is unable to terminate VA might be explained by the lack of any direct effect of adenosine on the ventricular myocardium.[14] Most cases of adenosine insensitive OT-VA may be caused by reentry and automaticity mechanisms. The origin sites of these OT-VAs were usually located on the septum of RVOT and might not be suitable for nonirrigated catheter ablation.[14] In a prior study, reentry VT originating from LVOT that could not be terminated by adenosine was successfully ablated from the aortic sinus.[7] Various sites including the aortic sinus, the great cardiac vein, and the anterior interventricular vein that could generate ectopic impulses have been identified.[9] In these cases, intramyocardial or epicardial ablations with an irrigated catheter for adenosine-insensitive OT-VA are usually indicated.

**Lesion depth of ablation**

During RFCA, the local temperature increase is proportional to the energy applied per second and to the heat transduction capacity of the local medium.[22] Ablation with nonirrigated catheters might result in unpredictable power delivery because of variations in endocardial contact and local blood flow. Since irrigated catheters are equipped with active cooling of the tip electrode by saline, larger and deeper ablation lesions could be produced compared with a nonirrigated catheter.[23,24] Since the origin depth or the critical isthmus of VA may be located intramyocardially or epicardially,[9] ablation using the irrigated catheter or epicardial approach is recommended.[25]

In line with above-mentioned suggestions, we postulated that adenosine sensitive VA is more likely originated from endocardium and therefore amenable to nonirrigated catheter ablation. In contrast, adenosine insensitive VA is more likely to have epicardial/deep endocardial origin and amenable to irrigated catheter ablation. The cause of slightly high recurrence rate in adenosine insensitive patients with

**Table 4: The success rate and the recurrent rates (n = 216)**

| Group (n = 216) | Catheter type (n) | Effective (effective rate) (n = 188) (%) | Ineffective (ineffective rate) (n = 28) (%) | Recurrent (recurrent rate) (n = 10) (%) |
|----------------|------------------|----------------------------------------|------------------------------------------|----------------------------------------|
| S (n = 122)   | NA (84)          | 76 (90.5)                              | 8 (9.5)                                  | 1 (1.3)                                |
|               | IA (38)          | 36 (94.7)                              | 2 (5.3)                                  | 1 (2.8)                                |
| I (n = 94)    | NA (60)          | 44 (73.3)                              | 16 (26.7)                                | 6 (13.6)                               |
|               | IA (34)          | 32 (94.1)                              | 2 (5.9)                                  | 2 (6.3)                                |

The recurrent rate was significant lower in S group than that in I groups (*P* < 0.05). S: Sensitive; I: Insensitive; NA: Nonirrigated ablation catheter; IA: Irrigated ablation catheter.
nonirrigated catheter ablation might also be associated with epicardial/deep endocardial origin.

**Study limitations**

This study has several limitations. First, adenosine sensitivity could only be reliably determined in the presence of OT-VA. Second, a match of QRS complexes between pace mapping and VA was determined as ≥10/12 leads and not the exact match of 12/12.

Third, there is no anatomical evidence to define the origin depth of OT-VA in our patients.

**Conclusions**

Adenosine insensitivity is associated with a lower success rate and higher recurrence rate for OT-VA patients undergoing nonirrigated catheter ablation. Thus, an irrigated catheter should be considered for OT-VA ablation in adenosine insensitive patients.

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