Differentiation of Papillary Muscle from Fascicular and Mitral Annular Ventricular Arrhythmias in Patients With and Without Structural Heart Disease

Running title: Al’Aref et al.; Differentiation of Left Ventricular Arrhythmias

Subhi J. Al’Aref, MD; James E. Ip, MD, FHRS; Steven M. Markowitz, MD, FHRS;
Christopher F. Liu, MD, FHRS; George Thomas, MD; Daniel Frenkel, MD;
Nikhil C. Panda, MD; Jonathan W. Weinsaft, MD; Bruce B. Lerman, MD, FHRS;
Jim W. Cheung, MD, FHRS

Department of Medicine, Division of Cardiology, Weill Cornell Medical College, New York, NY

Correspondence:
Jim W. Cheung, MD
Department of Cardiology
Weill Cornell Medical College
520 East 70th Street 4th Floor
New York, NY 10065
Tel: (212) 746-2158
Fax: (212) 746-6951
E-mail: jae9029@med.cornell.edu

Journal Subject Codes: [106] Electrophysiology, [171] Electrocardiology
Abstract:

Background - Idiopathic left ventricular arrhythmias (VAs) as well as those due to structural heart disease can originate from the papillary muscles, fascicles and mitral annulus. Differentiation of these arrhythmias can be challenging since they present with a right bundle branch block morphology by electrocardiography. We sought to identify clinical, electrocardiographic and electrophysiological features that distinguish these left VAs in patients with and without structural heart disease.

Method and Results - Patients undergoing catheter ablation for papillary muscle, fascicular or mitral annular VAs were studied. Demographic data, electrocardiographic and electrophysiological findings were analyzed. Fifty-two VAs in 51 patients (32 [63%] male; mean age 61 ± 15 years) with papillary muscle (n = 18), fascicular (n = 15) and mitral annular (n = 19) origins were studied. Patients with papillary muscle VAs were older and had higher prevalence of left ventricular dysfunction (67% vs. 13% of fascicular VA patients [P = 0.009]) and coronary artery disease (78% vs. 37% of mitral annular VA patients [P = 0.036]). Papillary muscle VAs were distinguished electrocardiographically from fascicular VAs by longer QRS durations and lower prevalence of r < R' V1 QRS morphology and from mitral annular VAs by lower prevalence of positive precordial lead concordance. Using a stepwise electrocardiographic algorithm, the accuracy rates for the diagnosis of papillary muscle VAs, fascicular VAs and mitral annular VAs were 83%, 87% and 89%, respectively.

Conclusions - Specific electrocardiographic characteristics including QRS morphology and precordial lead morphology can help distinguish between papillary muscle, fascicular and mitral annular VAs.

Keywords: papillary muscle, mitral valve annulus, ventricular arrhythmia, electrocardiography, fascicular
Introduction

The left ventricular anterior and posterior papillary muscles (Pap) give rise to ventricular arrhythmias in both structurally normal and abnormal hearts. Ventricular arrhythmias (VAs) originating from the papillary muscles have been shown to exhibit distinct clinical and electrocardiographic features. Given that papillary muscles are anatomically complex structures, catheter ablation of Pap VAs can be challenging and are associated with lower success rates than ablation of left ventricular fascicular arrhythmias. Studies on the differentiation of Pap VAs from other idiopathic left VAs, such as mitral annular (MA) VAs are lacking. In this study, we characterize the clinical, electrocardiographic and electrophysiological features of left Pap VAs in patients undergoing catheter ablation and compare these features to those of left fascicular and focal mitral annular VAs. We sought to identify an electrocardiographic algorithm to distinguish left Pap VAs from fascicular and MA VAs.

Methods

Study Population

The subjects comprised 51 consecutive patients undergoing catheter ablation of symptomatic ventricular arrhythmia (31 [61%] presenting as premature ventricular contractions (PVCs) and 20 [39%] as sustained or non-sustained ventricular tachycardia [VT]) arising from either the left ventricular papillary muscles, left ventricular fascicles or mitral annulus at the Weill Cornell Medical Center. This study was approved by the Institutional Review Board of Weill Cornell Medical College.

Electrocardiogram characteristics (12-lead and Holter monitor)

All patients had standard 12-lead electrocardiogram (ECG) recordings made at the time of electrophysiological testing using the Prucka CardioLab (GE Healthcare, Waukesha, Wisconsin)
recording system using low frequency and high-frequency filters of 0.05 and 150 Hz, respectively. Measurements were performed with electronic calipers at uniform lead gain at a sweep speed of 100 mm/sec. The following VA ECG characteristics were recorded: bundle branch block morphology (right or left), axis (right or left, inferior or superior), QRS duration, morphology of the QRS complex in V1 (R, R′, rR′, qR, QR, qR′, qR′, Rs, rS, RSr′, Rsr′, rSR′, rsR′, and variable) (see Supplementary Table 1). Lead V1 VA QRS morphology was classified as r < R′ if two distinct positive deflections were present and the amplitude of the first positive deflection was less than the second positive deflection. Lead V5 VA QRS morphology was classified as R ≥ S if the amplitude of the R wave was greater than amplitude of the S wave or if no S wave was present. Ventricular arrhythmia ECGs were defined as having positive precordial concordance if R > s in all six precordial leads. These criteria were adjudicated by two observers (SJA and JWC) with initial inter-observer agreement on V1 QRS complex morphology adjudication of 92% and on all other variables of 100%. Discrepancies were resolved by consensus.

Electrophysiological study and catheter ablation

After written informed consent was obtained, electrophysiological testing was performed. Patients were locally anesthesized with 0.25% bupivacaine and sedated with midazolam and fentanyl. The ventricular stimulation protocol included up to triple ventricular extrastimuli at up to 2 paced cycle lengths from the right ventricular apex and right ventricular outflow tract. Isoproterenol infusion (up to 20 mcg/min) was given in 45 (87%) cases to assess for arrhythmia facilitation as characterized by increase in PVC frequency or VT inducibility. The presence of multiple morphologies of PVCs or VT during the electrophysiology study was recorded.

Electroanatomic mapping (CARTO, CARTO XP or CARTO 3, Biosense Webster,
Diamond Bar, CA) was performed in all cases, using the Biosense Navistar 4 mm (n = 8), Biosense Navistar 8 mm (n = 1), Biosense Thermocool Navistar irrigated 3.5 mm (n = 26), Biosense Thermocool SF irrigated 3.5 mm (n = 11), and Biosense Thermocool RMT irrigated 3.5 mm (n = 8) ablation catheters (Biosense Webster, Diamond Bar, CA). For 1 MA VA ablation case, both a Biosense Navistar 4 mm and Biosense Navistar 8 mm non-irrigated ablation catheter were used and for 2 Pap VA cases, both Biosense Thermocool RMT irrigated 3.5 mm and Biosense Thermocool SF irrigated 3.5 mm ablation catheters were used. Remote magnetic navigation mapping (Stereotaxis, St. Louis, MI) was performed in 8 (16%) cases based on operator preference. For Pap and MA VAs, sites for ablation were determined by the earliest sites of VA activation as characterized by electroanatomic mapping, local activation > 20 msec pre-VA QRS onset, polarity switch between proximal and distal ablation electrogram recordings, “QS” unipolar electrograms during VA or pace mapping. During mapping of 6 (11%) VAs (4 Pap VAs and 2 MA VAs), pace mapping was the primary modality used to identify the site of VA origin due to presence of infrequent VA ectopy during the procedure. This was performed by identifying sites of near 12/12 lead ECG pace map match as confirmed visually by the operator. In all Pap VA cases, catheter positions and relationship to papillary muscle location were assessed using intra-cardiac echocardiography (ICE) (Acunav, Siemens, Mountain View, California). Mitral annular VAs were defined by the presence of both atrial and ventricular electrograms at the site of VA origin. The presence of fractionation, fascicular or Purkinje potentials at the site of earliest VA activation was annotated. In cases of ablation of fascicular VAs, the location of the left anterior and posterior fascicles as identified by the presence of sharp fascicular potentials either during sinus rhythm or VA was recorded. Sites with diastolic potentials consistent with slowed Purkinje conduction were targeted for ablation. Overall, acute
success of ablation was defined as complete abolition of targeted PVCs and, if applicable, lack of VT inducibility during a post-ablation observation period of at least 30 minutes. Post-ablation clinical follow-up was available for 42 (82%) patients. All available follow-up clinical histories, ECGs and Holters were reviewed for arrhythmia recurrence.

**Cardiac magnetic resonance imaging**

Cardiac magnetic resonance (CMR) imaging prior to catheter ablation was performed in 14 (27%) patients. Myocardial scar/infarction was assessed via use of a inversion recovery gradient echo pulse sequence, which was performed 10-30 minutes following administration of gadolinium-based contrast (0.20 mmol/kg), during which inversion times were tailored to null viable myocardium (typical inversion time 250-350 msec). Myocardial scar/infarction within each of the papillary muscles was identified based on regional enhancement within each of the papillary muscles, in accordance with previously established methods.7

**Follow-up**

All dates of follow-up either in the hospital or in the office after ablation were recorded. Medical records were reviewed to assess for documentation of recurrent arrhythmias. For patients who underwent PVC ablation, Holter reports prior to ablation and after ablation were analyzed. Results from repeat electrophysiology studies and catheter ablation procedures performed for recurrent clinical VA were reviewed.

**Statistical Analysis**

Statistical analysis was performed using SPSS version 19 (SPSS Inc., Chicago, IL).

Continuous variables were expressed as the mean ± standard deviation or median (interquartile range [IQR]: 25th percentile, 75th percentile) based on normality of distribution. For pairwise comparisons of categorical variables, the Fisher exact test was used and for comparisons of > 2
groups of categorical variables, the Chi-square test was used. For comparisons of > 2 groups of normally distributed continuous variables, one-way ANOVA was performed. For comparisons of 2 groups of normally distributed continuous variables, Student’s t-test was performed. If significant differences were found, a post-hoc analysis using the Scheffe test was performed. Comparisons were considered statistically significant based on a \( P \) value of < 0.05.

**Results**

**Clinical Characteristics**

Fifty-one patients (32 [63\%] male; mean age 61 ± 15 years; range 27 to 89 years) comprised the study population. The distribution of 52 VAs among the study patients are summarized in Figure 1, which included 18 (35\%) Pap VAs (Figure 2), 15 (29\%) fascicular VAs (Figure 3) and 19 (36\%) MA VAs (Figure 4). Among the Pap VAs, 9 (50\%) VAs arose from each papillary muscle. Of the 19 MA VAs, 6 (32\%) were mapped to epicardium and ablated within the coronary venous system. Of note, one patient had both Pap VA and fascicular VA, both of which were targeted with ablation and were therefore included in the analysis.

Baseline clinical characteristics of patients with Pap VAs, fascicular VAs and MA VAs are detailed in Table 1. Patients with Pap VAs were older than fascicular VA patients (age 68 ± 10 vs. 53 ± 17 years; \( P = 0.018 \)). Patients with Pap VAs had a higher prevalence of left ventricular dysfunction (defined as left ventricular ejection fraction < 50\%) than fascicular VA patients (67\% vs. 13\%; \( P = 0.009 \)) as well as a higher prevalence of coronary artery disease than MA VA patients (78\% vs. 37\%; \( P = 0.036 \)). With respect to baseline medical therapy for VAs, a higher proportion of patients with Pap VAs were on beta-blocker therapy and a higher proportion of patients with fascicular VAs were on calcium channel blocker therapy.

CMR was performed median 17.5 days (IQR: 4.5, 33 days) prior to ablation in 6 (42\% of
all patients undergoing CMR) Pap VA patients, 4 (29%) fascicular VA patients and 4 (29%) MA VA patients. No myocardial scar was detected in the patients with fascicular VAs and MA VAs. One patient with Pap VA had isolated posteromedial papillary muscle scar, which correlated with the site of VA origin, while 2 of the 5 remaining Pap VA patients had evidence of LV chamber wall scar (n=1 inferoseptal, n=1 lateral) but no evidence of scar within the papillary muscle themselves.

**Electrocardiographic Characteristics**

The ECG characteristics of the Pap VAs, fascicular VAs and MA VAs are summarized in Table 2. Every patient’s VA had a right bundle branch block morphology in lead V1. Compared to patients with fascicular VAs, the presenting clinical arrhythmia in patients with Pap VAs was more likely to be PVC than VT (78% vs. 33%; P = 0.010). The QRS durations of Pap VA and MA VA were significantly longer than that of fascicular VA (Table 2). Among MA VAs, epicardial MA VAs tended to have longer QRS durations when compared to endocardial MA VAs (173 ± 26 msec vs. 148 ± 25 msec; p = 0.06). When compared separately in a pairwise fashion, both epicardial and endocardial MA VAs had longer QRS durations than fascicular VAs (173 ± 26 msec and 148 ± 25 msec vs. 127 ± 24 msec; p = 0.035 and p = 0.001, respectively).

Fascicular VAs had a significantly higher prevalence of an r < R' pattern in V1 (80% vs. 6% of Pap VAs; P < 0.001 and vs. 42% of MA VAs; P = 0.038). All mitral annular VAs had R ≥ S in lead V5 (100% vs. 22% of Pap VAs; P < 0.001 and vs. 11% of fascicular VAs; P < 0.001).

Representative ECG examples of Pap, fascicular and MA VAs are shown in Figure 5.

With respect to VA localization based on ECG axis, 9 of 11 (82%) Pap VAs with superior axis were localized to the posteromedial papillary muscle, 11 of 12 (92%) fascicular VAs with superior axis were localized to the left posterior fascicle, and 4 out of 4 (100%) MA
VAs with superior axis were localized to the posterior half of the mitral annulus. Among all VAs with an inferior axis, 7 of 7 (100%) Pap VAs originated from the anterolateral papillary muscle, 2 of 3 fascicular VAs from the left anterior fascicle, and 15 of 15 (100%) MA VAs from the anterior half of the mitral annulus.

A proposed stepwise algorithm summarizing the ECG findings of Pap VAs, fascicular VAs and MA VAs demarcated on the basis of inferior and superior axis morphologies are displayed in Figures 6A and B. A comparison of the ECG features among the inferior and superior axis VA subgroups are detailed in the Supplementary Table 2. Among VAs with an inferior axis, the presence of VA QRS ≤ 130 msec was associated with 100% sensitivity and 100% specificity for differentiating fascicular VAs from Pap and MA VAs. The presence of positive precordial concordance had an 87% sensitivity and 71% specificity for differentiating MA VAs from Pap VAs. Among VAs with a superior axis, the presence of R ≥ S in lead V5 was associated with 100% sensitivity and 100% specificity for differentiating MA VAs from Pap and fascicular VAs. The presence of V1 r < R' had an 83% sensitivity and 91% specificity for differentiating fascicular VAs from Pap VAs. Overall, the combined use of the two stepwise algorithms for all study left VAs yielded accuracy rates of 83%, 87% and 89% for the diagnosis of Pap VAs, fascicular VAs and MA VAs, respectively.

**Electrophysiological Study Findings**

The electrophysiological findings are summarized in Table 3. Compared to patients with fascicular VAs, patients with Pap VAs were significantly less likely to have inducible VT during electrophysiological study (67% vs. 22%; P = 0.015). The rates of VT inducibility among patients who presented with VT and not PVCs as their clinical arrhythmia were 3 of 4 (75%) among Pap VA patients, 10 of 10 (100%) among fascicular VA patients, and 6 of 7 (86%)
among MA VA patients. Fascicular and Purkinje potentials were found more frequently at the site of successful ablation of fascicular VA when compared to Pap VA (100% vs. 22%; \( P < 0.001 \)) and when compared to MA VA (100% vs. 0%; \( P < 0.001 \)) (Figure 3). There were no significant differences in electrophysiological study findings with respect to presence of pleomorphic VA morphologies, isoproterenol VA facilitation and timing from electrogram to QRS onset at site of successful ablation. Acute ablation success rates for Pap VAs, fascicular VAs and MA VAs were 83%, 100%, and 95%, respectively.

**Follow-up**

Forty-two (82%) patients had follow-up over a median of 219 (IQR: 37, 842) days while 19 (18%) patients were lost to follow-up after catheter ablation. There were no significant differences in clinical characteristics between the patients who had follow-up and those who were lost to follow-up. Among 28 patients with follow-up who had catheter ablation for PVCs, the median PVC burden was decreased from 10.6% (IQR: 6.3%, 23.8%) to 0.15% (IQR: 0.01%, 0.34%), \( P < 0.001 \). None of the patients who underwent initial PVC ablation required repeat ablation for the same clinical PVC targeted at index procedure. Among the 14 patients with follow-up who had catheter ablation of VT, 2 (14%) had repeat ablation of the same clinical VT, with one originating from the left posterior fascicle and the other from the aorto-mitral continuity.

**Discussion**

The left ventricular papillary muscles have been shown to be a source of ventricular ectopy in patients with and without structural heart disease. Given the distinct challenges that arrhythmias from the papillary muscles can present during catheter ablation, the recognition of specific ECG patterns that can distinguish these arrhythmias from other idiopathic left ventricular arrhythmias
is important. We found a higher prevalence of structural heart disease among patients with Pap VAs compared to patients with fascicular VAs and MA VAs. Moreover, we identified VA QRS duration, V1 QRS pattern and precordial lead concordance as specific features that can help localize these ventricular arrhythmias. This is the first study, to our knowledge, that compares Pap VAs in patients with and without structural heart disease to both fascicular VAs and MA VAs.

Clinical and electrophysiological features of papillary muscle ventricular arrhythmias

In our study, patients with Pap VAs were older and had more structural heart disease as manifest by a higher prevalence of decreased ejection fractions and coronary artery disease. Unlike patients with fascicular VAs, over 75% patients with Pap VA in our study were not inducible for sustained VT at electrophysiologic study. Moreover, the majority of patients with Pap VA presented with PVCs and not VT as their clinical arrhythmia. In the only previous study to compare patients with and without structural heart disease with Pap VAs to fascicular VAs, an increased prevalence of structural heart disease was seen among patients with Pap VAs, although this difference did not reach statistical significance due to low overall number of Pap VAs (n = 9).\textsuperscript{6}

Although some cases of Pap VAs may be directly associated with scar due to myocardial infarction\textsuperscript{4}, others can occur in apparently structurally normal hearts.\textsuperscript{1} Focal myocardial scarring confined to the papillary muscle as detected by CMR was present in one patient without prior history of myocardial infarction in our series, which is a phenomenon that has been described previously.\textsuperscript{6} Increased myocardial fibrosis due to aging, hypertension and coronary artery disease may predispose patients to Pap VAs. Anatomic disruptions of existing areas of maximal refractoriness at the Purkinje-ventricular tissue interface may lead to focal reentry.\textsuperscript{8} However, it
should be noted that in our study, 5 of the other 6 Pap VA patients who had CMRs prior to ablation did not have evidence of scar at the site of arrhythmia origin. Therefore, the underlying mechanisms behind Pap VAs are likely heterogeneous.

**Distinguishing electrocardiographic characteristics of papillary muscle, fascicular and mitral annular arrhythmias**

We identified several electrocardiographic hallmarks of papillary muscle, fascicular and mitral annular VAs. Specifically, VA QRS duration, V₁ r and R' amplitudes, and precordial transition can help distinguish these three categories of VAs. In our study, fascicular VAs were distinguished by shorter QRS durations and the presence of a V₁ r < R' amplitude pattern. The shorter QRS duration likely reflects the proximal exit of fascicular VAs from the His-Purkinje system, which occurs in contradistinction to the distal Purkinje exit of Pap VAs and the myocardial exit of MA VAs. Moreover, the presence of a V₁ r < R' amplitude pattern among fascicular VAs that mimics typical right bundle branch block aberration⁹ is another manifestation of His-Purkinje network activation. With fascicular VAs, we postulate that the left ventricle is depolarized more rapidly via the Purkinje system than with Pap and MA VAs, which results in unopposed late activation of the right ventricular outflow tract leading to a large R' amplitude in lead V₁. Furthermore, we found that all mitral annular VAs ECG patterns had R ≥ s in lead V₅. This reflects the more basal location of MA VAs compared to fascicular and Pap VAs. Specifically, anterior MA VAs display positive precordial concordance due to the positive electrical forces of ventricular activation directed toward the apical V₆ lead. In comparison, since the papillary muscles and the mid-fascicular system lie in the mid-segment of the heart in the long axis orientation, positive concordance is not seen in the precordial VA ECG leads.

Although we were able to identify specific ECG patterns that were more commonly seen...
in one left ventricular origin than another, there was still considerable overlap in these patterns among the different groups. We therefore proposed a stepwise approach as outlined in Figure 6 that achieves a high sensitivity and specificity (83-100%) for distinguishing among these forms of left ventricular arrhythmias. However, not all patients were accurately differentiated using our ECG algorithm. For example, there was one group of Pap and MA VA patients that could not be differentiated completely on the basis of positive precordial lead concordance. This may have been explained in part by presence of anterolateral Pap VAs that had exit sites close to the mitral annulus. Another group of Pap and fascicular VA patients was not completely differentiated on the basis of V1 r and R’ ratio which may reflect variations in VA exit along the septum (e.g. more distal exit from the Purkinje network may yield a more “atypical” right bundle branch block pattern).

Only one previous study to date has compared all three categories of Pap VA, fascicular VA and MA VA ECG patterns, but the study excluded patients with structural heart disease and only included MA VA patients with posteroseptal and anterolateral mitral annular sites of origin. The ECG algorithm developed in our study helps differentiate left ventricular VA subtypes and can be applied more broadly to patients with and without structural heart disease and may be used in patients with mitral annular VAs of any location.

Study limitations
First, as this is a single-center retrospective study of relatively uncommon ventricular arrhythmias, the clinical and ECG hallmarks identified here may not be generalizable to all patients with Pap, fascicular and MA VAs. A prospective validation cohort study, ideally with multi-center participation, would address this limitation. Second, given that patients with and without structural heart disease were included, considerable heterogeneity in VA mechanism
may exist. The impact of the absence or presence of structural heart disease on our ECG findings did not appear to be significant. For example, VA QRS durations were longer among patients with Pap and MA VAs when compared to fascicular VAs when patients with and without structural heart disease were analyzed separately (data not shown). Third, cardiac MRIs were not routinely done in all study patients, which precludes definitive conclusions regarding the prevalence of focal papillary scar in patients with Pap VA. Finally, in six patients, pace-mapping was performed to identify the VA site of origin. Given the limited spatial resolution of pace-mapping, some decrease in the accuracy in the VA localization in these cases may have been possible.

Conclusions

A stepwise ECG approach that incorporates QRS duration, V1 QRS morphology and precordial lead transition can help distinguish the Pap, fascicular and MA VAs. An understanding of the distinguishing clinical, ECG and electrophysiologic features of these three categories of left ventricular VAs can help facilitate mapping and ablation of these arrhythmias.

Acknowledgments: We would like to thank Dr. Paul D. Kligfield for thoughtful discussions and input on this manuscript.

Conflict of Interest Disclosures: Dr. Jim W. Cheung has received speaker honoraria from St. Jude Medical as well as fellowship grant support from Biosense Webster and St. Jude Medical. Dr. Steven M. Markowitz has received consulting fees from Boston Scientific and St. Jude Medical. Dr. Christopher F. Liu has received speaker honoraria from St. Jude Medical. The rest of the authors have no relevant disclosures.
References:


**Table 1:** Baseline Clinical Characteristics of Papillary Muscle VA Patients Compared to Fascicular and Mitral Annular VA Patients

<table>
<thead>
<tr>
<th></th>
<th>Pap VA (n = 18)</th>
<th>Fascicular VA (n = 15)</th>
<th>MA VA (n = 19)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, years</td>
<td>68 ± 10</td>
<td>53 ± 17</td>
<td>62 ± 15</td>
<td>0.018†</td>
</tr>
<tr>
<td>Male Sex, n (%)</td>
<td>13 (72)</td>
<td>8 (53)</td>
<td>11 (58)</td>
<td>0.496</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>14 (78)</td>
<td>6 (40)</td>
<td>12 (63)</td>
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<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>5 (28)</td>
<td>3 (20)</td>
<td>3 (16)</td>
<td>0.666</td>
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<td>Coronary Artery Disease, n (%)</td>
<td>14 (78)</td>
<td>7 (47)</td>
<td>7 (37)</td>
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<tr>
<td>Prior Myocardial Infarction, n (%)</td>
<td>4 (22)</td>
<td>1 (8)</td>
<td>1 (5)</td>
<td>0.213</td>
</tr>
<tr>
<td>Heart Failure, n (%)</td>
<td>10 (56)</td>
<td>4 (27)</td>
<td>7 (37)</td>
<td>0.224</td>
</tr>
<tr>
<td>Left ventricular EF &lt; 50%, n (%)</td>
<td>12 (67)</td>
<td>2 (13)</td>
<td>8 (42)</td>
<td>0.009†</td>
</tr>
<tr>
<td>Beta-blockers, n (%)</td>
<td>13 (72)</td>
<td>4 (27)</td>
<td>9 (47)</td>
<td>0.032†</td>
</tr>
<tr>
<td>Calcium Channel Blockers, n (%)</td>
<td>2 (11)</td>
<td>6 (40)</td>
<td>0 (0)</td>
<td>0.005§</td>
</tr>
<tr>
<td>Anti-Arrhythmic Drugs, n (%)</td>
<td>2 (11)</td>
<td>2 (13)</td>
<td>1 (5)</td>
<td>0.705</td>
</tr>
</tbody>
</table>

Pap = papillary; MA = mitral annular; VA = ventricular arrhythmia; EF = ejection fraction

*All displayed p values are based on three-way comparisons; pair-wise p values are denoted as follows: †p < 0.05 for Pap VA vs. fascicular VA; ‡p < 0.05 for Pap VA vs. MA VA; §p < 0.05 for fascicular VA vs. MA VA
Table 2: Electrocardiographic Characteristics of Papillary Muscle VA Patients Compared to Left Ventricular Fascicular or Mitral Annular Arrhythmias

<table>
<thead>
<tr>
<th></th>
<th>Pap VA (n = 18)</th>
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<th>MA VA (n = 19)</th>
<th>*P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting VA: PVC, n (%)</td>
<td>14 (78)</td>
<td>5 (33)</td>
<td>13 (68)</td>
<td>0.024†</td>
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<tr>
<td>VA QRS duration, mean (msec)</td>
<td>153 ± 27</td>
<td>127 ± 25</td>
<td>158 ± 27</td>
<td>0.006†‡</td>
</tr>
<tr>
<td>Positive Precordial Concordance, n (%)</td>
<td>2 (11)</td>
<td>1 (7)</td>
<td>13 (68)</td>
<td>&lt;0.001‡§</td>
</tr>
<tr>
<td>V5 Morphology (R ≥ s), n (%)</td>
<td>4 (22)</td>
<td>2 (13)</td>
<td>19 (100)</td>
<td>&lt;0.001‡§</td>
</tr>
<tr>
<td>V1 Morphology (r &lt; R'), n (%)</td>
<td>1 (6)</td>
<td>12 (80)</td>
<td>8 (42)</td>
<td>&lt;0.001†‡§</td>
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<tr>
<td>V1 Q wave, n (%)</td>
<td>3 (17)</td>
<td>0 (0)</td>
<td>6 (32)</td>
<td>0.056</td>
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<td>V1 QRS morphologies (n)</td>
<td>Rr' (11)</td>
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<td></td>
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<td></td>
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<td>qrR' (1)</td>
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Pap = papillary; MA = mitral annular; VA = ventricular arrhythmia; PVC = premature ventricular contraction; msec = millisecond.

*All displayed p values are based on three-way comparisons; pair-wise p values are denoted as follows: †p < 0.05 for Pap VA vs. fascicular VA; ‡p < 0.05 for fascicular VA vs. MA VA; §p < 0.05 for Pap VA vs. MA VA.
Table 3: Electrophysiological Characteristics of Papillary Muscle VA Patients Compared to Fascicular and Mitral Annular Arrhythmias

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<th>MA VA (n = 19)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inducible sustained VT, n (%)</td>
<td>4 (22)</td>
<td>10 (67)</td>
<td>7 (37)</td>
<td>0.032†</td>
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<tr>
<td>Isoproterenol facilitation, n/total (%)</td>
<td>9/15 (60)</td>
<td>8/14 (57)</td>
<td>5/17 (29)</td>
<td>0.340</td>
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<td>EGM pre-QRS Potential, mean, msec</td>
<td>23 ± 6</td>
<td>26 ± 13</td>
<td>25 ± 9</td>
<td>0.673</td>
</tr>
<tr>
<td>Fascicular/Purkinje Potential, n (%)</td>
<td>4 (22)</td>
<td>15 (100)</td>
<td>0 (0)</td>
<td>&lt; 0.001†‡</td>
</tr>
<tr>
<td>Pleomorphic VA, n (%)</td>
<td>4 (22)</td>
<td>2 (13)</td>
<td>1 (5)</td>
<td>0.319</td>
</tr>
<tr>
<td>Successful radiofrequency ablation, n (%)</td>
<td>15 (83)</td>
<td>15 (100)</td>
<td>18 (95)</td>
<td>0.178</td>
</tr>
</tbody>
</table>

VA = ventricular arrhythmia; VT = ventricular tachycardia; EGM = electrogram.
*All displayed p values are based on three-way comparisons; pair-wise p values are denoted as follows: †p < 0.05 for Pap VA vs. fascicular VA; ‡p < 0.05 for fascicular VA vs. MA VA

Figure Legends:

Figure 1: Schematic diagram illustrating distribution of left ventricular arrhythmias. Sites of origin of papillary muscle VAs (green dots), mitral annular VAs (yellow dots) and fascicular VAs (blue dots) are shown. AL = anterolateral; PM = posteromedial; Pap = papillary muscle; LAF = left anterior fascicle; LPF = left posterior fascicle

Figure 2: Anatomical and electrophysiological localization of papillary muscle PVC. A.

Intracardiac echocardiographic view showing contact between the ablation catheter and the base.
of the posteromedial papillary muscle during radiofrequency ablation of focal left ventricular arrhythmia (*red star* marking the contact point). **B.** An electroanatomical map in cranial RAO projection with clipped view showing the positions of the anterolateral (AL Pap) and posteromedial (PM Pap) papillary muscles (*in purple*) as outlined by intracardiac echocardiography (CARTO, Biosense Diamond Bar, California). Activation map reveals site of origin of PVC at the base of the posteromedial papillary muscle (*red star*). **C.** Surface ECG 12 leads, distal bipolar (*MAP 1-2*) and unipolar (*MAP 1*) intracardiac electrograms recorded from the early site are shown. Local activation precedes QRS by 21 msec.

**Figure 3:** ECG and electrophysiological characteristics of left posterior fascicular VT. **A.** Twelve-lead surface ECG of ventricular tachycardia showing \( r < R' \) pattern in lead \( V_1 \) (QRS duration 86 msec). **B.** Electroanatomical map of left ventricle illustrating the location of the left anterior and left posterior fascicles (*purple dots and blue lines*). Sites with fascicular potentials and late potentials are shown (*cyan dots*). An inset shows ECG leads I, aVF and lead V1 during sinus rhythm with corresponding electrograms (EGM) recorded at one of these sites. Fascicular potentials (FP) and late potentials (LP) are seen. VT was successfully ablated at this site. FP = fascicular potential; LP = late potential.

**Figure 4:** Anatomical and electrophysiological localization of mitral annular VA. **A.** Electroanatomical maps of the left ventricle showing the origin of the PVCs (*red star*) from the anterior interventricular vein – great cardiac vein (AIV-GCV) junction are shown in the **A.** cranial right anterior oblique projection and **B.** posterior-anterior projection. Contours of the aortic cusps and left ventricle generated by intracardiac echocardiography are also shown.
(CARTO, Biosense Diamond Bar, California). C. Surface ECG 12 leads, distal bipolar (MAP 1-2), proximal bipolar (MAP 3-4) and unipolar (MAP 1) intracardiac electrograms recorded during PVC from the early site are shown. Local activation precedes QRS by 23 msec. Both atrial and ventricular electrograms are present on the bipolar electrograms at this site. Ablation at the early site led to complete abolition of PVCs. LCC = left coronary cusp; RCC = right coronary cusp; NCC = noncoronary cusp.

Figure 5: Representative 12 lead ECGs of papillary muscle, fascicular and mitral annular ventricular arrhythmias with corresponding locations on schematic diagram. AL = anterolateral; PM = posteromedial; Pap = papillary muscle; LAF = left anterior fascicle; LPF = left posterior fascicle

Figure 6: Algorithm for differentiation of focal left ventricular arrhythmia. A. Flow chart shows algorithm for differentiation of inferior axis VA into papillary, fascicular or mitral annular arrhythmia based on QRS duration and positive precordial concordance. B. Flow chart shows algorithm for differentiation of superior axis VA into papillary, fascicular or mitral annular arrhythmia based on QRS morphology in leads V1 and V5. Percentages displayed are calculated as n/n_total where n_total = total number of VAs within relevant subgroup after classification based on inferior vs. superior axis.
Left Ventricular VA with Inferior Axis (n = 25)

QRS ≤ 130 msec

Yes (n = 3)

3 Fascicular VA (100%)

No (n = 22)

Positive Precordial Concordance

Yes (n = 15)

13 Mitral Annular VA (87%)
2 Papillary VA (29%)

No (n = 7)

5 Papillary VA (71%)
2 Mitral Annular VA (17%)
B

Left Ventricular VA with Superior Axis (n = 27)

R ≥ S in lead V₅

Yes (n = 4)
4 Mitral Annular VA (100%)

No (n = 24)

V₁ r < R'

Yes (n = 12)
10 Fascicular VA (83%)
1 Papillary VA (9%)

No (n = 12)
10 Papillary VA (91%)
2 Fascicular VA (17%)
Differentiation of Papillary Muscle from Fascicular and Mitral Annular Ventricular Arrhythmias in Patients With and Without Structural Heart Disease
Subhi J. Al'Aref, James E. Ip, Steven M. Markowitz, Christopher F. Liu, George Thomas, Daniel Frenkel, Nikhil C. Panda, Jonathan W. Weinsaft, Bruce B. Lerman and Jim W. Cheung

Circ Arrhythm Electrophysiol. published online April 29, 2015;
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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SUPPLEMENTAL MATERIAL
Supplemental Table 1.

ECG QRS morphology of study ventricular arrhythmias in lead \( V_1 \) were characterized as follows with Q, R, S, and R' waves as defined using previously published criteria:\(^{1,2}\)

\[\text{I. Monophasic subtypes} \]
\[\text{a. R: single positive deflection (R)} \]
\[\text{b. Rr': Initial positive deflection (R) amplitude } \geq \text{ second positive deflection (r') amplitude with no negative deflection below baseline} \]
\[\text{c. rR': Initial positive deflection (r) amplitude } < \text{ second positive deflection (R') amplitude with no negative deflection below baseline} \]

\[\text{II. Biphasic subtypes} \]
\[\text{a. qR: initial negative deflection (q } \geq 0.1 \text{ mV amplitude) followed by monophasic single positive deflection (R) with q amplitude } < \text{ R amplitude} \]
\[\text{b. QR: initial negative deflection (Q } \geq 0.1 \text{ mV amplitude) followed by monophasic single positive deflection (R) with Q amplitude } \geq \text{ R amplitude} \]
\[\text{c. qRr': initial negative deflection (q } \geq 0.1 \text{ mV amplitude) followed by positive deflection (R) amplitude } \geq \text{ second positive deflection (r') amplitude with no negative deflection below baseline with q amplitude } < \text{ R amplitude} \]
\[\text{d. qrR': initial negative deflection (q } \geq 0.1 \text{ mV amplitude) followed by positive deflection (r) amplitude } < \text{ second positive deflection (R') amplitude with no negative deflection below baseline with q amplitude } < \text{ R amplitude} \]
\[\text{e. Rs: initial positive deflection (R) amplitude } \geq \text{ negative deflection (s) amplitude} \]
\[\text{f. rS: initial positive deflection (r) amplitude } < \text{ negative deflection (S) amplitude} \]

\[\text{III. Triphasic subtypes} \]
\[\text{a. RSr': Initial positive deflection (R) amplitude } \geq \text{ second positive deflection (r') amplitude separated by negative deflection below baseline (s) with amplitude } \geq \text{ dominant R deflection amplitude} \]
\[\text{b. Rsr': Initial positive deflection (R) amplitude } \geq \text{ second positive deflection (r') amplitude separated by negative deflection below baseline (s) with amplitude } < \text{ dominant R deflection amplitude} \]
\[\text{c. rSR': Initial positive deflection (R) amplitude } < \text{ second positive deflection (r') amplitude separated by negative deflection below baseline (s) with amplitude } \geq \text{ dominant R deflection amplitude} \]
\[\text{d. rsR': Initial positive deflection (R) amplitude } < \text{ second positive deflection (r') amplitude separated by negative deflection below baseline (s) with amplitude } < \text{ dominant R deflection amplitude} \]

\[\text{IV. Variable} \]
\[\text{a. QRS complexes exhibiting variability that precluded morphology adjudication. In this study all cases of variable VA } V_1 \text{ QRS morphology consisted of cases where alternating Rr' and rR' morphologies were seen in lead } V_1 \]
References

**Supplemental Table 2.**

**Inferior axis VAs (total n = 25)**

<table>
<thead>
<tr>
<th></th>
<th>Pap VA (n = 7)</th>
<th>Fascicular VA (n = 3)</th>
<th>MA VA (n = 15)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting VA: PVC, n (%)</td>
<td>6 (86)</td>
<td>3 (100)</td>
<td>9 (60)</td>
<td>0.24</td>
</tr>
<tr>
<td>VA QRS duration, mean (msec)</td>
<td>154 ± 15</td>
<td>108 ± 15</td>
<td>164 ± 23</td>
<td>0.001†,‡</td>
</tr>
<tr>
<td>Positive Precordial Concordance, n (%)</td>
<td>2 (29)</td>
<td>1 (33)</td>
<td>13 (87)</td>
<td>0.015‡,§</td>
</tr>
<tr>
<td>V₃ Morphology (R ≥ s), n (%)</td>
<td>4 (58)</td>
<td>1 (33)</td>
<td>15 (100)</td>
<td>0.06</td>
</tr>
<tr>
<td>V₁ Morphology (r &lt; R'), n (%)</td>
<td>0 (0)</td>
<td>2 (67)</td>
<td>7 (47)</td>
<td>0.052</td>
</tr>
<tr>
<td>V₁ Q wave, n (%)</td>
<td>2 (29)</td>
<td>0 (0)</td>
<td>4 (27)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Pap = papillary; MA = mitral annular; VA = ventricular arrhythmia; PVC = premature ventricular contraction; msec = millisecond.

*All displayed p values are based on three-way comparisons; pair-wise p values are denoted as follows: †p < 0.05 for Pap VA vs. fascicular VA; ‡p < 0.05 for fascicular VA vs. MA VA; §p < 0.05 for Pap VA vs. MA VA.

**Superior axis VAs (total n = 27)**

<table>
<thead>
<tr>
<th></th>
<th>Pap VA (n = 11)</th>
<th>Fascicular VA (n = 12)</th>
<th>MA VA (n = 4)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting VA: PVC, n (%)</td>
<td>8 (73)</td>
<td>2 (17)</td>
<td>4 (100)</td>
<td>0.003†,‡</td>
</tr>
<tr>
<td>VA QRS duration, mean (msec)</td>
<td>153 ± 34</td>
<td>132 ± 25</td>
<td>132 ± 9</td>
<td>0.18</td>
</tr>
<tr>
<td>Positive Precordial Concordance, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>V₃ Morphology (R ≥ s), n (%)</td>
<td>0 (0)</td>
<td>1 (8)</td>
<td>4 (100)</td>
<td>&lt;0.001‡,§</td>
</tr>
<tr>
<td>V₁ Morphology (r &lt; R'), n (%)</td>
<td>1 (9)</td>
<td>10 (83)</td>
<td>1 (25)</td>
<td>0.001†,‡</td>
</tr>
<tr>
<td>V₁ Q wave, n (%)</td>
<td>1 (9)</td>
<td>0 (0)</td>
<td>2 (50)</td>
<td>0.031‡</td>
</tr>
</tbody>
</table>

Pap = papillary; MA = mitral annular; VA = ventricular arrhythmia; PVC = premature ventricular contraction; msec = millisecond.

*All displayed p values are based on three-way comparisons; pair-wise p values are denoted as follows: †p < 0.05 for Pap VA vs. fascicular VA; ‡p < 0.05 for fascicular VA vs. MA VA; §p < 0.05 for Pap VA vs. MA VA.