Ubiquitous Myocardial Extensions into the Pulmonary Artery Demonstrated by Integrated Intracardiac Echocardiography and Electroanatomic Mapping: Changing the Paradigm of Idiopathic Right Ventricular Outflow Tract Arrhythmias

Running title: Liu et al.; Arrhythmias from Pulmonary Arterial Myocardium

Christopher F. Liu, MD; Jim W. Cheung, MD; George Thomas, MD; James E. Ip, MD; Steven M. Markowitz, MD; Bruce B. Lerman, MD

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

Correspondence:
Christopher F. Liu, MD
Division of Cardiology
Weill Cornell Medical College
520 E. 70th Street, Starr-4
New York, NY 10021
Tel: (212) 746-2655
Fax: (212) 746-6951
Email: chl7001@med.cornell.edu

Abstract:

**Background** - Idiopathic ventricular arrhythmias of left bundle branch block, inferior axis morphology are usually localized to the right ventricular outflow tract (RVOT), presumably below the pulmonic valve (PV). However, the PV location is usually not confirmed by direct visualization.

**Methods and Results** - Intracardiac echocardiography (ICE) was used to visualize and tag the PV annulus, which was then integrated with 3-dimensional voltage maps of the RVOT. Distances were measured from the furthest extent of myocardial signal (bipolar voltage ≥ 1.5 mV) to the PV annulus. This was performed in 24 control patients and 24 prospective patients with RVOT arrhythmias. Myocardial signal beyond the pulmonic valve was found in 92% of controls and 88% of RVOT arrhythmia patients (p=1.000). Average myocardial extension was further on the septal side than the free wall side for both control patients (5.6 mm [IQR 3.6 – 7.7] vs 1.7 mm [IQR (-) 0.1 – (+) 4.0], p=0.002) and RVOT arrhythmia patients (5.7 mm [IQR 2.7 – 7.7] vs 1.4 mm [IQR (-) 0.8 – (+) 4.8], p=0.004). Eleven (46%) RVOT arrhythmia foci were localized beyond the valve in the pulmonary artery (median 8.2 mm above PV, IQR 6.6-10.3 mm); these locations were confirmed as supravalvular by direct ICE visualization.

**Conclusions** - Myocardial voltage extension into the pulmonary artery in humans is ubiquitous and can be demonstrated in vivo using 3D-integrated ICE to localize the pulmonic valve. These extensions frequently serve as origins of presumed RVOT arrhythmias; ICE localization of the pulmonic valve allows reclassification of these as pulmonary arterial arrhythmias.

**Key words**: ventricular arrhythmia, intracardiac echocardiography, electrophysiology mapping, pulmonary valve, pulmonary artery
Introduction

Idiopathic ventricular tachycardia (VT) and premature ventricular contractions (PVCs) of left bundle branch block (LBBB), inferior axis morphology frequently originate from the right ventricular outflow tract (RVOT) region in structurally normal hearts\(^1,2\) and are effectively treated with catheter ablation\(^3\). Most cases of RVOT arrhythmias are thought to originate from below the pulmonic valve. By convention, the absence or marked diminution of myocardial voltage and the inability to capture the myocardium during high voltage pacing are used to determine the demarcation of the pulmonic valve\(^1\), thus presuming that myocardial signals terminate precisely at the level of the pulmonic annulus. However, this approach may underestimate the superior extent of the myocardium. Indeed, a correlation of myocardial extent with electrophysiologic features has never been validated. There have been reported cases of ventricular arrhythmias mapped and ablated well beyond the pulmonic valve, within the pulmonary artery (PA)\(^4-7\); in these cases, confirmation of the supravalvular site of the arrhythmia was confirmed by pulmonary angiography. However, the true incidence of supravalvular arrhythmia foci is not known, since the pulmonic valve is not seen with standard fluoroscopy, and contrast visualization of the pulmonic valve is not routinely obtained during electrophysiology procedures.

Intracardiac echocardiography (ICE) has become an important tool for real-time imaging of cardiac structures during ablation procedures. ICE integrated with 3-dimensional mapping allows real-time tagging of anatomic structures and integration with 3-dimensional electroanatomic maps. The location information from this “3-dimensional ultrasound” has been validated in animal models to be within 1.1 ± 1.1 mm of actual location\(^8\). This modality is often used in obtaining left atrial anatomy for ablation of atrial fibrillation\(^9\), as well as for localizing...
aortic cusps for ablation of ventricular arrhythmias originating from this region. Placement of the ICE catheter into the right ventricle allows direct visualization of the pulmonic valve, and echocardiography can be used to tag the pulmonic valve for integration into the 3-dimensional electroanatomic map. In this study, we assessed the relationship of myocardial tissue presence— as detected by voltage mapping—to the anatomic pulmonic valve annulus, which is defined by 3-dimensional-integrated echocardiographic mapping, in patients with RVOT-type ventricular arrhythmias and in a control group. In so doing, we sought to determine the presence of myocardial signal in the proximal pulmonary artery and to localize the precise sites of origin of RVOT arrhythmias with respect to the pulmonic valve.

**Methods**

**Study Population**

For the control group (Group 1), we examined 24 consecutive patients with structurally normal hearts who presented for electrophysiology study and ablation of supraventricular arrhythmias; these patients were not known to have RVOT arrhythmias. In the RVOT arrhythmia group (Group 2), we prospectively examined 24 consecutive patients undergoing catheter ablation of idiopathic ventricular arrhythmias originating from the region of the right ventricular outflow tract (left bundle branch block morphology, inferior frontal axis, precordial transition V3 or later). Only patients undergoing ablation were included. All procedures were performed following institutional guidelines of the Weill Cornell Medical Center / New York-Presbyterian Hospital, and all patients gave written informed consent. The study was approved by the Institutional Review Board of Weill Cornell Medical College.

**Voltage Mapping**

During sinus rhythm, we obtained a detailed 3-dimensional electroanatomic voltage map of the
RVOT region in each patient. At least 30 points were taken from the tricuspid inflow to the proximal pulmonary artery using either a 4mm-solid tip (Navistar) or 3.5mm-irrigated tip (Navistar Thermocool) catheter and the CARTO XP or CARTO3 system (Biosense Webster Inc, Diamond Bar, CA, USA). The interelectrode distance was 2 mm. Signals were filtered at 30 to 500 Hz and were displayed at 200 mm/s. Maps were displayed with local bipolar voltage color thresholds 0.5 mV – 1.5 mV. Since the initial report by Marchlinski et al\textsuperscript{10}, bipolar voltage threshold of $\geq 1.5$ mV has been used to delineate normal ventricular myocardium. Therefore, care was taken to collect the most superior (distal) points with bipolar voltage $\geq 1.5$ mV; this was done circumferentially around the RVOT/pulmonic valve region, and these most distal points were used to define the extent of normal myocardium by voltage. The maps were obtained in gated mode, and care was taken to ensure that all voltage points were gated with sinus rhythm beats, since PVCs are known to shift the location significantly compared with sinus rhythm\textsuperscript{11}.

**Echocardiography-rendered Anatomic Mapping of the Pulmonic Valve**

In each patient, a separate anatomic pulmonic valve (PV) map using 3-dimensional-integrated intracardiac echocardiography (ICE) was also created. The ICE-rendered anatomic map was created in a blinded fashion as the voltage map was hidden from view. A 10 Fr phased-array ICE catheter (SoundStar; Biosense Webster Inc, Diamond Bar, CA, USA) was positioned in the heart from femoral venous access with the tip advanced across the tricuspid valve into the right ventricle, and the imaging plane was rotated to scan cranially, allowing direct visualization of the pulmonic valve and pulmonary artery. The ICE catheter and associated scanning sector were then rotated in small increments to scan the entire pulmonic valve annulus. The visualized valve hinge points (at least 20 circumferential points for each patient) were tagged and registered to the 3-dimensional anatomic map via CartoSound (Biosense Webster Inc, Diamond Bar, CA). The
anatomic points were acquired using the same ECG gating (sinus rhythm QRS complex) as the voltage map. Respiratory gating was also applied.

**Voltage and Anatomic Correlation**

After the voltage and ultrasound maps were obtained independently, we superimposed the two respective maps for each patient. For purposes of analysis the pulmonic valve was divided into 6 cross-sectional segments: Septal-1 (posterior), -2 (mid), -3 (anterior) and Free Wall-1 (posterior), -2 (mid), -3 (anterior) (Figure 1). This is similar to the previous scheme used by Dixit et al for classifying site of origin of RVOT arrhythmias. For each segment, we measured the shortest perpendicular distance from the ICE-defined anatomic annulus to the most distal electroanatomic point with bipolar voltage $\geq 1.5$ mV (as surrogate for myocardial tissue). The distance was recorded as positive (+) if the voltage point was beyond the valve annulus (on the pulmonary artery side), or negative (-) if the voltage point was proximal to the valve annulus (on the ventricular side). Figure 2 provides an example of this type of measurement for a point above the pulmonic valve, with confirmed visualization by ICE. For purposes of comparing septal and free wall sides, the average (Avg) distances for the 3 septal segments and for the 3 free wall segments in each patient were used.

**Group 2: Electrocardiographic and Electrophysiologic Characterization of Ventricular Arrhythmias**

In the patients with RVOT arrhythmias, after the initial voltage and ICE maps were created, an electrophysiology study was performed to assess for inducible sustained VT or increased ventricular ectopy. Following the baseline study, which included the introduction of up to triple ventricular extrastimuli from the right ventricular apex and RVOT, as well as burst pacing, the protocol was repeated during the infusion of isoproterenol. Isoproterenol was also infused alone
(up to 10 mcg/minute) to assess for increased ventricular ectopy or induction of ventricular tachycardia. If sustained VT was induced, adenosine 12 mg was given in a rapid bolus and response of the VT was recorded. Analysis of the surface ECG during ventricular arrhythmia included QRS duration; R-wave amplitudes in leads II, III, and aVF; ratio of Q-wave amplitudes in leads aVR and aVL; ratio of R-wave to S-wave in lead V2; and the precordial R-wave transition zone (earliest lead with R>S).

**Group 2: Mapping and Ablation of Ventricular Arrhythmias**

Activation mapping of spontaneous or induced ventricular tachycardia or the patient’s clinical PVC was performed, in addition to pace mapping. Note was made of any discrete multi-component potentials during activation mapping. Pace mapping was done using bipolar stimulation of threshold amplitude at 2 ms pulse width. An optimal pace map was defined as an identical match of all 12 surface leads during pacing compared with the spontaneous VT or PVC.

With the solid-tip catheter, radiofrequency (RF) ablation was performed with 50W and a temperature limit of 55-60°C, for 30-90 seconds. With the irrigated catheter, RF ablation was performed with 20-50W and irrigation rate of 17-30 mL/minute, for 30-60 seconds. The successful ablation site was defined as the site of ablation that rendered the clinical VT or PVC noninducible, with or without programmed stimulation and isoproterenol following at least a 30-minute waiting period. All ablation points in the 3-dimensional map were also gated in sinus rhythm for purposes of comparison to the voltage and pulmonic valve maps. All patients underwent 24-hour Holter monitoring after the procedure at 4-6 weeks, and were additionally followed for recurrence of symptoms.

**Statistical Analysis**

Continuous variables are expressed as mean ± standard deviation or as median (interquartile
range [IQR]), depending on normality of distribution. Comparisons of continuous variables were made using the 2-tailed Student’s t test for normal data, and using the 2-tailed Mann-Whitney U test for non-normal data. Comparisons of categorical variables were made using Fisher’s exact test. Statistical calculations were performed using SPSS 16.0 (SPSS Inc, Chicago, IL). P value of < 0.050 was considered statistically significant.

Results

Twenty-four patients (17 men, 7 women; mean age 50±16 years) with structurally normal hearts and supraventricular tachycardia comprise the control group (Group 1). Twenty-four patients (10 men, 14 women; mean age 50±19 years) underwent mapping and ablation of RVOT arrhythmias (Group 2). The baseline characteristics of the two groups are shown in Table 1. Five patients in Group 2 had left ventricular ejection fraction of < 50%.

Pulmonary Arterial Myocardial Extensions

In the control group, voltage maps were created with a mean of 57 ±20 contact points in the RVOT; anatomic pulmonic valves were defined using a mean of 30 ±6 circumferential annular echocardiographic tags. The median distances (+ denotes myocardium extending above the valve) from the pulmonic valve to the most superior site in each segment with a voltage ≥1.5mV were: (+)3.9 mm (IQR 0.6 – 6.6) in Septal 1; (+)5.6 mm (IQR 3.3 – 6.9) in Septal 2; (+)6.9 mm (IQR 4.5 – 11.1) in Septal 3; 0 mm (IQR (-)1.7 – (+)3.5) in FW 1; 0 mm (IQR 0 – 3.5) in FW 2; and (+) 2.9 mm (IQR 0 – 7.6) in FW 3 (Figure 3A). Using the average (Avg) distances, there was greater extension of myocardial voltage beyond the valve on the septal side (median Avg distance 5.6 mm; IQR 3.6 – 7.7) compared with the free wall side (median Avg distance 1.7 mm; IQR (-)0.1 – (+) 4.0), p=0.002 (Figure 3B). Twenty-two of 24 patients (92%) had at least 1 segment with myocardial voltage that extended beyond the pulmonic valve; 20 patients (83%)
had at least 2 segments extending beyond the valve. An example of myocardial extension above the pulmonic valve in a control patient is shown in Figure 2. All voltage points with ≥1.5 mV were contiguous with the RVOT myocardium, i.e., there were no islands of myocardial tissue.

In Group 2 patients, voltage maps were created with a mean of 57 ±19 contact points in the RVOT; anatomic pulmonic valves were defined using a mean of 29 ±6 circumferential annular echocardiographic tags. The median distances from the pulmonic valve to the most superior site in each segment with a voltage ≥1.5mV were: (+)3.7 mm (IQR 0.4 – 6.9) in Septal 1; (+)4.2 mm (IQR 0.6 – 9.6) in Septal 2; (+)6.6 mm (IQR 0.8 – 8.6) in Septal 3; 0 mm (IQR 0 – 3.4) in FW 1; 0 mm (IQR (-2.2 – (+4.6) in FW 2; and (+) 2.4 mm (IQR 0 – 6.3) in FW 3 (Figure 3A). As was seen in the control patients, using average (Avg) distances there was greater extension of myocardial signal beyond the valve on the septal side (median Avg distance 5.7 mm; IQR 2.7 – 7.7) compared with the free wall side (median Avg distance 1.4 mm; IQR (-0.8 – (+) 4.8), p=0.004 (Figure 3B). In the RVOT arrhythmia group, twenty-one of 24 patients (88%) had at least 1 segment with myocardial voltage that extended beyond the pulmonic valve (p=1.000 for comparison with Group 1); 19 patients (79%) had at least 2 segments extending beyond the valve. As was observed in Group 1, all myocardial voltage points were contiguous with the RVOT myocardium.

As illustrated in Figure 3B, average (Avg) myocardial extension was not significantly different between the control patients and RVOT arrhythmia patients. On the septal side the median Avg myocardial voltage distance was 5.6 mm (IQR 3.6 – 7.7) beyond the pulmonic valve for control patients, compared with median Avg distance 5.7 mm (IQR 2.7 – 7.7) for RVOT arrhythmia patients, p=0.726. On the free wall side the median Avg myocardial signal distance was 1.7 mm (IQR (-) 0.1 – (+) 4.0) beyond the pulmonic valve for control patients, compared
with median Avg distance 1.4 mm (IQR (-) 0.8 – (+) 4.8) for RVOT arrhythmia patients, p=0.672.

**Origin of RVOT Ventricular Arrhythmias (Group 2)**

Of the 24 patients who underwent mapping and successful catheter ablation in the RVOT region, 14 (58%) had their ventricular arrhythmia ablated on the septal side, whereas 10 patients had their arrhythmia ablated on the free wall side. Eleven patients in the group (46%) had the origin of their ventricular arrhythmia mapped and ablated at myocardium that extended into the pulmonary artery as visualized by ICE (Group 2A). The median distance of the successful ablation site for these 11 patients was 8.2 mm (IQR 6.6-10.3 mm) beyond the valve (Figures 4-6; supplemental video). Seven of these sites were on the septal side, and 4 were on the free wall side. Mean sinus rhythm voltage at the successful ablation site was 2.8 ± 1.7 mV; 10 of the 11 (91%) successful ablation sites had sinus rhythm voltage ≥1.5 mV.

Of the remaining 13 patients in the RVOT group whose ventricular arrhythmias were not mapped above the valve (Group 2B), 9 were ablated coincident with the pulmonic valve annulus as visualized by ICE, and the remaining 4 were ablated below the pulmonic valve (subvalvular RVOT). Mean voltage at the successful ablation site was 2.0 ± 0.7 mV in Group 2B.

During follow-up, all 24 patients in Group 2 remained free of their targeted ventricular arrhythmia as determined by symptoms and 24-hour Holter monitoring (average follow up of 14 ± 11 months).

The patients with ventricular arrhythmias originating from supravalvular locations (Group 2A) were found to have more extensive myocardium above the pulmonic valve compared with the patients having arrhythmias originating from the valvular and subvalvular RVOT (Group 2B) (Figure 7A). On the septal side, the median Avg myocardial voltage distance...
was 7.0 mm (IQR 5.0 – 8.3) beyond the pulmonic valve for Group 2A patients, compared with 2.7 mm (IQR 0 – 6.0) for Group 2B patients (p=0.007). On the free wall side, the median Avg myocardial signal distance was 4.3 mm (IQR 0.9 – 5.5) beyond the pulmonic valve for Group 2A patients, compared with 0 mm (IQR (-) 0.9 – (+) 2.3) for Group 2B patients (p=0.059) (Figure 7B).

The successful ablation sites were measured relative to the most distal extent of myocardium in their respective cross-sectional segments; (-) denotes distance below the extent of myocardial signal of 1.5 mV. In Group 2A patients the median distance from the ablation sites to the extent of myocardial signal was 0 mm; i.e., the ablation site was precisely at the furthest extent of the myocardium (IQR: (-)3.9 – 0 mm). In Group 2B patients the median distance was also 0 mm (IQR: (-)1.7 – 0). These distances were not significantly different between 2A and 2B patients (p=0.332), i.e., whether the actual ablation site was supravalvular or subvalvular.

Clinical and ECG Characteristics of Pulmonary Arterial Ventricular Arrhythmias

The clinical and electrocardiographic properties associated with ventricular arrhythmias ablated above the pulmonic valve are summarized in Table 2. The average QRS duration of the ventricular arrhythmias originating above the pulmonic valve (Group 2A) was 161 ± 29 ms, and was not significantly different from those originating at or below the valve (160 ± 18 ms; p=0.948). There was no significant difference with regard to R-wave amplitude in any of the inferior leads (p values 0.861-0.949), nor in the Q-wave ratio of aVR to aVL (p=0.685) and the r/S ratio in lead V2 (p=0.664). Precordial transition zone at V3 or earlier was seen in 3 of the 11 patients in Group 2A, compared with 7 of the 13 patients in Group 2B, but this did not reach statistical significance (p=0.240).
Electrophysiologic Characteristics of Pulmonary Arterial Ventricular Arrhythmias

The electrophysiologic and ablation findings of the ventricular arrhythmias originating above the pulmonic valve (Group 2A) are summarized in Table 3. Two patients had inducible sustained VT, both of which terminated in response to adenosine. A third patient had bursts of nonsustained VT inducible on high dose isoproterenol that terminated with adenosine. Catecholamine-facilitation of the ventricular arrhythmias was seen in 8 of 11 patients with pulmonary arterial origin (Group 2A), compared with 11 of 13 patients with subvalvular RVOT origin (Group 2B), p=0.630. Comparing Group 2A and Group 2B, there were no significant differences in the earliest activation times, best pace match leads, number of ablation attempts, or sinus rhythm voltage at the successful ablation sites (Table 4). No discrete multi-component potentials were observed in any of the successful ablation sites of Group 2A or 2B.

Discussion

The principal finding of this in vivo study is that myocardial tissue nearly always extends beyond the pulmonic valve into the pulmonary artery, and can be the focal source of VT or PVCs in nearly 50% of unselected patients with RVOT arrhythmias. To our knowledge, this is the first prospective study demonstrating the incidence of pulmonary arterial origin of idiopathic RVOT-type arrhythmias. There was no difference in the degree of pulmonary arterial myocardial extension between control patients and RVOT arrhythmia patients. Furthermore, there were no discrete ECG findings that distinguished the source of arrhythmia as above or below the pulmonic valve. Our findings challenge conventional understanding of the anatomic relationship between myocardial tissue in the RVOT and the pulmonary artery, as well as the precise source of RVOT arrhythmias in many patients. Since most cases of RVOT-type arrhythmias are

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thought to arise from the subvalvular aspect of the RVOT, ventricular arrhythmia originating from the pulmonary artery is now shown to be more frequent than previously recognized.

The extension of myocardial tissue into the great vessels is commonly observed, as seen in the superior vena cava, pulmonary veins, and aorta. Idiopathic ventricular arrhythmias are frequently seen to originate from the aortic sinuses of Valsalva and aortic root\textsuperscript{12}. This phenomenon is relatively easy to appreciate since these arrhythmias are usually mapped via the retrograde approach, and hence the location of the catheter is easily seen to be at or above the aortic valve fluoroscopically. In contrast, because the RVOT is routinely mapped with catheter advancement in the anterograde direction (from right ventricle to pulmonary artery), there is no fluoroscopic landmark for identifying the pulmonic valve. Hence, during conventional catheter mapping, local electrogram amplitude is typically used to define the location of the pulmonic valve, and loss of local electrogram signal with catheter advancement into the distal RVOT is presumed to indicate passage beyond the pulmonic valve into the pulmonary artery\textsuperscript{1}. This method assumes that myocardium extends precisely to level of the pulmonic valve and not beyond. Pulmonary angiography has been used in previous series to determine catheter location with respect to the pulmonic valve\textsuperscript{4,5,7}. However, since the pulmonic valve is tilted, standard angiographic views may not accurately reflect the relationship of the catheter to the valve.

Intracardiac echocardiography (ICE) is often used in mapping and ablation of arrhythmias from the outflow tract region, and has been previously described as a method to visualize the ablation catheter in the pulmonary artery\textsuperscript{13}. In our study, the integration of pulmonic valve anatomy from ICE and myocardial electrophysiology from voltage mapping allowed us to demonstrate contiguity of RVOT myocardium with pulmonary arterial myocardium, and additionally allowed quantitative measurement of these myocardial extensions.
Autopsy studies focusing on the prevalence of myocardium extending beyond the pulmonic valve have also shown that this is a common finding, occurring in up to 74% of hearts\textsuperscript{14,15}. In these series of autopsy specimens from patients without known arrhythmias, myocardium extended for average distances of 3.2 to 4.0 mm above the pulmonic valve into the pulmonary artery. These reports are consistent with the findings in our study.

We did not find the extension of myocardial signal into the pulmonary artery to be statistically different between the control patients (Group 1) and RVOT arrhythmia patients (Group 2). This suggests that myocardial extension alone may not predict the occurrence of idiopathic ventricular arrhythmias. In both our control patients and RVOT arrhythmia patients, we found that the myocardial signal extended a greater distance above the pulmonic valve on the septal side compared with the free wall side. We postulate that this may be due to tilting of the pulmonic valve; \textit{i.e.}, the septal side of the valve attaches more caudally whereas the free wall side attaches more cranially (closer to the extent of myocardium) (Figure 4).

Although the phenomenon of ventricular arrhythmias originating from the pulmonary artery has been appreciated, it is thought to be an uncommon finding. The paucity of reports describing this finding affirms its supposed novelty. However, our study shows that this phenomenon is more common than previously recognized. In our prospective cohort of consecutive RVOT arrhythmia patients, nearly half of the RVOT arrhythmias were ablated in the pulmonary artery. The ECG and ablation characteristics were not significantly different from the arrhythmias ablated in the subvalvular RVOT proper. This suggests that many of the currently understood RVOT-type (LBBB, inferior axis) arrhythmias are in fact of pulmonary arterial origin. Indeed, of the 11 patients with RVOT-type arrhythmias ablated in supravalvular locations, 10 (91%) exhibited sinus rhythm voltage of \( \geq 1.5 \text{ mV} \) that was contiguous with RVOT
myocardium. Using conventional mapping criteria\(^1\), these sites would have been assumed to be RVOT sites below the pulmonic valve, and the pulmonary arterial locations would not have been recognized without visualization of the valve.

In the previous series reported by Sekiguchi et al, ventricular arrhythmias originating in the pulmonary artery demonstrated distinguishing ECG characteristics – including larger R-wave amplitudes in the inferior leads, larger Q wave ratio in aVL/aVR, and R/S ratio in V2 – compared to arrhythmias originating in the subvalvular RVOT\(^5\). These ECG differences were not observed in our series, likely due to methodological differences for identifying the pulmonary arterial arrhythmias. Whereas prior published series utilized pulmonary arteriogram for defining the site of ablation in selected patients\(^4,5,7\), we used integrated real-time echocardiography for direct visualization of the pulmonic valve and ablation sites in unselected patients. As is the case for the aortic valve, 3-D integrated echocardiography is a more precise method for defining the pulmonic valve, which is anatomically tilted and therefore difficult to circumferentially define via standard angiographic views. As a result, it is likely that our study demonstrates a more sensitive method for identifying points above the pulmonic valve than methods used in prior studies.

Previous work in developmental biology has shown that the right ventricular outflow tract develops from a secondary source of cardiomyocytes distinct from the primary heart field in both avian\(^16\) and mammalian\(^17\) systems. It has also been shown that outflow tract myocardium and proximal pulmonary trunk vascular smooth muscle derive from the same group of cells in the arterial pole of the heart, and a combination of cellular processes – including apoptosis and absorption – contribute to disappearance of myocardium from the pulmonary trunk during embryonic development\(^16,18\). When these processes are incomplete or aberrant, residual
myocardial tissue may persist above the pulmonic valve in the adult heart. These developmental variations likely account for the observations made in our study and the prior autopsy series\textsuperscript{14,15}, suggesting that the final myocardial boundary between the outflow tract and proximal pulmonary artery is not always precisely fixed at the pulmonic valve.

Interestingly, patients with pulmonary arterial arrhythmias (Group 2A) had a greater degree of myocardial extension than patients with non-pulmonary arterial arrhythmias (Group 2B), but there is inherent selection bias in this post hoc analysis, and this may well represent normal variation in the extent of myocardium beyond the valve. It is more revealing that in the overall RVOT-type arrhythmia patients (Group 2), the median distance from the successful ablation sites to the furthest extent of myocardium in the respective segment was 0 mm – i.e., the successful ablation site was precisely at the location where the myocardial signal terminates. This was regardless of whether the arrhythmia was ablated in the pulmonary artery (Group 2A) or in the RVOT proper (Group 2B). It is possible that myocardial termination adjacent to vascular tissue tends to be more arrhythmogenic; perhaps due to structural reasons, this hypothesis merits further study and may implicate pulmonic valvular tissue in the pathogenesis of idiopathic ventricular arrhythmias from the RVOT and pulmonary artery.

Limitations

Voltage mapping is subject to bias toward finding less tissue extension beyond the valve, since poor tissue contact and undersampling will tend to favor underestimating the extent of myocardial tissue. Therefore, these measurements may in fact be an underestimate of the true myocardial extension present. Furthermore, the bipolar voltage threshold of $>1.5$ mV was established for normal myocardium in the ventricle proper\textsuperscript{10}. Although autopsy studies have shown small strands of myocardium extending above the pulmonic valve\textsuperscript{15}, their voltage
characteristics are unknown. Some of these thinner strands may go undetected if their
electrogram amplitude is <1.5 mV, the voltage map threshold. However, this scenario would
again bias the data toward underestimating the true extent of supravalvular tissue, thus further
strengthening the conclusion that the presence of myocardial sleeves above the pulmonic valve is
a common and underappreciated phenomenon.

Conclusion

Integrated voltage and echocardiographic mapping shows frequent extension of right ventricular
myocardium beyond the pulmonic valve into the pulmonary artery in vivo; this extension is
greater on the septal side than the free wall side, and occurs in humans without ventricular
arrhythmias. A significant proportion of idiopathic RVOT-type ventricular arrhythmias originate
from this pulmonary artery myocardium. The pulmonary arterial origin of these arrhythmias can
be more readily recognized with real-time echocardiographic localization of the pulmonic valve.

Conflict of Interest Disclosures: Dr. Liu has received research grant support from Biosense
Webster. Dr. Cheung has received fellowship grant support from Biosense Webster. The other
authors report no potential conflicts.

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Table 1: Patient Characteristics of the Two Study Groups.

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<th>Group 1 (Control) N=24</th>
<th>Group 2 (RVOT Arrhythmia) N=24</th>
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<td>Age, years</td>
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<td>Male, n (% [95% CI])</td>
<td>17 (71 [53-89])</td>
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<td>HTN, n (% [95% CI])</td>
<td>9 (38 [19-57])</td>
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<td>LV Ejection Fraction</td>
<td>60 ± 6</td>
<td>56 ± 9</td>
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RVOT = right ventricular outflow tract; HTN = hypertension.
Table 2: Clinical and Electrocardiographic Characteristics of RVOT Arrhythmias Ablated Above the Pulmonic Valve

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<th>Patient</th>
<th>Age</th>
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<th>QRS Duration of PVC/VT (ms)</th>
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<td>112</td>
<td>1.5</td>
<td>2.9</td>
<td>0.02</td>
<td>V4</td>
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<tr>
<td>18</td>
<td>65</td>
<td>F</td>
<td>63</td>
<td>160</td>
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<td>0.9</td>
<td>0</td>
<td>V3</td>
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<tr>
<td>19</td>
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<td>0.9</td>
<td>0.2</td>
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<tr>
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<td>M</td>
<td>56</td>
<td>153</td>
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<td>0.8</td>
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<tr>
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<tr>
<td>23</td>
<td>46</td>
<td>M</td>
<td>43</td>
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<tr>
<td>24</td>
<td>58</td>
<td>M</td>
<td>50</td>
<td>131</td>
<td>1.4</td>
<td>0.4</td>
<td>0.2</td>
<td>V5</td>
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</table>

LVEF=Left ventricular ejection fraction; PVC = premature ventricular contraction; VT = ventricular tachycardia
### Table 3: Electrophysiologic Characteristics of RVOT Arrhythmias Ablated Above the Pulmonic Valve

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical Arrhythmia</th>
<th>Isoproterenol Response (Increased Ectopy)</th>
<th>Inducible VT</th>
<th>VT Induction Method</th>
<th>Adenosine Response</th>
<th>EAT (mm)</th>
<th>Pace Match (# of leads)</th>
<th>RF Applications</th>
<th>Successful Ablation Site</th>
<th>Distance of Ablation Site Above PV (mm)</th>
<th>Ablation Site Voltage in Sinus Rhythm (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>PVC</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-24</td>
<td>12</td>
<td>6</td>
<td>FW 2</td>
<td>8</td>
<td>4.4</td>
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<tr>
<td>7</td>
<td>PVC</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-26</td>
<td>11</td>
<td>1</td>
<td>FW 3</td>
<td>7</td>
<td>2.6</td>
</tr>
<tr>
<td>8</td>
<td>NSVT</td>
<td>+</td>
<td>Sustained</td>
<td>Iso + AP or VP</td>
<td>Termination</td>
<td>-46</td>
<td>11</td>
<td>2</td>
<td>Septal 3</td>
<td>11</td>
<td>4.6</td>
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<tr>
<td>11</td>
<td>PVC</td>
<td>+</td>
<td>Non-sustained</td>
<td>Iso + VES</td>
<td>Termination</td>
<td>-18</td>
<td>11</td>
<td>4</td>
<td>Septal 3</td>
<td>13</td>
<td>2.3</td>
</tr>
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<td>PVC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>11</td>
<td>10</td>
<td>Septal 2</td>
<td>6</td>
<td>2.8</td>
</tr>
<tr>
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<td>NSVT</td>
<td>+</td>
<td>Sustained</td>
<td>Iso + VP</td>
<td>Termination</td>
<td>-18</td>
<td>12</td>
<td>9</td>
<td>Septal 3</td>
<td>9</td>
<td>2.3</td>
</tr>
<tr>
<td>20</td>
<td>PVC</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-18</td>
<td>11</td>
<td>5</td>
<td>Septal 2</td>
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<td>6.6</td>
</tr>
<tr>
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<td>NSVT</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-21</td>
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<td>5</td>
<td>Septal 3</td>
<td>13</td>
<td>1.4</td>
</tr>
<tr>
<td>22</td>
<td>PVC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-24</td>
<td>11</td>
<td>4</td>
<td>Septal 2</td>
<td>8</td>
<td>1.6</td>
</tr>
<tr>
<td>23</td>
<td>PVC</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-28</td>
<td>11</td>
<td>6</td>
<td>FW 3</td>
<td>10</td>
<td>0.6</td>
</tr>
<tr>
<td>24</td>
<td>PVC</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-34</td>
<td>12</td>
<td>3</td>
<td>FW 3</td>
<td>4</td>
<td>1.5</td>
</tr>
</tbody>
</table>

RVOT = right ventricular outflow tract; PVC = premature ventricular contraction; VT = ventricular tachycardia; Iso = isoproterenol; AP = atrial pacing; VP = ventricular pacing; VES = ventricular extrastimuli; EAT = earliest activation time; FW = free wall; PV = pulmonic valve; RF = radiofrequency.
Table 4: Comparison of Clinical Characteristics and Electrophysiologic Findings between Groups of RVOT Arrhythmia Patients

<table>
<thead>
<tr>
<th></th>
<th>Group 2A (N=11)</th>
<th>Group 2B (N=13)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pulmonary Artery</td>
<td>RVOT Proper</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>48 ± 19</td>
<td>52 ± 20</td>
<td>0.618</td>
</tr>
<tr>
<td>Male, n (% [95% CI])</td>
<td>5 (45 [16-74])</td>
<td>5 (38 [12-64])</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypertension, n (% [95% CI])</td>
<td>2 (18 [0-40])</td>
<td>2 (15 [0-34])</td>
<td>1.000</td>
</tr>
<tr>
<td>LV Ejection Fraction</td>
<td>58 ± 10</td>
<td>54 ± 9</td>
<td>0.289</td>
</tr>
<tr>
<td>Cardiomyopathy (LVEF &lt;50%), n (%[95% CI])</td>
<td>3 (27 [1-53])</td>
<td>2 (15 [0-34])</td>
<td>0.630</td>
</tr>
<tr>
<td>RF Applications, n</td>
<td>5.0 ± 2.7</td>
<td>7.2 ± 4.2</td>
<td>0.160</td>
</tr>
<tr>
<td>Earliest Activation Time, ms</td>
<td>(-) 26 ± 8</td>
<td>(-) 28 ± 9</td>
<td>0.524</td>
</tr>
<tr>
<td>Best pace match, # leads</td>
<td>11.4 ± 0.5</td>
<td>11.7 ± 0.6</td>
<td>0.178</td>
</tr>
<tr>
<td>Successful site SR Voltage, mV</td>
<td>2.8 ± 1.8</td>
<td>2.0 ± 0.7</td>
<td>0.157</td>
</tr>
</tbody>
</table>

RVOT = right ventricular outflow tract; PVC = premature ventricular contraction; RF = radiofrequency; SR = sinus rhythm.

Figure Legends:

Figure 1. Left panel: RAO cranial view of a right ventricular outflow tract voltage map (color thresholds 0.5-1.5 mV) showing cross sectional division of the outflow tract / pulmonic valve area into 3 septal segments (1-3 from posterior to anterior) and 3 free wall segments (1-3 from posterior to anterior). Yellow arrow: most distal point in FW3 segment with bipolar voltage ≥1.5 mV. Right panel: Schematic representation of the 6 cross-sectional segments as seen from cranial view. RVOT = right ventricular outflow tract; FW = free wall.
Figure 2. Myocardial signal in the pulmonary artery of a control patient (Group 1). **Left:** Mapping catheter is seen in CartoSound frame to be well above the pulmonic valve, as confirmed by the location of the tip on the Carto anatomical map. **Middle:** Superimposed voltage map and ICE-defined pulmonic valve annulus (gray shell with orange tags). Measured distance from catheter point to the annulus is 5.5 mm. **Right:** Local electrogram bipolar voltage 5.3 mV at the catheter point. RVOT = right ventricular outflow tract.

Figure 3. Distribution of extension of myocardial signal (≥1.5 mV bipolar voltage) beyond the pulmonic valve, compared between the control patients without known RVOT-type ventricular arrhythmias (Group 1) and the RVOT arrhythmia patients (Group 2). **A:** Box plot for analysis by respective RVOT cross-sectional segments (p = nonsignificant within each segment). Dark line = median; box = interquartile range (IQR). **B:** Dot plot for analysis of average (Avg) distances by RVOT sides (septal and free wall sides). Dark line = median; whiskers = interquartile range (IQR). RVOT = right ventricular outflow tract; FW = free wall. (+) Distance denotes myocardium above valve; (-) distance denotes myocardium below valve.

Figure 4. Patient 7 of Group 2. **Left:** ECG of PVC with earliest activation time 26ms pre-PVC. (ECG leads as labeled; Abl d = ablation distal; Abl p = ablation proximal; RVa = right ventricular apex). **Middle:** Ablation catheter is seen in CartoSound frame to be well above the pulmonic valve. **Right:** Superimposed voltage map and ICE-defined pulmonic valve annulus (green). Measured distance from catheter ablation point to the annulus is 7.4 mm. **Right inset:** Local electrogram bipolar voltage 2.57 mV at the ablation point during sinus rhythm QRS. PVC = premature ventricular contraction; RV = right ventricle; RVOT = right ventricular outflow tract.
tract; LVOT = left ventricular outflow tract.

**Figure 5.** Patient 11 of Group 2. **A:** ECG of PVC with earliest activation time 21ms pre-PVC. (ECG leads as labeled; Abl d = ablation distal; Abl p = ablation proximal; RVa = right ventricular apex). **B:** Local electrogram bipolar voltage 2.24 mV at the ablation point during sinus rhythm QRS. **C:** Superimposed voltage map and ICE-defined pulmonic valve annulus (green). Measured distance from catheter ablation point to the annulus is 13.5 mm. **D:** Ablation catheter at successful site is seen in CartoSound frame to be well above the pulmonic valve. RV = right ventricle; RVOT = right ventricular outflow tract.

**Figure 6.** Patient 24 of Group 2. **A:** ECG of PVC with earliest activation time 34ms pre-PVC. (ECG leads as labeled; Abl d = ablation distal; Abl p = ablation proximal; RVa = right ventricular apex). **B:** Superimposed voltage map (color threshold 0.5-1.5 mV) and ICE-defined pulmonic valve annulus (green). Site of successful ablation is above the pulmonic valve. **Top middle inset:** Local electrogram bipolar voltage 1.5 mV at the ablation point during sinus rhythm QRS. **C:** Ablation catheter is seen in ICE frame to be well above the pulmonic valve. **D:** Integrated map with Cartosound frame of ablation site. **E:** Cartosound frame with ablation point (red circle) visualized beyond the pulmonic valve in the pulmonary artery. RV = right ventricle; RVOT = right ventricular outflow tract.

**Figure 7.** Distribution of extension of myocardial signal (≥1.5 mV bipolar voltage) above the pulmonic valve, compared between patients with RVOT arrhythmia ablated above the pulmonic valve (supravalvular; Group 2A) and patients with arrhythmia ablated at or below the pulmonic
valve (subvalvular; Group 2B). A: Box plot for analysis by respective RVOT cross-sectional segments. Dark line = median; box = interquartile range (IQR). B: Dot plot for analysis of average (Avg) distances by RVOT sides (septal and free wall sides). Dark line = median; whiskers = interquartile range (IQR). RVOT = right ventricular outflow tract; FW = free wall. (+) Distance denotes myocardium above valve; (-) distance denotes myocardium below valve.
Superimposed RVOT Voltage Map and ICE-defined Pulmonic Valve

ICE Image from RV

RVOT

Pulmonary Artery

Catheter Tip

5.5 mm

Pulmonary Valve Annulus Tags from CartoSound

Pulmonary Artery

Pulmonic Valve Annulus Tags RVOT

Abl Dis

1.5 mV

0.5 mV

Distance: 5.5 mm

0.49 cm

726 LAT

CL (ms)

3 2.68 5.31 121

LAT (ms) Uni (mV) Imp (lA)
Control vs. RVOT Arrhythmia Patients

Average Myocardial Voltage Extension Relative to Pulmonic Valve (mm)

- Controls (Group 1, n=24)
- RVOT Arrhythmia (Group 2, n=24)

Significant differences:
- p=0.004
- p=0.002
Tricuspid RV apex RV Septum RVOT Septum Pulmonary Artery Pulmonary Valve Annulus RVOT Catheter Tip at Ablation Site ICE Image from RV Pulmonic Valve Annulus

Sinus rhythm bipolar egm 2.2 mV

Abl d Abl p RVa RV apex RV Septum Tricuspid Valve
Catheter Tip at Ablation Site

Sinus rhythm bipolar egm 1.5 mV

Pulmonic Valve Annulus

Ablation Site on Cartosound

RVOT

Pulmonary Artery

Pulmonary Artery
RVOT Arrhythmia Patients

Average Myocardial Voltage Extension Relative to Pulmonic Valve (mm)

- Septal
- Free Wall

Supravalvular (Group 2A, n=11)
Subvalvular (Group 2B, n=13)

p=0.007
p=0.059
Ubiquitous Myocardial Extensions into the Pulmonary Artery Demonstrated by Integrated Intracardiac Echocardiography and Electroanatomic Mapping: Changing the Paradigm of Idiopathic Right Ventricular Outflow Tract Arrhythmias
Christopher F. Liu, Jim W. Cheung, George Thomas, James E. Ip, Steven M. Markowitz and Bruce B. Lerman

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Supplemental Video. Patient 24. **Left:** Superimposed voltage map and ICE-defined pulmonic valve annulus (green). Site of successful ablation (dark red dot) is above the pulmonic valve. **Right:** Ablation catheter is seen in ICE image to be well beyond the pulmonic valve in the pulmonary artery (ICE catheter in right ventricle imaging upward at pulmonary artery).