An easy-to-use, operator-independent, clinical model to predict the left vs. right ventricular outflow tract origin of ventricular arrhythmias

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Received 17 October 2014; accepted after revision 25 November 2014; online publish-ahead-of-print 11 February 2015

Aims
To identify clinical characteristics able to predict a left ventricular outflow tract (LVOT) origin in outflow tract ventricular arrhythmias (OTVAs).

Methods and results
We included 117 consecutive patients (training sample) with successful radiofrequency ablation of OTVA in one centre. A predictive model for LVOT origin was obtained using clinical data. The model was prospectively validated in a second population (testing sample) of 143 patients from two additional centres. In training sample, mean age was 54 ± 17 years, 72 patients (61%) were male, and 63 (54%) had cardiovascular risk factors. Sixty (51%) patients had LVOT origin. Independent predictors for LVOT origin were the presence of hypertension [odds ratio (OR) 2.17, confidence interval (CI) 0.91–6.20, \( P = 0.09 \)], male gender (OR 4.83, 95% CI 1.89–12.33, \( P = 0.001 \)), and age ≥ 50 years (OR 4.46, 95% CI 1.57–12.7, \( P = 0.005 \)). A simple score was constructed with these three variables to predict LVOT origin (mean predicted probability of 15% for score 0, 26% for score 1, 60% for score 2, and 87% for score 3, \( P = 0.001 \)) and reached 80% sensitivity and 75% specificity. The score was validated in the testing sample and was not inferior to previously described electrocardiogram algorithms.

Conclusion
Patients currently referred for OTVA ablation are older, more frequently men, and with a higher probability for LVOT origin than previously described. A LVOT origin is associated with the presence of hypertension, male gender, and older age, and can be anticipated by using a simple clinical score.

Keywords
Outflow tract • Ventricular arrhythmias • Site of origin • Radiofrequency ablation • Cardiovascular risk factors

Introduction
Outflow tract ventricular arrhythmias (OTVA) are considered a benign entity, more common in young women and usually arising from the right ventricular outflow tract (RVOT).2 However, the ability to map complex or difficult-to-access structures like aortic root, or epicardium, together with the use of electroanatomic mapping systems, has permitted identifying other sites of origin.3 Moreover, new clinical scenarios have been described, such as PVC-induced or PVC-worsened cardiomyopathy, in which ablation of premature ventricular complexes (PVC) could be of substantial benefit.4,5 Therefore, the patient population with OTVA referred for ablation is growing and changing.

Recent series show a higher rate of comorbidities in patients referred for OTVA ablation, as well as a higher percentage of left ventricular outflow tract (LVOT) origin.5–7 In addition, the acute and long-term success rates are suboptimal, especially when the OTVA originates in the LVOT, despite the improvement in mapping and ablation techniques and even when procedures are performed at high-volume centres.5,8,9 The prediction of LVOT origin based on
What’s new?

- Outflow tract ventricular arrhythmias (OTVAs) are considered a benign entity, more common in young women and usually arising from the right ventricular outflow tract. However, we have shown that patients currently submitted for OTVA ablation are older, more frequently men, and with a higher probability for left ventricular outflow tract (LVOT) origin than previously described.
- Baseline patient characteristics in patients with OTVA differ depending on the site of origin (left vs. right). Patients with LVOT origin are significantly older, more frequently men, and more frequently had LV dysfunction, hypertension, dyslipidaemia, and diabetes.
- A simple and operator-independent score constructed with three variables (age, gender, and presence/absence of hypertension) predicts LVOT origin with 80% sensitivity and 75% specificity. This score was first internally tested and thereafter validated in an external population and is not inferior to previously described electrocardiogram algorithms.

Electrocardiogram analysis

In order to test the previously described ECG criteria to distinguish LVOT vs. RVOT origin in a large unselected series of patients and to compare their accuracy with that of the clinical predictive model, all surface ECGs from the training sample and the external population were analysed. Two independent and well-trained electrophysiologists analysed all ECG parameters/criteria in the training sample in order to determine the inter-observer variability. A single observer analysed each of the ECGs in the testing population. The following parameters were analysed:

1) V2 transition ratio10 computing the percentage R-wave during PVC (R/R + S) divided by the percentage R-wave in sinus rhythm; (ii) R-wave duration index (obtained as a percentage by dividing the QRS complex by the longer R-wave duration in lead V1 and V2) and 3) R/S wave amplitude index (obtained as the greater percentage of the R/S-wave amplitude ratio in lead V1 or V2).11

Electrophysiological study

In the training sample, conventional ablation was performed in 31 (26%) patients using a 4-mm irrigated-tip catheter. The CARTO ( Biosense Webster, Diamond Bar, CA) electroanatomic mapping system was used in 86 (74%) patients to guide ablation. In these patients, a 3.5-mm irrigated-tip catheter (NaviStar, Biosense Webster) was used for mapping and ablation. Selection of target ablation sites was based on the activation map in 95 patients (81%), pace mapping in 16 patients (14%), and a combination of both in 6 patients (5%). When the ventricular arrhythmia (VA) was not eliminated after 30 s, energy delivery was discontinued and another site was selected for further application. In the testing sample, the CARTO electroanatomic mapping system was used in 120 (84%) patients. Target ablation site selection was based on the activation map in 111 patients (78%), pace mapping in 13 (9%) patients, and a combination of both in 19 (13%) patients.

Ablation was considered successful if the targeted OTVA was eliminated and non-inducible after isoproterenol infusion. The site where RF application eliminated the OTVA was considered the SOO.

Methods

Training sample

Data of consecutive patients submitted for OTVA ablation to a high-volume, tertiary referral centre were prospectively collected between April 2008 and March 2013. Patients included in this study had undergone a successful ablation of OTVA. No patient was excluded because of co-morbidities, structural heart disease, or the suspected SOO of the OTVA. Patients with unsuccessful ablation in whom the SOO could not be identified/proven were excluded. Demographic, clinical, ECG, and electrophysiological data of 117 patients with successful OTVA ablation were obtained and analysed. After analysis of the association between the clinical variables and the SOO of the OTVA (i.e. RVOT vs. LVOT) in the training sample, a predictive model for the SOO was obtained by using the variables with independent predictive value.

External validation

To validate the model, it was applied in a testing sample from two additional high-volume referral centres. These centres do not apply any selection criteria that might bias the patient sample. Therefore, unselected consecutive patients with successful ablation of OTVA constituted this testing sample. The same data as for the training sample were collected and analysed for the testing sample of 143 patients.

Statistical analysis

Continuous variables are presented as the mean value ± standard deviation and categorical variables as total number and percentages. To compare means of two variables, Student’s t-test was used. Proportions were compared using χ² test. Receiver operating curve (ROC) analysis was used to evaluate the optimal cut-off of age for predicting LV origin. Logistic regression analysis was used to study the effects of baseline characteristics in predicting LVOT origin. Variables that showed a statistically significant effect (P < 0.10) on univariate analyses were entered in a multivariate logistic regression. A backward stepwise selection algorithm was applied to select the final model. At each step, the least significant variable was discarded from the model until all variables in the model reached P value of < 0.10. Odds ratio (OR) and 95% confidence interval (CI) also were calculated. The model obtained with the training sample was used to predict the LV origin in the testing, external sample. A simplified score was constructed using the independent predictor variables and used to generate mean predicted probabilities for a LVOT origin. The misclassification error of the model for both samples has been calculated and reported. The Cohen’s kappa coefficient was calculated to assess the inter-observer variability in ECG criteria measurement. All P values are two sided and considered statistically significant if < 0.05. Data were analysed with R software version 3.0.1 (R project for statistical computing).
Results

Training sample

One hundred and seventeen patients that underwent successful catheter ablation of OTVA were analysed. The majority of patients were men [72 patients (61%)], with a mean age of 54 ± 17 years. Fifty-four patients (46%) had hypertension (HT), 40 patients (34%) had dyslipidaemia (DLP), and 13 patients (11%) had diabetes mellitus (DM). Mean left ventricular ejection fraction (LVEF) was 48 ± 14%. Baseline characteristics of the patient sample are reported in detail in Table 1.

The presenting OTVA was PVC in 75 (64%) patients, non-sustained ventricular tachycardia in 20 patients (17%), and sustained ventricular tachycardia in 22 patients (19%). In nine patients (8%), two OTVA morphologies were found; therefore, 126 OTVAs were targeted for ablation. In all these patients, the SOO of the first OTVA was the type of OTVA was the same outflow tract as that of the first clinical morphology (6 LVOT and 3 RVOT). The SOO of the VA was the LVOT in 60 (51%) patients. The clinical characteristics of patients according to SOO are shown in Table 1.

Left ventricular outflow tract vs. right ventricular outflow tract origin

Patients with LVOT-VA were significantly older (61 ± 16 vs. 47 ± 16 years, \( P < 0.001 \)) and more frequently male [48 (80%) vs. 24 (42%); \( P < 0.001 \)] as compared with RVOT-VA patients. The ROC analysis showed that 50 years was the best cut-off age for predicting LVOT origin, with a sensitivity of 82%, specificity of 64%, and area under the curve of 0.76 (95% CI 0.66–0.85).

In addition, patients with LVOT-VA more frequently had dyslipidaemia \( (P < 0.001) \), DM \( (P = 0.002) \), HT \( (P < 0.001) \), and a lower LVEF \( (P < 0.001) \), shown in Table 1.

Table 1  Baseline characteristics of the training patient sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Left ventricle origin (n = 60)</th>
<th>Right ventricle origin (n = 57)</th>
<th>Total (n = 117)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 ± 16</td>
<td>47 ± 16</td>
<td>54 ± 17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>49 (82%)</td>
<td>23 (40%)</td>
<td>72 (62%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>43 ± 14</td>
<td>53 ± 12</td>
<td>48 ± 14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>40 (67%)</td>
<td>14 (25%)</td>
<td>54 (46%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>30 (50%)</td>
<td>10 (18%)</td>
<td>40 (34%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12 (20%)</td>
<td>1 (2%)</td>
<td>13 (11%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>38 (63%)</td>
<td>31 (54%)</td>
<td>69 (59%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>11 (18%)</td>
<td>1 (2%)</td>
<td>12 (10%)</td>
<td>0.01</td>
</tr>
<tr>
<td>PVC</td>
<td>35 (58%)</td>
<td>40 (70%)</td>
<td>75 (64%)</td>
<td>0.33</td>
</tr>
<tr>
<td>NSVT</td>
<td>13 (22%)</td>
<td>7 (12%)</td>
<td>20 (17%)</td>
<td></td>
</tr>
<tr>
<td>SVT</td>
<td>12 (20%)</td>
<td>10 (18%)</td>
<td>22 (19%)</td>
<td></td>
</tr>
</tbody>
</table>

LVEF, left ventricle ejection fraction; PVC, premature ventricle complexes; NSVT, non-sustained ventricular tachycardia; SVT, sustained ventricular tachycardia.

Clinical predictors

Univariate and multivariate analyses were performed to identify predictors for LVOT origin (Table 2). In the univariate analysis, HT, DM, DLP, male gender, LV dysfunction (defined as LVEF ≤ 50%), and age > 50 years were associated with LVOT origin. In the multivariate analysis, HT (OR 2.17, 95% CI 0.91–6.20, \( P = 0.09 \)), male gender (OR 4.83, 95% CI 1.89–12.33, \( P < 0.001 \)), and age > 50 years (OR 4.46, 95% CI 1.57–12.70, \( P = 0.005 \)) were independent predictors of LVOT origin.

Based on the clinical variables, the best model to predict LVOT origin was composed of HT, male gender, and age > 50 years. Figure 1A–C shows the probability of a LVOT origin according to these variables. The proposed model correctly predicted the SOO in 77% of patients (misclassification error, 23%) in the training patient sample. Based on the independent predictor variables, a simple score was constructed giving 1 point to each variable. In the training sample, 20 (18%) patients received a score of 0, 34 (29%) patients scored 1, 25 (21%) patients scored 2, and 38 (32%) patients scored 3 points. This simple risk score was significantly related to the VA origin \( (P < 0.001); \) see Figure 2). The probability of a LVOT origin was 15% for patients with score 0, 26% for patients with score 1, 60% for patients with score 2, and 87% for patients with score 3. In the training sample, dichotomizing the score results as presumable RVOT origin (score 0 and score 1) and presumable LVOT origin (score 2 and score 3), the clinical score had 80% sensitivity and 75% specificity in identifying a LVOT origin.

Table 3 shows the association between the specific SOO in each outflow tract and the baseline clinical variables. Significant associations between SOO and baseline clinical variables were found for all the variables individually. The subvalvular LVOT and the epicardial LVOT were the specific SOO with the highest risk scores, due to a stronger association with HT, male gender, and older age.

Testing sample: validation of the model

One hundred and forty-three patients from two external centres were analysed for the validation of the model. Seventy-five (52%) were men, with a mean age of 49.7 ± 16 years. Fifty-eight (41%) patients had OTVA with a LVOT origin. Table 4 shows the baseline characteristics of this population.

Using the clinical score in this population, the probability of LVOT origin was 18% for patients with score 0, 33% for patients with score 1, 58% for patients with score 2, and 77% for patients with score 3. Figure 2 shows the probability distribution for both populations. In this testing population, the model correctly predicted the SOO in 70% of patients (misclassification error, 30%). In this population, the clinical score had 61% sensitivity and 75% specificity in identifying a LVOT origin.

Electrocardiogram criteria

V2 transition ratio had 71% sensitivity and 71% specificity in identifying a LVOT origin with disagreement between observers in 12% of the patients (Cohen’s kappa coefficient of 0.79). R-wave duration and R/S wave amplitude indexes had 60% sensitivity and 79% specificity in identifying a LVOT origin with disagreement between observers in 25% of the patients (Cohen’s kappa coefficient of 0.55).
To improve the accuracy to identify a LVOT origin, basic ECG information could be added to the clinical score. With this purpose, an easy to obtain ECG information such as the R/S transition in precordial leads was considered in a second step. The precordial R/S transition was defined as the first precordial lead with a dominant R wave. An early transition (precordial transition prior to V3) added an extra point to the score whereas a late transition (precordial transition later than V3) decreased the score by 1 point. With this second step this hybrid algorithm reaches 73% sensibility and 81% specificity in the whole population.

Figure 3 shows the probability distribution with the hybrid, two-step algorithm for both samples separately.

Patients with V3 transition in surface electrocardiogram

The SOO is often difficult to predict by ECG features for PVCs with a left bundle branch like morphology and a precordial R/S transition in lead V3. A V3 transition can be observed in LVOT and RVOT SOO. Therefore, the validity of the proposed score was checked in all patients from the three centres with a left bundle branch block like morphology and an R/S transition in V3 \( n = 90 \) (35%); LVOT 47 (52%). In this specific population, the clinical model had 66% sensitivity and 70% specificity. Moreover, the distribution of probabilities using the clinical score did not differ in patients with R/S transition in V3 with respect to the distribution of probabilities in the whole population \( (P = 0.66) \).

Electrocardiogram criteria in this specific population performed worse: V2 transition ratio had 68% sensitivity and 53% specificity and R-wave duration and R/S wave amplitude indexes had 47% sensitivity and 66% specificity for LVOT origin.

Discussion

This study observed a higher prevalence of LVOT origin than previously described in patients referred for RFA of OTVA. Baseline patient characteristics were different depending on the SOO. Patients with LVOT origin were significantly older, more frequently men, and more frequently had LV dysfunction, HT, DLP, and DM.
The newly developed, easy-to-use clinical score based on clinical variables can predict the RVOT vs. LVOT origin. Outflow tract VA are considered idiopathic and benign VA, not associated with structural heart disease and more frequently observed in young women without cardiovascular risk factors. In this classical population, the majority of VAs arises from the RVOT. However, contrary to the previously accepted profile, the present patient population referred for RFA in high-volume centres (represented by three centres) had a mean age of 52 years, most were male (56%), and they had frequently classic cardiovascular risk factors. In this population, nearly half of the patients had OTVA with LV origin. This higher percentage of LVOT origin has important practical implications because it forces the physician to consider mapping of more complex structures such as the aortic root, the distal coronary sinus, or even the epicardium. Therefore, predicting the probability of LVOT origin is of great interest for patient counselling, operator procedural planning, and estimating the probability of complications.

### Table 3 Site of successful ablation and its relationship with the patient’s clinical baseline characteristics in the training sample

<table>
<thead>
<tr>
<th></th>
<th>LVOT subvalvular (n = 28)</th>
<th>Aortic cusps (n = 24)</th>
<th>CS/LV summit (n = 8)</th>
<th>RVOT septal (n = 32)</th>
<th>RVOT freewall (n = 25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>23 (82%)</td>
<td>20 (83%)</td>
<td>6 (75%)</td>
<td>12 (37%)</td>
<td>11 (44%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age &gt;50 years</td>
<td>26 (93%)</td>
<td>12 (50%)</td>
<td>6 (75%)</td>
<td>8 (25%)</td>
<td>6 (24%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HT</td>
<td>21 (75%)</td>
<td>12 (50%)</td>
<td>7 (87%)</td>
<td>10 (31%)</td>
<td>4 (16%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DLP</td>
<td>13 (46%)</td>
<td>11 (46%)</td>
<td>6 (75%)</td>
<td>7 (22%)</td>
<td>3 (12%)</td>
<td>0.002</td>
</tr>
<tr>
<td>DM</td>
<td>6 (21%)</td>
<td>5 (21%)</td>
<td>1 (12%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>0.032</td>
</tr>
<tr>
<td>LVEF &lt; 50%</td>
<td>18 (64%)</td>
<td>11 (46%)</td>
<td>5 (62%)</td>
<td>10 (31%)</td>
<td>5 (20%)</td>
<td>0.017</td>
</tr>
<tr>
<td>Mean clinical SCORE</td>
<td>2.2 ± 0.9</td>
<td>1.6 ± 1</td>
<td>2.3 ± 1</td>
<td>0.89 ± 1</td>
<td>0.79 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HT, hypertension; DLP, dyslipidaemia; DM diabetes mellitus; LVOT, left ventricle outflow tract; CS, coronary sinus; LV, left ventricle; RVOT, right ventricular outflow tract. SCORE, clinical score based on HT + Age > 50 years + Gender (male); see Results, clinical predictors section.

### Table 4 Baseline characteristic of the testing sample according to the site of origin of the ventricular arrhythmia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Left ventricle origin (n = 58)</th>
<th>Right ventricle origin (n = 85)</th>
<th>Total (n = 143)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 ± 16</td>
<td>44 ± 14</td>
<td>49.7 ± 16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>39 (67%)</td>
<td>36 (42%)</td>
<td>75 (52.4%)</td>
<td>0.004</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>54 ± 10</td>
<td>59 ± 7</td>
<td>57 ± 9</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (29%)</td>
<td>12 (14%)</td>
<td>29 (20%)</td>
<td>0.034</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>18 (31%)</td>
<td>14 (16%)</td>
<td>32 (22%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (9%)</td>
<td>6 (7%)</td>
<td>11 (8%)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

LVEF, left ventricle ejection fraction.
Patients with left ventricular outflow tract origin

A previous single-centre study showed an association between LVOT origin of the VA, age, and gender. However, this study only included patients with normal LVEF and without structural heart disease and did not analyse the influence of other clinical variables for a RVOT vs. LVOT origin. This study confirms these preliminary data in a population of three European centres and contributes evidence for an association between LVOT origin and HT, DLP, and DM, as well as with the presence of LV dysfunction.

The relationship between cardiovascular risk factors like HT, DM, or advanced age and focal fibrosis in the myocardium is well established. Animal models have shown that chronic pressure increase and volume overload lead to the development of atrial and VAs. It is also known that LV fibrosis foci can serve as the substrate for PVC as well as non-sustained ventricular tachycardia. Moreover, mid-wall fibrosis was associated with monomorphic VA in non-ischaemic cardiomyopathy. Fibrosis may lead to inhomogeneity in both conduction and refractoriness and may be responsible for the higher percentage of arrhythmias arising from the LVOT. Further studies are needed to explore whether treatment of risk factors such as HT may prevent VA or may be part of LVOT VA treatment.

Clinical predictors of site of origin

To predict the SOO of OTVA before the ablation procedure is of practical relevance because it could help physicians in patient counselling regarding the potential ablation success and associated procedural risks specific for a left-sided approach. In addition, it may help planning the approach most appropriate and perhaps reducing procedure time and complication rate. Several algorithms have been developed to determine the SOO of OTVA, based on surface ECG analysis. However, the accuracy of these algorithms has not been tested in a large population of consecutive patients different from those of the original publication. This study shows that the sensitivity and specificity are 70% and further decrease when the algorithms are applied to patients with V3 transition. They require skills in ECG analysis and interpretation and are prone to considerable inter-observer dependence/variability, as demonstrated in this study. Moreover, they cannot be applied in all patients such as those with paced rhythms, intraventricular conduction disorders or patent structural heart disease. With this study we have developed a simple model of three clinical variables that can be easily and obtained before the procedure. The proposed model is easy-to-use and has no inter-observer variability. The model was tested in a large testing population with a sensitivity and specificity not inferior to the ECG algorithms and even superior for OTVA with V3 transition. These results strengthen the validity of the model, as despite slightly different baseline characteristics (as shown in Table 5), the prediction model delivers comparable results in both populations. Finally, a hybrid model that takes into consideration the preordial lead transition into a second step, achieves a sensitivity and specificity superior to that of the ECG algorithms.

In view of the characteristics of the population currently submitted for OTVA ablation, the proposed prediction model can be a helpful and useful tool, especially for those cases in which ECG algorithms...
are inconclusive or for the population for whom they are not validated (e.g. patients with paced QRS, intraventricular conduction disorders or structural heart disease). As the clinical prediction model is not influenced by surface ECG features, it is particularly helpful in OTVA with a R/S transition in precordial lead V3.

Limitations
The main limitation of this study is its retrospective nature. The patients included came from high-volume and tertiary referral hospitals; therefore, they may not be fully representative for the total population of patients with OTVA considered for ablation. A contrast-enhanced cardiac magnetic resonance was not systematically obtained before the ablation procedure and therefore the presence/absence of fibrosis in the outflow tracts could not be evaluated. Finally, the percentage of LVOT origin may be underestimated because patients with unsuccessful ablation were excluded and it is known that this particular location is related to high probability for ablation failure.

Conclusions
Patients currently submitted for OTVA ablation are older, more frequently men, and with a higher probability for LVOT origin than previously described. A LVOT origin is associated with the presence of HT, male gender, and older age and can be anticipated by using a simple clinical score.

Conflict of interest: none declared.

References