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ELECTROPHYSIOLOGY

Validation of a clinical model for predicting left versus right ventricular outflow tract origin of idiopathic ventricular arrhythmias

Luc Bourquin MMed[1] | Thomas Küffer MSc[2] | Babken Asatryan MD, PhD[2] | Patrick Badertscher MD[1] | Samuel H. Baldinger MD[2] | Sven Knecht PhD[1] | Jens Seiler MD[2] | Florian Spies MSc[1] | Helge Servatius MD[2] | Michael Kühne MD[1] | Fabian Noti MD[2] | Stefan Osswald MD[1] | Andreas Haeberlin MD, PhD[2] | Hildegard Tanner MD[2] | Laurent Roten MD[2] | Tobias Reichlin MD[1,2] | Christian Sticherling MD, MPH[1]

[1]Department of Cardiology and Cardiovascular Research Institute Basel (CRIB), University Hospital Basel, Basel, Switzerland

[2]Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Correspondence
Luc Bourquin, University Hospital Basel, Department of Cardiology, Petersgraben 4, CH-4031 Basel, Switzerland.
Email: luc.bourquin@usb.ch

Abstract

Background: Prediction of the chamber of origin in patients with outflow tract ventricular arrhythmias (OTVA) remains challenging. A clinical risk score based on age, sex and presence of hypertension was associated with a left ventricular outflow tract (LVOT) origin. We aimed to validate this clinical score to predict an LVOT origin in patients with OTVA.

Methods: In a two-center observational cohort study, unselected patients undergoing catheter ablation (CA) for OTVA were enrolled. All procedures were performed using an electroanatomical mapping system. Successful ablation was defined as a ≥80% reduction of the initial overall PVC burden after 3 months of follow-up. Patients with unsuccessful ablation were excluded from this analysis.

Results: We included 187 consecutive patients with successful CA of idiopathic OTVA. Mean age was 52 ± 15 years, 102 patients (55%) were female, and 74 (40%) suffered from hypertension. A LVOT origin was found in 64 patients (34%). A score incorporating age, sex and presence of hypertension reached 73% sensitivity and 67% specificity for a low (0–1) and high (2–3) score, to predict an LVOT origin. The combination of one ECG algorithm (V_2S/V_3R-index) with the clinical score resulted in a sensitivity and specificity of 81% and 70% for PVCs with R/S transition at V_3.

Conclusion: The published clinical score yielded a lower sensitivity and specificity in our cohort. However, for PVCs with R/S transition at V_3, the combination

ABBREVIATIONS: CA, catheter ablation; CI, confidence interval; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MI, myocardial infarction; OR, odds ratio; PCI, percoutaneous coronary intervention; PVC, premature ventricular complexes; ROC, receiver operator characteristics; RVOT, right ventricular outflow tract; SOO, site of origin; SR, sinus rhythm; TZ, transition zone; TZI, transition zone index.

Tobias Reichlin and Christian Sticherling contributed equally to this work and are joint last authors.

with an existing ECG algorithm can improve the predictability of LVOT origin.

KEYWORDS
ablation, outflow tract tachycardia, premature ventricular complex, ventricular tachycardia

1 | INTRODUCTION

Outflow tract ventricular arrhythmias (OTVA) are the most common type of idiopathic VA. Although considered benign, highly symptomatic patients require therapy. Moreover, some patients develop cardiomyopathy[1,2] and in rare cases premature ventricular complexes (PVC) may trigger ventricular fibrillation.[3,4] Therapeutic options are pharmacotherapy or radiofrequency catheter ablation, the latter shows high success rates and low complication rates.[5–8]

OTVA can arise from the right (RVOT) or left ventricular outflow tract (LVOT). Knowing the site of origin (SOO) affects the procedural strategy, thereby allowing to avoid excessive mapping and ablation. VA arising from the LVOT may be referred to a specialized center for ablation due to the more complex anatomy and the potential risks involved.[9,10] Albeit rare, coronary artery injury and stroke may occur when ablating in the aortic root or the left ventricle.[11–15] Furthermore, there is a lower success rate compared to VA originating in the RVOT-VA.[13,16]

Surface 12-lead ECG characteristics of the VA are primarily used to distinguish between left from right outflow tract origins. PVCs originating from the RVOT normally have a left bundle branch block (LBBB) configuration with late R/S transition $\geq V_3$ whereas LVOT PVCs have an early R/S transition $\leq V_3$, with both entities displaying an inferiorly directed axis.[17,18] Consequently, PVCs with precordial transition at V_3 may be either originate on the right or left side. For better discrimination, several ECG algorithms have been developed in the past years including V_2 transition ratio,[19] V_2S/V_3R index,[20] transition zone index (TZI),[21] or the combination of these.[22,23]

To simplify the process of predicting the site of origin of idiopathic VA, Penela et al. developed an easy-to-use clinical score to predict LVOT origin, reporting a sensitivity and specificity of 71% and 74%, respectively.[24] The score consists of three clinical parameters (arterial hypertension, male sex and age >50 years), each equally weighted[24] (Table S1).

The aim of this study was to externally validate the proposed clinical score to predict LVOT origin in patients with VA referred for ablation in two tertiary referral centers in Switzerland.

2 | METHODS

This is a retrospective analysis of a prospective, observational cohort study of consecutive patients undergoing catheter ablation procedures for PVCs or idiopathic ventricular tachycardia conducted in the two largest electrophysiological referral centers in Switzerland between January 2013 and June 2019. The study has been approved by the locally appointed ethics committee and complies with the Declaration of Helsinki.

Procedural data were documented during each intervention and medical history was obtained by reviewing patients' records. Follow-up visits were conducted by the referring cardiologists. Structural heart disease as underlying cause for the arrhythmia was ruled out using echocardiography and/or cardiac magnetic resonance imaging (cMRI) at physician's discretion. All patients were given a 24-h Holter ECG before and after 3 months to the procedure. Successful ablation was defined as more than 80% reduction of the initial overall PVC burden or if no VT was detectable in 24 h ECG. The SOO was assumed to be the site of successful ablation. Patients with repeat procedures and/or CA at more than one site were excluded.

2.1 | Procedure

Patients were sedated with midazolam, propofol and fentanyl at the physicians' discretion. The RVOT was initially mapped. If no suitable site was found in the RVOT and R/S transition was at V_3 or earlier, the distal coronary sinus was mapped followed by the LVOT including the aortic root. Mapping and ablation were performed using an irrigated 3.5 mm tip ablation catheter (ThermoCool Smarttouch SF), ThermoCool SF or RMT Navistar, Biosense Webster, Diamond Bar, CA, United States) and the CARTO3 electro-anatomical mapping system (Biosense Webster, Diamond Bar, CA, United States).

For patients with frequent PVCs, activation mapping was used to determine the earliest site of endo- or epicardial depolarization. Additional pace mapping was performed by comparing paced and intrinsic PVC morphologies on surface ECG both visually and automatically (PASO; CARTO, Biosense Webster) to confirm the ablation site. Energy was then applied if the distal bipolar signal started before earliest onset of the QRS complex on surface ECG and if the unipolar signal showed a QS configuration. In case of rare PVCs during intervention, sedation was reduced and isoprenaline was applied to increase the PVC burden. If activation mapping was still not feasible, pace mapping just above the pacing threshold level was performed.

2.2 | Electrocardiogram

The R- and S-Amplitudes were measured from the stored, pre-procedural 12-lead ECG. The following measurements were obtained;

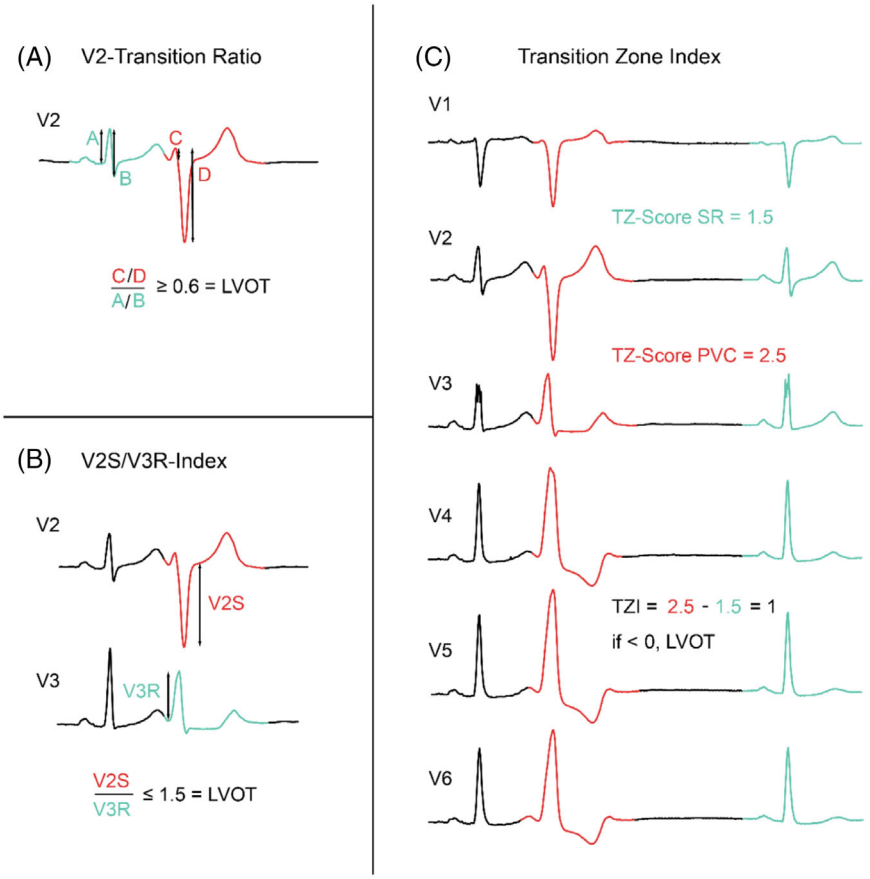

FIGURE 1 ECG algorithms, ECG algorithms to differentiate right and left-sided outflow tract ventricular arrhythmia. TZ, transition zone; SR, sinus rhythm; PVC, premature ventricular complex; LVOT, left ventricular outflow tract; TZI, transition zone index. [Color figure can be viewed at wileyonlinelibrary.com]

R-wave in V_3 (PVC), R- and S-wave in V_2 (PVC and sinus rhythm (SR)). The V_2 Transition ratio was calculated by dividing R-wave/QRS-amplitude in the PVC by R-wave/QRS-Amplitude in SR[19]; the V_2S/V_3R corresponds to the S-wave in V_2 divided by the R-wave in V_3, both for the PVC[20]; TZI was calculated as the transition zone (TZ) score of the PVC minus the TZ score of the sinus beat. TZ was defined as the precordial lead, where R/S-transition occurs (ratio R/S wave = 0.9–1.1). If transition occurred between two leads, steps of 0.5 were applied[21] (Figure 1).

2.3 | Statistical analysis

Continuous variables are expressed as means ± standard deviations if normally distributed or as median with interquartile range. Categorical variables are described as absolute numbers and percentage. Groups were compared using Student's *t*-test or Wilcoxon rank sum test for continuous variables and χ^2 or Fisher's exact test for proportions.

To evaluate predictors for left ventricular origin of the clinical model, univariate and multivariate logistic regression models were applied. Selected variables were the same as proposed in the derivation study.[24] A second logistic regression model was performed where variable selection was done using a backward stepwise Akaike information criteria (AIC) algorithm. Results are reported as odds ratios (OR) with 95% confidence interval (CI). A p-value < 0.05 was considered statistically significant for all tests.

Receiver operator characteristics (ROC) curves were used to determine discriminative power of the clinical score and ECG characteristics to predict LVOT origin.

A calibration plot was created to assess transferability of the described predictive values to our cohort.

To compare the discriminative parameters of the clinical score and ECG-algorithms, Mc Nemars test for paired data was applied. All analyses were performed using R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Patients' characteristics

Overall, 270 patients underwent idiopathic OTVA ablation during the study period. Excluded from the analysis were 83 patients: 17 patients who had ablation at more than one site, 53 patients with unsuccessful ablation procedures, five patients with repeat procedures, and eight patients were lost to follow-up. The remaining 187 patients were included in the analysis (Figure S1). There was no difference in the sustained ablation success rates between right- versus left-sided origin of VA (LVOT 80% vs. RVOT 77%, $p = 0.7$, $n = 240$).

The remaining 187 patients were included in the study. Baseline patient characteristics are summarized in Table 1. The successful ablation sites were in the RVOT in 123 (66%) patients and in the LVOT

TABLE 1 RVOT, right ventricular outflow tract; LVOT, left ventricular outflow tract; PVC, premature ventricular complex; VT, ventricular tachycardia; nsVT, non-sustained ventricular tachycardia; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention. Round brackets contain the standard deviation or the proportion of the population in percent, square brackets contain the interquartile range separated by comma.

Baseline characteristics of the validation cohort				
Variable	**RVOT**	**LVOT**	**Overall**	***p***
N	**123**	**64**	**187**	
Age (years)	49 (± 14)	59 (± 15)	52 (± 15)	<0.001
Sex (male)	48 (39%)	37 (58%)	85 (45%)	0.02
Cardiomyopathy	13 (11%)	13 (20%)	26 (14%)	0.11
PVC-induced cardiomyopathy	4 (3%)	4 (6%)	8 (4%)	
CAD	6 (5%)	3 (5%)	9 (5%)	
Other	3 (2%)	6 (9%)	9 (5%)	
PVC	105 (85%)	61 (95%)	166 (89%)	0.07
VT/nsVT	40 (33%)	9 (14%)	49 (26%)	0.01
PVC-burden (%)	18 [9, 29]	25 [20, 31]	22 [11, 30]	0.02
LVEF (%)	60 [55, 65]	58 [51, 60]	60 [55, 65]	0.001
LV dysfunction (LVEF < 50%)	7 (6%)	12 (19%)	19 (10%)	0.01
Antiarrhythmic drugs	80 (65%)	45 (70%)	125 (67%)	0.58
Amiodarone	5 (4%)	3 (5%)	8 (4%)	
Betablocker	59 (48%)	41 (64%)	100 (53%)	
Calcium-channel-blockers	24 (20%)	11 (17%)	35 (19%)	
Hypertension	36 (29%)	38 (59%)	74 (40%)	<0.001
Diabetes	8 (7%)	7 (11%)	15 (8%)	
Dyslipidemia	22 (18%)	18 (28%)	40 (21%)	
Renal failure	0 (0%)	1 (2%)	1 (1%)	
History of CABG or PCI	9 (7%)	5 (8%)	14 (7%)	
History of myocardial infarction	3 (2%)	2 (3%)	5 (3%)	
History of valvular surgery	1 (1%)	0 (0%)	1 (1%)	
R/S transition				<0.001
$<V_3$	0 (0%)	27 (44%)	27 (15%)	
V_3	20 (17%)	26 (43%)	46 (26%)	
$>V_3$	99 (83%)	8 (13%)	107 (59%)	
Days to follow-up	92 [70, 120]	93 [66, 120]	92 [69, 120]	

in 64 (34%) patients. Mean age was 52 ± 15 years and 55% were women. Most of the patients suffered from PVCs (89%) and had a median pre-ablation PVC burden of 22%,[11–30] whereas 26% suffered from non-sustained or sustained VT. Median left ventricular ejection fraction (LVEF) was 60% [IQR 55–65]. Antiarrhythmic drugs (AAD) were taken by 67% of the patients at baseline (53% beta-blockers, 19% calcium-channel blockers, 4% amiodarone). Half of the population had at least one cardiovascular risk factor (hypertension (40%), dyslipidemia (21%) or diabetes (8%)). Twenty-six patients (14%) had a cardiomyopathy that was not considered to be the underlying cause for the arrhythmia: Among these, eight patients (4%) were diagnosed with a PVC-induced cardiomyopathy. 14 patients (7%) had a history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting, 5 patients (3%) had history of myocardial infarction (MI) and one patient (1%) had undergone valvular surgery (Table 1).

Patients with LVOT origin were older (59 years vs. 49 years, $p < 0.001$), more often men (58% vs. 39%, $p = 0.02$) and more often suffered from arterial hypertension (59% vs. 29%, $p < 0.001$). They presented with a higher pre-procedural PVC-Burden (25% vs. 18%, $p = 0.02$) and lower LVEF (58% vs. 60%, $p = 0.001$) than patients with RVOT origin.

3.2 | Procedural characteristics

Ablation procedures for LVOT-VA lasted generally longer (126 min vs. 105 min, $p < 0.001$) with higher radiation doses (DAP) and longer

TABLE 2 All variables in (A) were included into AIC stepwise backward variable selection algorithm for the adapted model (B). RVOT, right ventricular outflow tract; LVOT, left ventricular outflow tract; LVEF, left ventricular ejection fraction; OR, odds ratio; CI, confidence interval.

Univariate and multivariate analysis to predict left ventricular origin				
A Multivariable logistic regression model as suggested by Penela et al.				
	RVOT	**LVOT**	**Univariate OR (95% CI)**	**Multivariate OR (95% CI)**
Age > 50	51 (42%)	50 (78%)	5.0 (2.6–10.4, $p < 0.001$)	3.4 (1.6–7.6, $p = 0.002$)
Sex (male)	48 (39%)	37 (58%)	2.1 (1.2–4.0, $p = 0.02$)	1.8 (0.9–3.4, $p = 0.09$)
LVEF < 50%	7 (6%)	12 (19%)	3.8 (1.5–10.8, $p = 0.008$)	–
Hypertension	36 (29%)	38 (59%)	3.5 (1.9–6.7, $p < 0.001$)	2.0 (0.95–4.1, $p = 0.07$)
Diabetes	8 (7%)	7 (11%)	1.8 (0.6–5.2, $p = 0.30$)	–
Dyslipidemia	22 (18%)	18 (28%)	1.8 (0.9–3.7, $p = 0.11$)	–
B Adapted multivariable analysis				
	RVOT	**LVOT**	**Univariate OR (95% CI)**	**Multivariate OR (95% CI)**
Age > 50	51 (42%)	50 (78%)	5.0 (2.58–10.38, $p < 0.001$)	3.4 (1.6–7.6, $p = 0.002$)
Sex (male)	48 (39%)	37 (58%)	2.1 (1.16–3.99, $p = 0.02$)	1.7 (0.9–3.4, $p = 0.12$)
LVEF < 50%	7 (6%)	12 (19%)	3.8 (1.45–10.80, $p = 0.008$)	3.3 (1.2–10.2, $p = 0.03$)
Hypertension	36 (29%)	38 (59%)	3.5 (1.89–6.72, $p < 0.001$)	1.9 (0.9–4.0, $p = 0.08$)

fluoroscopy time (768 cGy*cm2 vs. 76 cGy* cm^2 $p < 0.001$, 11 min vs. 6 min, $p = 0.07$) but shorter ablation time (316 s vs. 462 s, $p = 0.003$) (Table S2).

3.3 | Clinical predictors

In univariate analysis LVOT origin was associated with age over 50 years (OR 5.0, CI 2.6—10.4), male sex (OR 2.1, CI 1.2—4.0), LVEF < 50% (OR 3.8, CI 1.5—10.8) as well as presence of arterial hypertension (OR 3.5, CI 1.9—6.7). The previously proposed variables were included into the multivariable analysis, where only age over 50 years remained as independent predictor for LVOT origin with an OR of 3.4 (1.6—7.6, $p = 0.002$). The OR for male sex was 1.8 (0.9–3.4, $p = 0.09$) and for arterial hypertension 2.0 (0.95–4.1, $p = 0.07$) (Table 2A).

Using an AIC stepwise backward variable selection algorithm, reduced LVEF (<50%) was additionally included into a second model which revealed an OR of 3.3 (1.2–10.2, $p = 0.03$) for reduced LVEF in the full model (Table 2B).

3.4 | Clinical scores including age, sex and hypertension

Applying the suggested clinical score to our cohort resulted in 49 (26%) patients with a score of 0, 50 (27%) with a score of 1, 54 (29%) with a score of 2 and 34 (18%) with a score of 3. The positive predictive values for LVOT origin for scores 0, 1, 2, and 3 were 14%, 20%, 48%, and 62%, respectively (Figure S2). Calibration plot of expected versus observed probabilities showed a slope of 0.71 and an intercept of 0.03 (Figure S3). ROC curve had an area under the curve (AUC) 0.73 (95% CI, 0.65–0.80) for the prediction of LVOT origin using the clinical score (Figure 2). If dichotomized in presumable RVOT (scores 0 and 1) or presumable LVOT (scores 2 and 3), the clinical score reached a sensitivity of 73%, a specificity of 67%, and a PPV and NPV of 53% and 83%, respectively (Table 3). There were no differences in sensitivity and specificity within the subgroups of right- or left-outflow tract site of origin (Table S3).

Applying the score to a subgroup of patients with R/S Transition at chest lead V_3 ($n = 46$), the clinical score reached a sensitivity of 62%, a specificity of 60%, and a PPV and NPV of 67% and 55%, respectively (Table 4).

3.5 | ECG criteria: R/S transition

Overall, 46 (26%) patients showed a precordial transition at chest lead V_3. In the LVOT group, 27 patients (44%) had a R/S transition earlier than chest lead V_3, 26 patients (43%) at V_3 and eight patients (13%) after V3 (Table S4). Seven patients (3.7%) had no 12-lead-ECG documented PVC.

R/S transition in chest lead earlier than V_3 had a sensitivity of 44% and a specificity of 100% for LVOT origin. Using V_3 as threshold resulted in a sensitivity of 87% and a specificity of 83%. Overall, R/S Transition for LVOT origin had an AUC of 0.9 (Figure 2). The PPV for LVOT origin in patients with precordial transition at chest lead V_3 was 57%.

3.6 | ECG algorithms in the V_3 subgroup: V_2 transition ratio, transition-zone index, V_2S/V_3R index, combination with clinical parameter

As LVOT origin has the highest uncertainty in patients with precordial transition at V_3, we compared the most common ECG algorithms

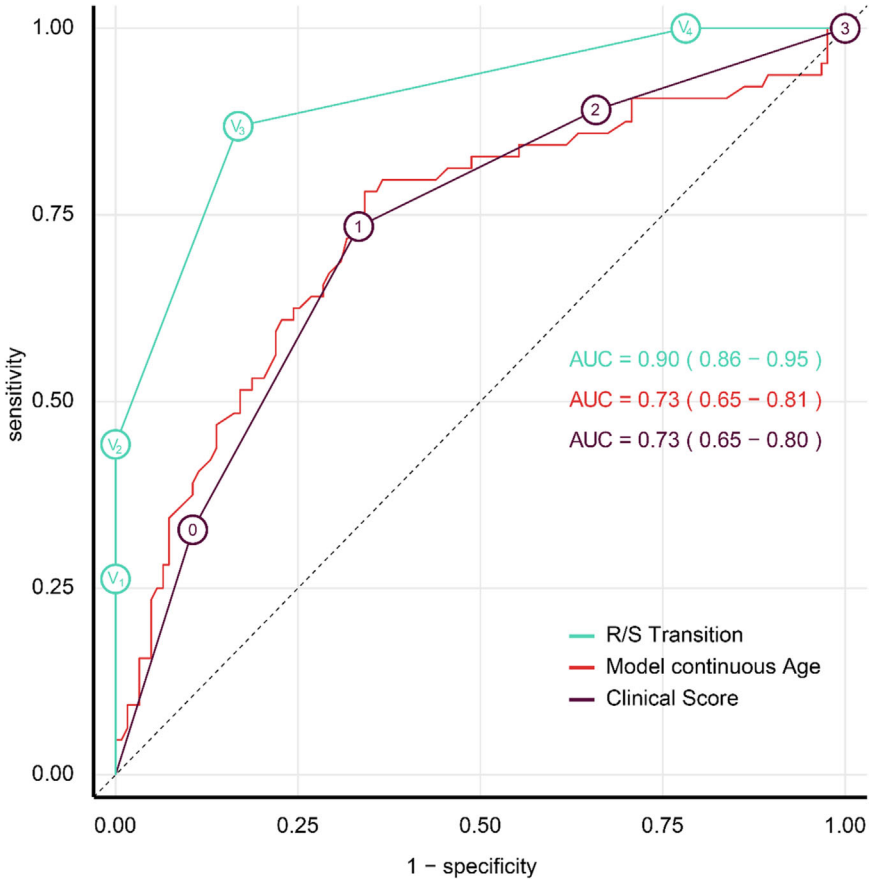

FIGURE 2 ROC for the clinical model, clinical Score and R/S-Transition, Different ROC with corresponding AUC. Red curve shows performance of the clinical model incorporating sex, presence of hypertension and age as continuous variable. Numbers indicate individual thresholds at a particular location on the ROC. AUC, area under the curve; ROC, receiver operating characteristic. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Discriminative and predictive parameter for left ventricular origin. Clinical score was dichotomized. Values ≤ 1 classified as presumed RVOT, ≥ 2 classified as presumed LVOT. First row shows reported values. PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; −LR, negative likelihood ratio.

Sensitivity, specificity, predictive values and likelihood ratios for LV origin ($n = 187$)							
Score	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**	**+LR**	**−LR**
Penela et al. (whole population)	*71%*	*74%*	*70%*	*75%*	*73%*	*2.7*	*0.4*
External validation of the clinical score	73%	67%	53%	83%	69%	2.2	0.4
R/S transition ≤ V_3	87%	83%	73%	93%	84%	5.2	0.2

with the clinical score in this subgroup ($n = 46$, 26%). TZI reached the highest sensitivity (92%), followed by V_2S/V_3R Index (85%), V_2 transition ratio (77%) and the clinical score (62%). Specificity was similar in all groups (TZI, V_2S/V_3R index, clinical score: 60%; V_2 transition ratio 65%) (Figure 3).

If patients with positive V_2S/V_3R index but no clinical risk factor for LVOT origin (Clinical score = 0) were reclassified as RVOT, the algorithm reached a sensitivity of 81% (−4%, $p = 0.32$), a specificity of 70% (+10%, $p = 0.16$) and a PPV and NPV of 78% and 74%, respectively (Figure 4, Table 4). No differences in sensitivity or specificity were observed between the subgroups of either right or left outflow tract origin (Table S5). Figure 5 shows representative ECGs with a true-positive, true-negative, false-positive and false-negative result.

4 | DISCUSSION

In this large cohort study of unselected patients with VA referred for ablation treatment in two tertiary referral centers in Switzerland, we externally validated a simple clinical score to predict LVOT origin.

We report three major findings. First, a previously proposed algorithm[24] relying merely on clinical information (age, sex, and presence of hypertension) yielded a sensitivity of 73% and specificity of 67% for the prediction of LVOT origin. Second, the model can improve the prediction of left ventricular origin in PVCs with R/S transition at V_3 when combined with a common ECG algorithm. Third, many patients referred for CA of idiopathic PVC/VT suffer from comorbidities and a relevant proportion from structural heart disease.

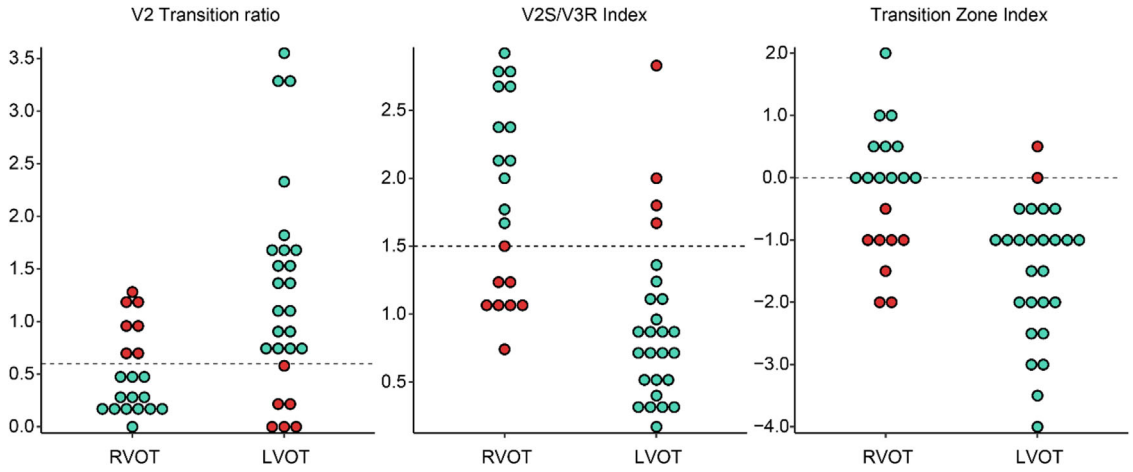

FIGURE 3 Dot plots for tested ECG-algorithms, Dots represent one case in the V3 precordial transition group. Cut-off values for left ventricular origin are ≥0.6 for V_2 transition ratio, ≤1.5 for V_2S/V_3R Index and <0 for transition zone index, indicated as dotted line. RVOT, right ventricular outflow tract; LVOT, left ventricular outflow tract. [Color figure can be viewed at wileyonlinelibrary.com]

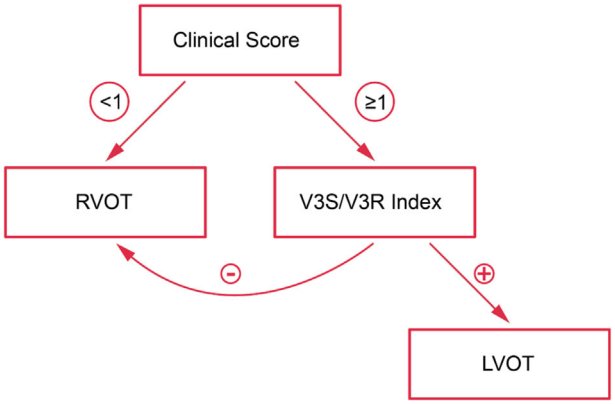

FIGURE 4 Suggested decision algorithm, Decision algorithm to predict left ventricular origin for premature ventricular complexes with R/S Transition at V_3 with a sensitivity of 81% and a specificity of 70%. LVOT, left ventricular outflow tract; RVOT, right ventricular outflow tract. [Color figure can be viewed at wileyonlinelibrary.com]

Our data confirms that LVOT origin of VA is associated with advanced age, arterial hypertension, and male sex as suggested by Penela et al.[24] However, only age remained a significant predictor in the multivariate analysis. Applying the proposed score to our cohort showed lower sensitivities and specificities than originally reported. Since the reported prevalence for LVOT origin was substantially higher in the derivation study, this led to a notable overestimation of the proposed predictive values. A potential selection bias favoring RVOT-VA due to higher success rates was ruled out, as they were similar in both groups. Notably, structural heart disease was not an exclusion criterion in their cohort. Consequently, scar related VAs could have been included, therefore leading to an inhomogeneous patient population with both scar related and idiopathic VAs, which in turn led to an increased prevalence of LVOT-VA.

Predicting LVOT origin of VA remains challenging. Easy to obtain ECG criteria such as R/S transition showed a high specificity of 100% for LVOT origin if transition occurred earlier than lead V_3, which is in line with other studies.[20,25,26] However, more than half of LVOT-VA had a precordial transition at or later than V_3 where left ventricular origin cannot reliably be predicted. Surface ECG algorithms have been shown to have lower sensitivities and specificities for VAs with precordial R/S transition at V_3.[22,24,27,28] Therefore, prediction models must focus on patients with precordial R/S transition at or later than V_3. Our analysis showed, that common ECG algorithms perform better in the V_3

TABLE 4 Discriminative and predictive parameter for left ventricular origin using different ECG-algorithms as well as clinical score, only for patients with R/S Transition at V_3. First row shows reported values. Clinical score was dichotomized. Values ≤1 were classified as presumed RVOT, ≥2 classified as presumed LVOT. Negative clinical score. Combined score means clinical score <1 and V_2S/V_3R index ≤1.5. CS, clinical score, PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; −LR, negative likelihood ratio.

Sensitivity, specificity, predictive values and likelihood ratios for LV origin in the V_3-transition group ($n = 46$)								
Algorithm	**Sensitivity**		**Specificity**		**PPV**	**NPV**	**Accuracy**	**+LR**	**−LR**
Penela et al. (whole population n = 90)	*66%*		*70%*		*70%*	*65%*	*68%*	*2.2*	*0.5*
Clinical score (CS)	62%		60%		67%	55%	60%	1.5	0.7
V_2S/V_3R Index	85%	$p = 0.32$	60%	$p = 0.16$	73%	75%	74%	2.1	0.3
ECG and clinical score combined	81%		70%		78%	74%	76%	2.7	0.3

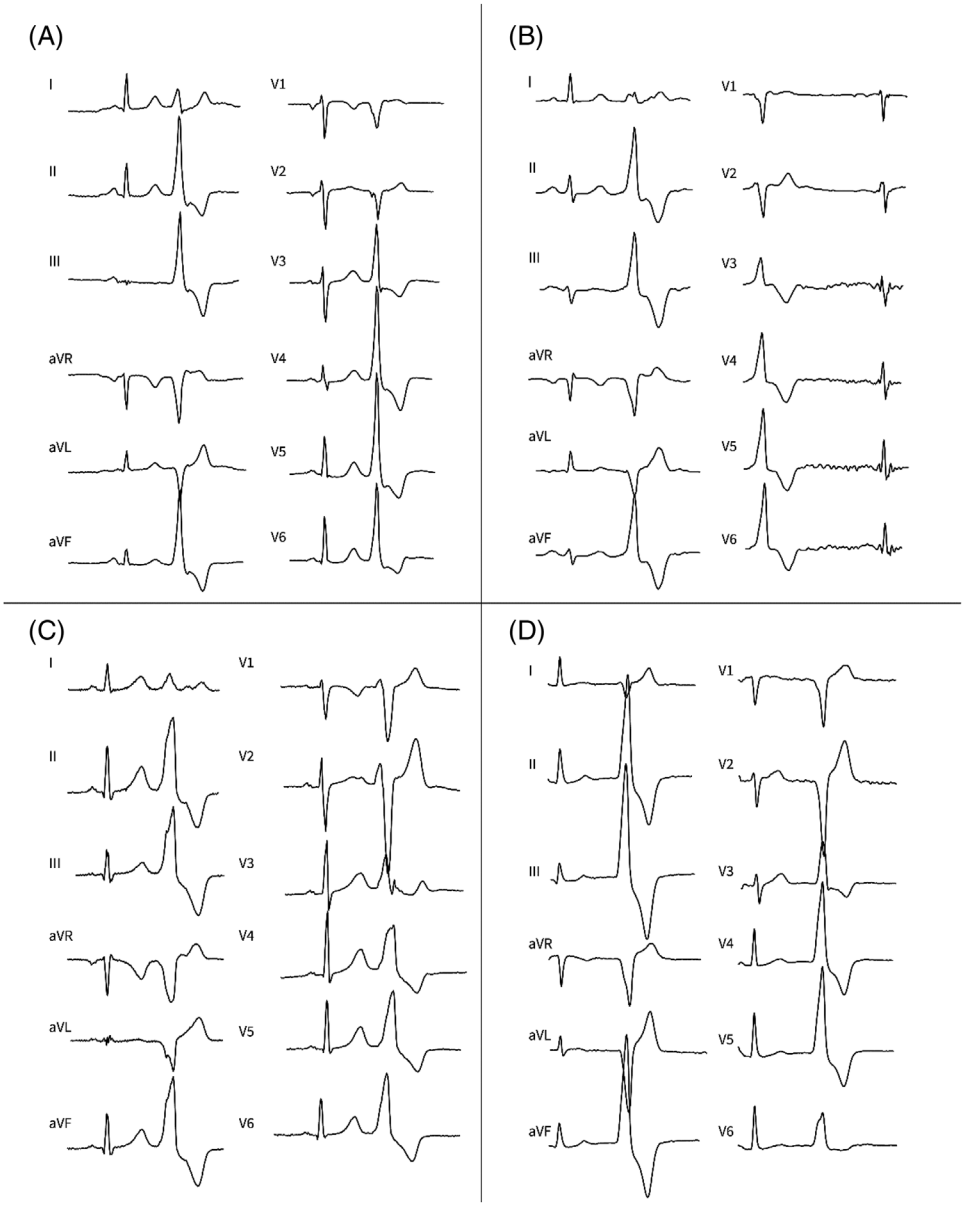

FIGURE 5 Representative ECGs, representative ECGs showing outflow tract PVCs with inferior axis and precordial transition at V_3, SOO are varying. Using the suggested decision algorithm; (A): 60-year-old woman with hypertension, SOO was the LVOT, true-positive. (B): 72-year-old woman with hypertension, SOO was the RVOT, false-positive. (C): 32-year-old woman without hypertension, SOO was the RVOT, true-negative. (D) 48-year-old man with hypertension, SOO was the LVOT, false negative.

subgroup compared to the clinical score, but specificities are lower than reported.[19–21] Combining both ECG algorithm and the clinical score has incremental value for the prediction of LVOT origin as it remarkably increased the specificity of the test. Moreover, the algorithm is likely to apply for all OTVA as no differences in sensitivity and specificity could be found between the SOO within the corresponding outflow tract.

We propose to use the V_2S/V_3R index, as it is the easiest to calculate and showed the best predictive values in our analysis. In this combination our algorithm reached a sensitivity of 81% and specificity of 70% in patients with transition in V_3. However, due to small sample size, this result did not reach statistical significance.

Hayashi et al.[29] described an increase in LVOT-VA ablations over the last decade with 10% in the early 2000 to 51% between 2011 and 2015 in a single center study. Of note, contemporary patients referred for ablation for OTVA are also older.[24,29] We show that older patients with reduced LVEF referred to catheter ablation have a higher probability for VAs originating from the LVOT. Almost 20% of all patients with idiopathic LVOT-VA had a reduced LVEF, which has also recently been described.[13,24] This finding may reflect a concealed structural heart disease not detected by routine examination. Particularly in patients with nonischemic, dilated cardiomyopathy, fibrosis in the basal LV septum and periaortic region is common and can serve as substrate for VA.[9,30] It is also well known that aging and pressure overload can

contribute to cardiac fibrosis.[31,32] Similarly, the association between hypertension and ventricular arrhythmia is well established.[33,34]

4.1 | Limitations

This was a retrospective, two-center study from tertiary referral centers, thus our results may not be transferable to the general population. Only patients with sustained ablation success were included to ensure correct SOO. This approach may have resulted in selection bias with inclusion of ablation procedures with higher success rates, which is thought to be RVOT ablation.[16] However, in our cohort, long-term ablation failure rates were not different for both groups. By selecting only successful ablation procedures, we might have missed patients who had a failed ablation due to other causes than the wrong ablation site. Additionally, drug regimen after the ablation procedure was not systematically assessed, which may have led in selecting patients with failed ablation but successful drug therapy.

It cannot be ruled out that some foci from one side have been ablated from the opposite side, especially in cases of VA originating from the aortic root or posterior RVOT which are anatomically adjacent structures.[9,35,36] Structural heart diseases, which could have potentially served as substrate for VA were not systematically ruled out using cMRI. Recent studies have shown concealed myocardial abnormalities in patients with apparently idiopathic PVC using cMRI data, especially in those with PVCs arising from the LVOT.[37–39] These could have served as anatomic substrate for VAs, leading to misclassification as idiopathic VA while structural heart disease was mostly ruled out using echocardiography.[39] Finally, further prospective studies are needed to assess the accuracy and usefulness of the algorithm.

4.2 | Conclusions

A published clinical score, encompassing older age, male sex, and presence of arterial hypertension, for prediction of LVOT origin of OTVA yielded a lower sensitivity and specificity in our cohort. However, for PVCs with R/S transition at V_3, the combination of both clinical aspects and ECG parameters could increase the prediction of the site of origin prior to the intervention.

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CONFLICT OF INTEREST STATEMENT

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ETHICS STATEMENT

Ethical approval was waived by the cantonal Ethics Committee of Bern (No. 2019-01930) in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

DATA AVAILABILITY STATEMENT

The data supporting the findings of the study are available on request. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Luc Bourquin MMed https://orcid.org/0000-0002-1115-342X
Babken Asatryan MD, PhD https://orcid.org/0000-0002-0050-5717
Patrick Badertscher MD https://orcid.org/0000-0001-9751-0557
Samuel H. Baldinger MD https://orcid.org/0000-0002-2296-4631
Sven Knecht PhD https://orcid.org/0000-0001-7122-021X
Florian Spies MSc https://orcid.org/0000-0001-8974-9541

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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