Hourly Variability in Outflow Tract Ectopy as a Predictor of its Site of Origin

Short title: Ectopy Variability Predicts Outflow Tract Origin

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Ethical statement: This study was given approval by the institutional review board on human research at our centre and the research methods adhered to the Declaration of Helsinki. All participants gave written informed consent.

Data availability: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Abstract

Introduction: Prior to ablation, predicting the site of origin (SOO) of outflow tract ventricular arrhythmia (OTVA), can inform patient consent and facilitate appropriate procedural planning. We set out to determine if OTVA variability can accurately predict SOO.

Methods: Consecutive patients with a clear SOO identified at OTVA ablation had their prior 24-hour ambulatory ECGs retrospectively analysed (derivation cohort). Percentage ventricular ectopic (VE) burden, hourly VE values, episodes of trigeminy/bigeminy, and the variability in these parameters were evaluated for their ability to distinguish right from left sided SOO. Effective parameters were then prospectively tested on a validation cohort of consecutive patients undergoing their first OTVA ablation.

Results: High VE variability (coefficient of variation ≥ 0.7) and the presence of any hour with < 50 VE, were found to accurately predict RVOT SOO in a derivation cohort of 40 patients. In a validation cohort of 29 patients, the correct SOO was prospectively identified in 23/29 patients (79.3%) using CoV, and 26/29 patients (89.7%) using VE < 50. Including current ECG algorithms, VE < 50 had the highest Youden Index (78), the highest positive predictive value (95.0%) and the highest negative predictive value (77.8%).

Conclusion: VE variability and the presence of a single hour where VE < 50 can be used to accurately predict SOO in patients with OTVA. Accuracy of these parameters compares favourably to existing ECG algorithms.

Key Words

Outflow tract ventricular arrhythmia

RVOT (right ventricular outflow tract) ectopy

LVOT (left ventricular outflow tract) ectopy

Radiofrequency ablation

Introduction

Outflow tract ventricular arrhythmias (OTVA) are the commonest form of ventricular arrhythmia in patients with structurally normal hearts (1). Arising from either the right or left ventricle, they are often benign, but can be associated with debilitating symptoms and ventricular dysfunction (2). Indications for ablation include drug refractory symptoms or high ectopic burdens (>10%) resulting in either left ventricular dilatation or systolic dysfunction.

Prior to OTVA ablation, predicting the site of origin (SOO) of the arrhythmia can inform patient consent and facilitate appropriate procedural planning. ECG algorithms have been devised to assist in these differentiating SOO and have varying degrees of success (3). Unfortunately, the algorithms can be complex, considered measurements are required, and results may be limited by incorrect lead positioning or due to population variations in cardiac orientation.

Behaviour of OTVA over a 24-hour period has not yet been studied as a discriminator of SOO, although consistency of ectopic burden has previously been shown to be associated with cardiomyopathy (4).

We propose an alternative approach to morphology based parameters, using OTVA variability across a 24-hour period to predict SOO. This is an attractive prospect given the easy availability of ambulatory monitors and their near ubiquitous role in the investigation of patients with OTVA.

Methods

A derivation cohort of consecutive patients, in whom OTVA ablation was performed at our centre, were retrospectively identified. Patients were included if there was an unambiguous SOO, in whom ectopy was successfully suppressed with radiofrequency (RF) ablation at a single site, with no recurrence during a 30 minute post-ablation waiting period as well as at least 90% reduction in ectopy burden on follow up 3 month Holter monitor. Patients with multiple ventricular arrhythmias were excluded. Patients with all bundle branch block morphologies were included in the main

analysis, however subgroup analysis of only those with non-right bundle branch block was performed to assess the utility of behavioural parameters in those with a truly ambiguous SOO.

For each patient, a single pre-ablation 24-hour ambulatory ECG was retrospectively analysed. Where possible, recordings performed prior to the introduction of anti-arrhythmic drugs (AAD) were selected. For every complete one-hour recording, the ventricular ectopic (VE) total was calculated. Variability in VE across the 24 hour period was assessed using the coefficient of variation (CoV) = standard deviation divided by the mean. Total number of bigeminy/trigeminy episodes and the variability (CoV) of this was also calculated. Percentage ectopic burden, mean heart rate and presence of sustained VT were also analysed. Patients with left and right sided SOO were compared and ROC curve analysis used to determine the optimal predictive parameter values. Circadian patterns in variability were analysed by comparing each patient's total VE CoV between four quartiles of the day (00:00-06:00, 06:00-12:00, 12:00-18:00 and 18:00-00:00). 24-hour ambulatory ECG analysis was performed blinded to the final diagnosis, including SOO as well as ECG morphology.

Parameters which were found to accurately predict SOO were then applied prospectively to a validation cohort of consecutive patients undergoing their first OTVA ablation. A single 24-hour ambulatory ECG, prior to AAD therapy where possible, was chosen for the primary analysis.

In order to assess inter-Holter reproducibility of the newly derived parameters, a supplementary analysis on any additional ambulatory ECGs was also performed on patients in whom multiple ambulatory monitors had been performed prior to ablation.

The predictive value of the derived parameters in determining SOO was calculated and compared to two well established morphological ECG-based algorithms shown to have the highest accuracy in a recent prospective analysis (5); transitional zone index (TZI) and V_2S/V_3R index (6,7).

TZI is defined as the precordial chest lead at which R wave transition is observed in the VE minus the equivalent lead for a sinus beat, with a TZI > 0 predicting a right sided SOO. The V_2S/V_3R index is

calculated by dividing the ectopic S-wave amplitude in V2 by the ectopic R-wave amplitude in V3, with a value > 1.5 also predicting a right sided SOO.

Electrophysiological study and ablation

All patients underwent ectopic ablation procedures under conscious sedation, with cessation of all anti-arrhythmic drugs at least five half-lives prior to the procedure. In each case a decapolar catheter was placed in the coronary sinus and 3D electroanatomical mapping was performed using a saline irrigated ablation catheter and one of two mapping systems: CARTO (Biosense Webster Inc., CA, USA) or NavX/Precision (Abbott Labs, IL, USA). Activation mapping was predominantly used to determine the SOO, with supplementary information provided by pace-mapping. Ablation was performed using a force sensing catheter with RF energy at 25-35W with a 17 ml/min flow rate. 30-60 second lesions were created with a target impedance drop of 10 Ohms and a temperature cut-off of 43 degrees Celsius.

Statistical analysis

Continuous data were expressed as mean +/- standard deviation and compared using Student's *t*-test, whilst categorical data were compared using either a Chi-square test or Fisher's exact test. Variables found to be predictors on univariate analysis with a p value of < 0.05 were entered into a binary logistic multivariate regression model to determine their predictive independence. Accuracy of the multivariate model was determined by the coefficient of determination (R^2- value) with a score closer to 1.0 indicating a superior model. Receiver operating characteristic (ROC) curve analysis was used to generate the best cut-off for the newly derived parameters. Accuracy of the model was calculated by the area under the curve (AUC). Newly derived models were compared to existing ECG-morphology algorithms using the Youden index (sensitivity + specificity – 100), where a perfect test scores 100, and a score <50 indicates limited diagnostic utility. A p value of < 0.05 was considered statistically significant throughout. Data were analysed using IBM SPSS Statistics 27.0 software (SPSS, Inc., IL, USA).

Results

Derivation Cohort Demographics

A total of forty consecutive patients were recruited to the derivation cohort. 23/40 (58%) had right ventricular outflow tract (RVOT) SOO and these patients were younger (42.8 ± 12.1 vs 56.1 ± 17.0, p = 0.006) and more likely to be female (73.9% vs 35.3%, p=0.024). Mean LV ejection fraction (LVEF) was also higher in the RVOT cohort (57.9 ± 5.0% versus 53.7 ± 7.0%, p = 0.031). There was no significant difference in co-morbidity prevalence or AAD usage between the two groups. In the RVOT cohort, 23/23 (100%) of VEs had a left bundle branch block (LBBB) morphology. In the left ventricular outflow tract (LVOT) cohort, the VE morphology was LBBB in 10/17 (58.8%), atypical right bundle branch block (RBBB) in 6/17 (35.3%) and indeterminate in 1/17 (5.9%). Full baseline characteristics are shown in Table 1. Precise locations of OTVAs are shown in supplemental data Table 1.

Ambulatory ECG analysis

VE variability was significantly higher in the RVOT cohort; mean CoV 1.09 ± 0.51 versus 0.42 ± 0.15 (p < 0.0001). The lowest number of VEs in a single hour was also significantly lower in the RVOT cohort, with any hourly total of < 50 VE observed in 22/23 (96%) of the RVOT cohort versus 1/17 (6%) of the LVOT cohort (p < 0.001). (Figure 1). Mean hourly combined VE was significantly lower in the RVOT cohort (253 ± 242) than the LVOT cohort (473 ± 191), p = 0.004. (Table 2).

Similarly, the total number of bigeminy or trigeminy episodes was significantly lower in the RVOT cohort (852 ± 855 versus 1572 ± 935, p = 0.02), but the hourly variability in this parameter was significantly higher in the RVOT cohort (CoV 1.72 ± 1.20 versus 0.69 ± 0.36, p = 0.001).

There was a wide range in total percentage VE burden (0.50 - 40.9%) but no significant difference between the RVOT and LVOT cohorts (16 ± 11.3% versus 24.2 ± 10.2% respectively, p = 0.3).

ROC curve analysis revealed that a CoV ≥ 0.7 predicted RVOT SOO with a sensitivity of 78% and a specificity of 94% (AUC 0.91, p < 0.0001), whilst any hour with < 50 VEs predicted a RVOT SOO with a

sensitivity of 96% and a specificity of 94% (AUC 0.96, $p < 0.0001$). (Figure 2). ROC curve analysis of other 24-hour Holter based parameters which were inferior to CoV ≥ 0.7 and any hour with < 50 VEs are shown in the supplementary data Figure 1. Subgroup analysis of only those with non-RBBB morphology VE (n = 34, 23 RVOT, 11 LVOT) revealed a similar mean CoV (1.09 ± 0.52 vs 0.46 ± 0.16 respectively). In the non-RBBB subgroup, sensitivity and specificity of the CoV ≥ 0.7 parameter to predict RVOT SOO was 78% and 91% respectively. Sensitivity and specificity of the < 50 VE parameter was 96% and 91% respectively.

Multivariate model

Multivariate regression models were generated for both of the novel parameters (CoV ≥ 0.7 and VE < 50) and included age, gender, LVEF, and VE burden. The two novel parameters were not included in the same model due to the risk of multicollinearity. The novel prediction parameters both remained significant in multivariate models. For CoV the R^2 value was 0.79 (SE 0.34) with both higher LVEF ($p=0.04$) and CoV ≥ 0.7 ($p=0.01$) predictors of a RVOT SOO. For VE < 50 in any hour, the R^2 value was 0.88 (SE 0.22) and < 50 VE was the only variate that significantly predicted a RVOT SOO ($p = 0.006$). The total VE burden did not emerge as an independent predictor of SOO.

Circadian variation

VE variability was significantly higher in the RVOT than the LVOT cohort in all quartiles of the day (supplementary data Table 2), however the mean difference was greatest in the 06:00-12:00 quartile; mean CoV RVOT vs LVOT 1.15 (± 0.55) vs 0.36 (± 0.15), mean difference 0.79, $p <0.0001$. Figure 3.

Validation Cohort Demographics

The two new parameters were tested prospectively on a validation cohort of twenty-nine consecutive patients (mean age 47.6 ± 18.8 years, 55.2% male), of whom 21/29 (72.4%) had a RVOT SOO. As was observed in the derivation cohort, those with a RVOT SOO were found to be of younger age (42.4 ± 16.6 versus 61.1 ± 19.9 years, p = 0.016) and to have a higher ejection fraction (55.1 ± 4.9 versus 45.9% ± 10.8, p = 0.047). There was no significant difference in co-morbidity prevalence or AAD usage. In those with a RVOT SOO, 21/21 (100%) had a LBBB VE. In the LVOT cohort, the VE morphology was LBBB in 6/8 (75.0%), atypical RBBB in 1/8 (12.5%) and indeterminate in 1/8 (12.5%). The full baseline characteristics of this cohort are shown in Table 3.

Prospective application of novel parameters to validation cohort

Using CoV ≥ 0.7, the SOO was correctly predicted in 23/29 (79.3%) of cases (sensitivity 81.0%, specificity 87.5%). Using VE < 50, the SOO was correctly predicted in 26/29 (89.7%) of cases (sensitivity 90.5%, specificity 87.5%). By comparison, the correct SOO was predicted in 24/29 (82.8%) of cases with both ECG algorithms: TZI (sensitivity 81.0%, specificity 87.5%) and V_2S/V_3R Index (sensitivity 90.5%, specificity 62.5%). Overall, VE < 50 had the highest Youden Index (78) and was the parameter that was most likely to both successfully predict a RVOT SOO (PPV = 95.0%) and correctly exclude a LVOT SOO (NPV = 77.8%). (Table 4)

Inter-Holter Reproducibility

Although a single Holter monitor per patient was used for derivation and validation of the novel parameters, 25/69 patients (36%) from both cohorts underwent multiple ambulatory ECGs prior to ablation. 44 supplemental Holter monitors (mean 1.8 per patient) were available to test reproducibility. When using the CoV ≥ 0.7 parameter, supplemental Holters agreed with the original prediction in 87.0%. When using the VE < 50 parameter, agreement with the original prediction was 91.3%.

Discussion

Right and left sided OTVA are often considered to be the same entity. They exhibit similar rates of inducibility during an electrophysiological study, have similar findings on magnetic resonance imaging and respond equally to both adenosine and verapamil, suggesting a common underling electrophysiological mechanism (cyclic adenosine monophosphate-mediated delayed afterdepolarisations) (8). Embryologically, the outflow tracts are also both formed from a common primitive heart tube, rather than having separate origins (8,9).

Adrenergic tone has been shown to be an important influence on all OTVA (10). Furthermore, whilst the autonomic nervous system (ANS) influences VE activity, the presence of modest burden ectopy has also been shown to alter the activity of cardiac neurons and VE-induced cardiomyopathy can be characterised by sympathetic hyperinnervation, which may exacerbate arrhythmogenesis (11,12). This suggests a bidirectional relationship between the ANS and VE.

Although these studies show mechanistic similarities between RVOT and LVOT, we have demonstrated that the behaviour of OTVA across a 24-hour period is dependent on SOO, which must imply a difference in the underlying mechanisms, or perhaps a difference in the autonomic influence on VE activity. We postulate that the differential balance between the parasympathetic and sympathetic innervation may be different in the two outflow tracts. This hypothesis is supported by canine models, where a higher density of sympathetic fibres, compared to parasympathetic fibres, has been identified in the RVOT (13). The density of these fibres is also particularly high at sites where VE and VT can be induced using high frequency electrical stimulation (14).

In human subjects, right-sided OTVA are known to be induced by periods of wakefulness and activity and are less pronounced during periods of sleep, further supporting a role for sympathetic hyperinnervation in the RVOT (13–15). Aortic root ganglionic plexi, in the region of the LVOT, have also been shown to have a higher relative density of parasympathetic (cholinergic) neurons compared to sympathetic (adrenergic) neurons (16).

Our data show that whilst the overall number of total VE as well as bigeminy/trigeminy episodes was higher in the LVOT group, the variability in both of these parameters was greater in the RVOT group, with wide fluctuations in VE activity throughout a 24-hour period and a greater probability of quiescent hours. This suggests that right-sided OTVA appears to be responsive to changes in sympathetic tone, whereas left-sided OTVA is less responsive to autonomic influences and has far more consistent activity throughout the day and night. This may also partially explain the predilection to LV systolic dysfunction that is more commonly observed in left-sided OTVA since there are no periods when the ventricle is given the opportunity to recover from the mechanically deleterious effects of frequent ectopy (4,17). The greater VE variability seen particularly in the morning hours (06:00-12:00) in the RVOT cohort occurs during a period of transition from sleep to wakefulness and a corresponding physiological surge in catecholamines that is seen during these hours (18) and contrasts with the more stable VE burden seen throughout the day in the LVOT cohort. This gives further evidence for a key role of the ANS in the behaviour of these arrhythmias.

Numerous morphological ECG algorithms have been developed to differentiate OTVA with right and left sided SOO. However, these are limited by the complex 3-dimensional anatomy of the outflow tracts (3,5,6), where subtle variations in ECG electrode positioning, cardiac rotation, or body habitus can all impact the QRS morphology of both sinus and ectopic beats (5,19,20). Parameters developed in an attempt to correct for cardiac rotation, such as TZI, correct for some but not all such limitations.

In this study we have devised and validated two novel non-morphological parameters for predicting SOO based on variations in ectopy activity over a 24-hour period. When applied prospectively both parameters are highly effective, with diagnostic accuracy comparing favourably to current ECG prediction parameters. The parameters remain highly predictive when those with RBBB morphology VE are excluded, confirming their utility in those with truly ambiguous SOO. Our parameters would not be impacted by cardiac rotation, chest wall shape or ECG electrode position. An example case is

displayed in Figure 4. In this case a 60 year old female has OTVA with a LBBB morphology in which the ECG parameters offer diverging opinions on the likely SOO; TZI predicting a left sided origin and V2S/V3R a right sided origin. In this example our novel parameters both predict that the SOO is right sided, which was confirmed on mapping. Since a 24-hour ECG monitor is nearly universal in the assessment of OTVAs, we find these two parameters to be particularly useful and easy to implement in clinical practice with a high degree of objectivity and reproducibility.

Limitations

This was a single centre study. Further validation of the prediction parameters by other centres would increase the robustness and clinical utility of these findings. The number of individuals included in the study is relatively low. However, this is comparable to similar studies using ECG-morphology based parameters.

In our cohort, the patients had relatively high mean ectopic burdens (16% for RVOT SOO, 24% for LVOT SOO). Consequently, we cannot be sure if these two parameters would work consistently in patients with significantly lower burdens of ectopy, as a low ectopic burden overall would be likely to increase the chance of any hour having < 50 VE. Nonetheless, it is encouraging that some patients in our cohort did have VE burdens as low as 0.5% and the prediction parameters were still diagnostic. Furthermore, despite there being a trend towards lower ectopic burdens in the RVOT cohort, which may bias towards having a single hour with < 50 VE, total VE burden was included in the multivariate model and was not found to be independently associated with SOO.

Finally, the patient population we used to derive these novel parameters had robust myocardial function with a mean LVEF of 53.7% and 57.9% for the RVOT and LVOT VE cohorts, respectively. In the setting of VE-induced cardiomyopathy with significant LV dysfunction, neuro-hormonal regulatory changes might alter the behaviour of the VEs, limiting the applicability of these parameters. This would require further assessment.

Conclusions

The behaviour of OTVA over a 24-hour period can be used to differentiate the site of origin, with a high degree of accuracy. In particular, the presence of any hour where VE < 50 is highly suggestive of a RVOT SOO. The predictive accuracy of these novel parameters compares favourably to current ECG algorithms and could be easily adopted in clinical practice.

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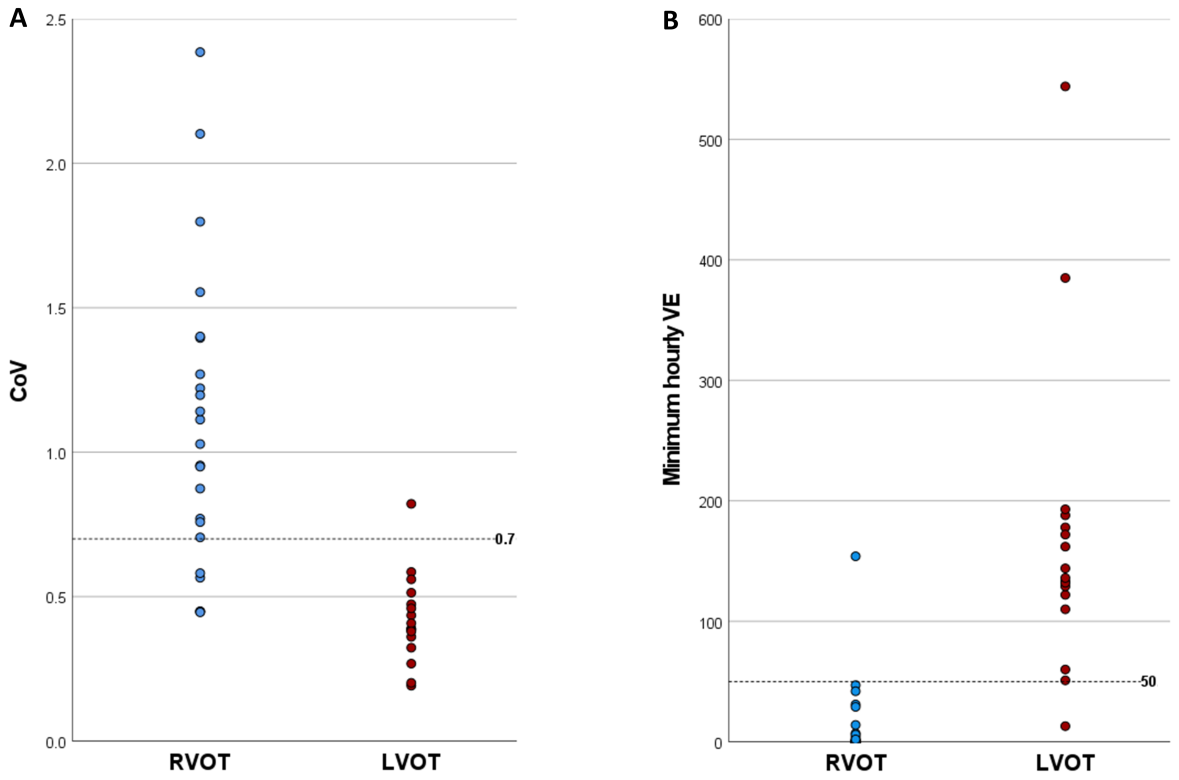


Figure 1: Scatterplot comparing CoV (A) and minimum hourly VE (B) of RVOT VE and LVOT VE.

Dotted line represents optimum cutoff to differentiate SOO based on ROC curve analysis.

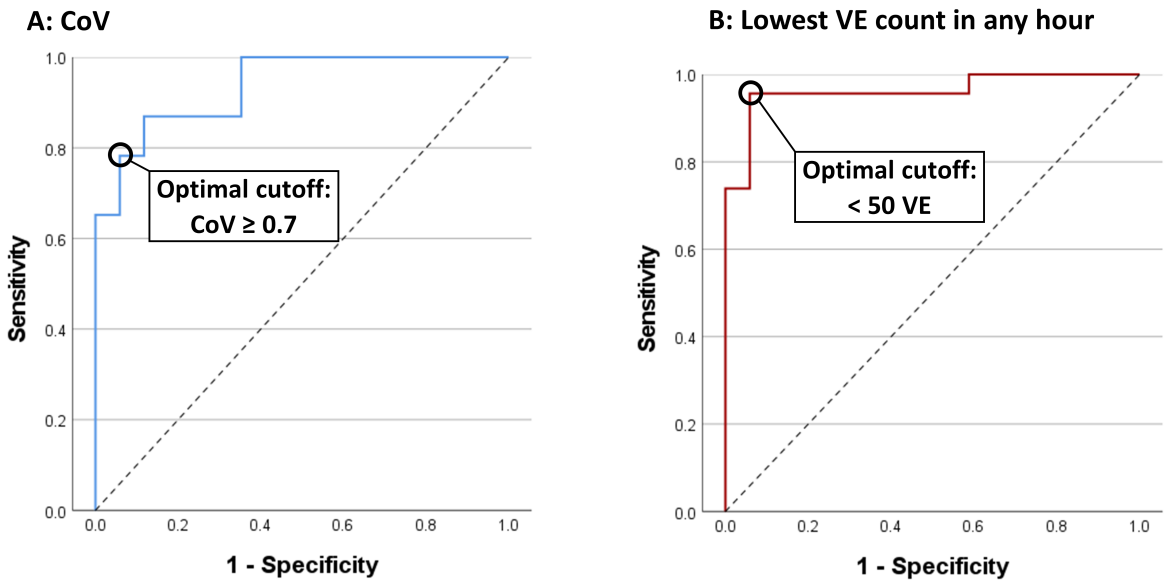


Figure 2: Receiver operating characteristic (ROC) curves demonstrating the predictive accuracy of two novel parameters of differentiating RVOT from LVOT SOO. A: CoV – the greater the CoV the more likely the SOO is RVOT. A cut-off value of ≥ 0.7 (black circle) had a sensitivity of 78% and a specificity of 94% for predicting RVOT SOO (AUC 0.91). B: Lowest VE count of any hour. A cut-off of < 50 VE (black circle) in any hour was predictive of RVOT SOO with a sensitivity of 96% and specificity of 94%, (AUC 0.96). Dotted line represents reference line of a random test with no diagnostic accuracy.

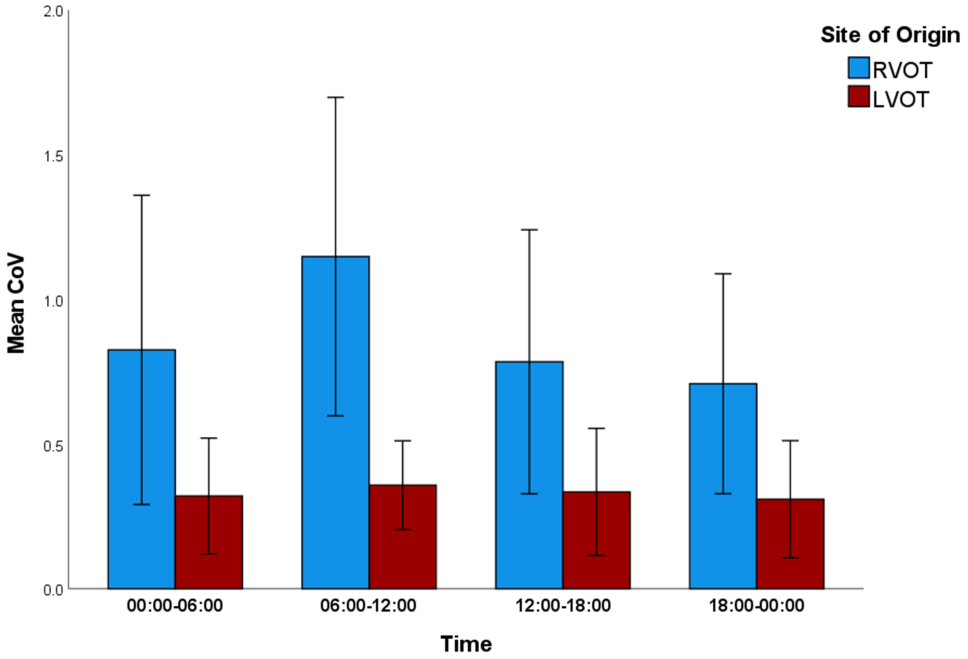
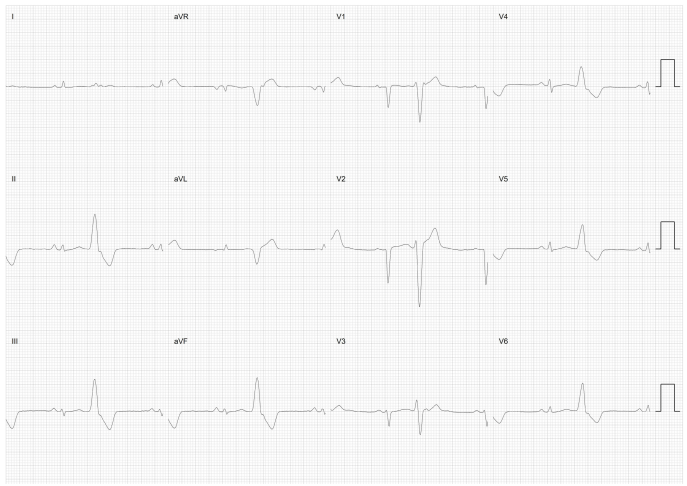


Figure 3: Bar chart comparing the **c**ircadian distribution of CoV between RVOT and LVOT cohorts. The 24 hour period is divided into quartiles. Mean CoV and standard deviations are shown. The greatest mean difference was seen between 06:00 and 12:00: RVOT vs LVOT 1.15 (± 0.55) vs 0.36 (± 0.15), mean difference 0.79, p <0.0001.



Hourly Trend Summary

Time	Pause	VT	R On T	Salvo	Triplet	Couplet	Bigeminy	Trigeminy	Brady	Prem VE	VE	VEscape	AF
Fri 09:47	0	0	0	0	0	0	0	0	0	3	0	0	0
Fri 10:00	0	0	0	0	0	0	0	1	0	26	0	0	0
Fri 11:00	0	0	0	0	0	0	0	46	0	259	0	0	0
Fri 12:00	0	0	0	0	0	0	29	65	0	422	5	0	0
Fri 13:00	0	0	0	0	0	1	25	64	0	436	9	0	0
Fri 14:00	0	0	0	0	0	0	102	60	0	420	1	0	0
Fri 15:00	0	0	0	0	0	0	129	49	0	477	4	1	0
Fri 16:00	0	0	0	0	0	0	101	84	0	445	6	2	0
Fri 17:00	0	0	0	0	0	0	64	49	0	457	38	1	0
Fri 18:00	0	0	0	0	0	0	72	71	0	341	5	0	0
Fri 19:00	0	0	0	0	0	0	81	99	0	310	4	0	0
Fri 20:00	0	0	0	0	0	0	129	77	0	196	2	0	0
Fri 21:00	0	0	0	0	0	0	49	61	0	161	8	11	0
Fri 22:00	0	0	0	0	0	0	5	31	0	57	1	0	0
Fri 23:00	0	0	0	0	0	0	0	14	0	59	0	0	0
Sat 00:00	0	0	0	0	0	0	0	0	0	0	0	0	0
Sat 01:00	0	0	0	0	0	0	0	0	0	22	0	0	0
Sat 02:00	0	0	0	0	0	1	0	0	0	104	0	0	0
Sat 03:00	0	0	0	0	0	0	0	0	0	22	0	0	0
Sat 04:00	0	0	0	0	0	0	0	0	0	17	0	0	0
Sat 05:00	0	0	0	0	0	0	0	0	0	37	0	0	0
Sat 06:00	0	0	0	0	0	1	0	0	0	75	0	0	0
Sat 07:00	0	0	0	0	0	0	0	40	0	260	18	8	0
Sat 08:00	0	0	0	0	0	0	0	2	0	113	1	0	0
Sat 09:00	0	0	0	0	0	0	0	0	0	10	0	0	0
Sat 09:44	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	3	786	813	0	4,729	102	23	0

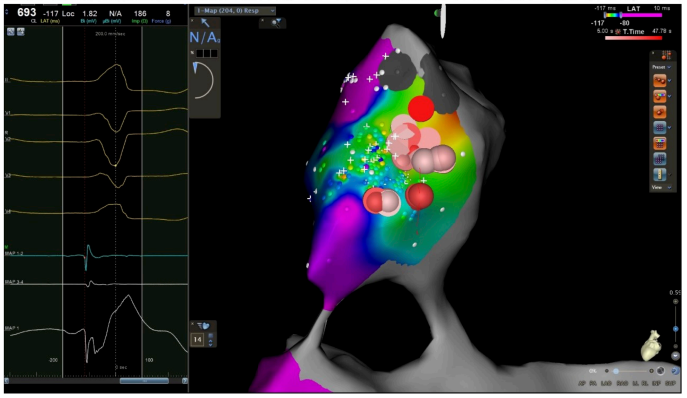


Figure 4: Example patient where ECG-morphology based criteria differed from each other. Novel 24-hour Holter parameters correctly predicted SOO. Above - Transition of the sinus beat (at V4) was earlier than ectopic transition (between V3 and V4): using TZI, an LVOT SOO would be expected. V_2S/V_3R Index gave a ratio of 5.2, predicting RVOT SOO. Middle - Analysis of her 24-hour Holter monitor revealed a CoV of 0.90 and the < 50 VE in any hour parameter was fulfilled (highlighted hour with zero VE), predicting RVOT SOO. Below – site of earliest activation mapped to postero-septal RVOT with favourable characteristics on unipolar electrogram.

Table 1. Baseline characteristics of the derivation cohort.

Variable	**Total (n = 40)**	**RVOT (n = 23)**	**LVOT (n = 17)**	**p-value**
Age	48.4 ± 15.7	42.8 ± 12.1	56.1 ±17.0	0.006
Female gender	23 (57.5%)	17 (73.9%)	6 (35.3%)	0.024
Ethnicity (Caucasian)	22/32 (68.8%)	16/22 (72.7%)	6/10 (60.0%)	NS
Hypertension	9 (22.5%)	5 (21.7%)	4 (23.5%)	NS
Diabetes	3 (7.5%)	1 (4.3%)	2 (11.8%)	NS
Coronary artery disease	5 (12.5%)	3 (13.0%)	2 (11.8%)	NS
BMI	27.8 ± 5.8	27.1 ± 5.6	29.0 ± 5.6	NS
LVEF %	56.1 ± 6.2	57.9 ± 5.0	53.7 ± 7.0	0.032
QRS morphology				
LBBB	33 (82.5%)	23 (100%)	10 (58.8%)	0.004
Indeterminate	1 (2.5%)	0 (0%)	1 (5.9%)	NS
Atypical RBBB	6 (15.0%)	0 (0%)	6 (35.3%)	0.009
AAD use	32 (80.0%)	18 (78.3%)	14 (82.4%)	NS
Beta-blocker	25 (62.5%)	15 (65.2%)	10 (58.8%)	NS
CCB	7 (17.5%)	5 (27.7%)	2 (11.8%)	NS
Flecainide	3 (7.5%)	1 (4.3%)	2 (11.8%)	NS
Amiodarone	1 (2.5%)	0 (0%)	1 (5.9%)	NS

AAD = anti-arrhythmic drug; BMI = body mass index; CCB = calcium channel blocker; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; RBBB = right bundle branch block; RVOT = right ventricular outflow tract.

Table 2: Comparison of 24-hour Holter monitor parameters between RVOT and LVOT VE cohorts.

Variable	**RVOT (n = 23)**	**LVOT (n = 17)**	**p-value**
Ectopic variability (CoV)	1.09 (± 0.51)	0.42 (± 0.15)	<0.0001
Presence of any hour with < 50 VE	22 (96%)	1 (6%)	<0.0001
Mean hourly combined VE	253 ± 242	473 ± 191	0.004
Total VE burden (%)	16.0 ± 11.3	24.2 ± 10.2	NS
Mean heart rate	74.6 ± 6.7	73.1 ± 6.0	NS
Total number of combined bigeminy/trigeminy episodes	852 ± 855	1572 ± 935	0.02
Combined bigeminy/trigeminy CoV	1.72 ± 1.20	0.69 ± 0.36	0.001
Presence of sustained VT	0 (0%)	1 (6%)	NS

CoV = coefficient of variation; LVOT = left ventricular outflow tract; RVOT = right ventricular outflow tract; VE = ventricular ectopy; VT = ventricular tachycardia.

Table 3: Baseline characteristics of the validation cohort.

Variable	**Total (n = 29)**	**RVOT (n = 21)**	**LVOT (n = 8)**	**p-value**
Age	47.6 ± 18.8	42.4 ± 16.6	61.1 ± 19.9	0.016
Male gender	16 (55.2%)	10 (47.6%)	6 (75.0%)	NS
Ethnicity (Caucasian)	19/24 (79.2%)	13/17 (76.5%)	6/7 (85.7%)	NS
Hypertension	5 (17.2%)	2 (9.5%)	3 (37.5%)	NS
Diabetes	0 (0%)	0 (0%)	0 (0%)	NS
Coronary disease	2 (6.9%)	1 (4.8%)	1 (12.5%)	NS
BMI	26.9 ± 4.8	25.4 ± 4.8	28.1 ± 6.0	NS
LVEF %	54.7 ± 4.8	55.1 ± 4.9	45.9 ± 10.8	0.047
QRS morphology				
LBBB	27 (93.1%)	21 (100%)	6 (75.0%)	NS
Indeterminate	1 (3.4%)	0 (0%)	1 (12.5%)	NS
Atypical RBBB	1 (3.4%)	0 (0%)	1 (12.5%)	NS
AAD	20 (69.0%)	13 (61.9%)	7 (87.5%)	NS
Beta-blocker	18 (62.1%)	11 (52.4%)	7 (88.5%)	NS
CCB	1 (3.4%)	1 (4.8%)	0 (0%)	NS
Flecainide	2 (6.9%)	1 (4.8%)	1 (12.5%)	NS
Total VE burden	19.8%	18.6%	22.9%	NS

AAD = anti-arrhythmic drug; BMI = body mass index; CCB = calcium channel blocker; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; RBBB = right bundle branch block; RVOT = right ventricular outflow tract.

Table 4: The value of ambulatory ECG based parameters in predicting a right-sided site of origin of outflow tract arrhythmia compared with established ECG-morphology algorithms.

Method	Sensitivity	Specificity	Youden Index	PPV	NPV
CoV ≥ 0.7	81	88	69	94%	64%
VE < 50	90	88	78	95%	78%
TZI > 0	81	88	69	94%	64%
$V_2S/V_3R > 1.5$	90	63	53	86%	71%

Youden Index = sensitivity + specificity – 100, PPV = positive predictive value (predicting a right sided origin), NPV = negative predictive value (excluding a left sided origin), CoV = coefficient of variation, VE = ventricular ectopic, VE < 50 refers to the presence of a single hour with less than 50 VEs on a 24-hour monitor, TZI = transitional zone index.