Isolated very low QRS voltage in the frontal leads predicts recurrence of neurally mediated syncope

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BACKGROUND The study was prompted by our observation that some patients with neurally mediated syncope (NMS) have an isolated QRS complex of very low voltage (≤0.3 mV cutoff), in 1 of the frontal leads on the 12-lead electrocardiogram.

OBJECTIVE To prospectively evaluate whether the presence of isolated very low voltage (VLV) predicts recurrence of NMS.

METHODS We included 205 patients (aged 50 ± 17 years) with a median of 3 syncopal episodes. Tilt testing was performed in all patients and was positive in 87 (42%). The patients were followed for a median of 14 months.

RESULTS VLV in frontal leads was present in 92 patients (45%). During the follow-up period 60 patients experienced recurrence of syncope. The actuarial total syncope recurrence rate at 1 year was 32% (95% confidence interval [CI] 23%–44%) in patients with isolated VLV in frontal plane leads, and 14% (95% CI 8%–24%) in patients without VLV (log-rank test \( P < .0001 \)). The significant relationship between the presence of isolated VLV in the frontal leads and syncope recurrence was retained in Cox multivariate analysis that included the history of presyncope and syncope as well as the left ventricular end-diastolic diameter. The presence of isolated VLV in frontal leads was associated with a 3-fold increase of the risk of recurrent syncope.

CONCLUSIONS Isolated very low QRS voltage in the frontal leads predicts recurrence of NMS independent of clinical factors that predict recurrence of syncope in such patients. This phenomenon may help generate new diagnostic tools and insights into the pathogenesis of NMS.

KEYWORDS Electrocardiogram; Neurally mediated syncope; QRS complex voltage; Syncope recurrence; Very low voltage

Methods

We included in this study 205 consecutive patients (aged 49 ± 20 years; 103 women) with suspected NMS and who all had a TTT as part of their diagnostic evaluation. Syncope was defined as a transient, self-limited loss of consciousness, with rapid onset and subsequent spontaneous recovery. Presyncope was defined as a condition in which patients felt impending syncope but did not have a transient loss of consciousness. In line with the current Heart Rhythm Society and European Society of Cardiology guidelines, NMS was diagnosed when the clinical features were suggestive of a reflex mechanism and competitive diagnoses could be excluded. We excluded patients with history of myocardial infarction, overt heart failure, left ventricular (LV) ejection fraction <40%, hypertrophic...
cardiomyopathy, dilated cardiomyopathy, significant valvular heart disease, evidence of sinus node dysfunction, second- or third-degree atrioventricular block, supraventricular or ventricu-
lar tachycardia, ventricular preexcitation, prolonged QT interval, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, symptomatic orthostatic hypotension, hyper-
sensitive carotid sinus syndrome, nonsyncopal loss of con-
sciousness, and subclavian steal syndrome.

Tilt table tests
All TTTs were part of the initial syncope workup and were per-
formed at the Cardiac Arrhythmia Service at Massachusetts General Hospital. Before the TTT test, all patients completed informed consent documents and fasted for at least 8 hours. A positive response was defined as either sudden loss of con-
sciousness or the development of presyncope occurring in as-
sociation with an abrupt decrease in systolic blood pressure to 80 mm Hg, and reproduction of clinical symptoms. If there was no positive response within 30 minutes, the patient was returned to the supine position and an isoproterenol infusion of 1 mg/min was started and was increased over 5 minutes to induce a 20% increment in the supine resting heart rate (maximum infusion, 5 mg/5 min). If a positive response occurred, the patient was returned to the supine position and the protocol was terminated. The response to TTT was re-
ported using the modi-
fi
ed VASIS (Vasovagal Syncope Inter-
national Study) classification, which consists of type 1 (mixed), type 2A (cardioinhibitory without >3 s of asystole), type 2B (cardioinhibitory with >3 s of asystole), or type 3 (vasodepressive). The study was approved by Massachusetts General Hospital Institutional Review Board.

Twelve-lead ECGs
The QRS voltage was measured in mm (1 mm = 0.1 mV) in each of the 12 leads of a resting ECG performed within 3 days from the TTT. All measurements were made with the use of digital calipers at 200% magnification calibrated for paper speed of 25 mm/s. ECGs were reviewed by the same investigator (D.B.) in a blinded fashion. After the completion of the study we tested intraobserver variability for the QRS amplitude measurements on a random sample of 20 tracings. There were 2 readings for each tracing. To minimize potential learning effects, readings were separated by 4 weeks and the results of the first review were not available at the second reading. Intraobserver variability was assessed as the difference between the 2 measurements expressed as a percentage of their mean averaged for the 20 tracings. The intraobserver variabilities for QRS voltage measurements in leads 1, 2, 3, aVR, aVL, and aVF were 4.7%, 2.9%, 4.9%, 3.4%, 4.6%, and 5.1%, respectively. The lowest QRS voltage (QRSmin) and highest QRS voltage (QRSmax) in the frontal and precordial leads were calculated. The ability of different QRSmin cutoffs to discriminate between patients who did and those who did not have syncope recurrence was evaluated by analyzing the area under receiver operating characteristic curves of sensitivity plotted vs 1 – specificity (Figure 2). The cutoff of 0.295 mV showed optimal discriminative power in our patient population: sensitivity 70.34% and speci-
fi
city 70.00%; area under the curve = 0.729. Therefore, for statistical analysis purposes the variable was dichotomized at 0.3 mV vs >0.3 mV. The sums of QRS voltages in the frontal leads and precordial leads were also determined.

Echocardiograms
All patients had comprehensive resting 2-dimensional and Doppler echocardiography imaging performed within 6 months from the TTT. The echocardiographic studies were performed according to the standards recommended by the American Society of Echocardiography. Standard diagnostic echocardiographic examinations were performed,
including measurement of the LV systolic and diastolic dimensions and LV ejection fraction.

**Follow-up**

We followed all our patients. Each was seen every 3–6 months in the Arrhythmia Clinic. The patients were followed for a median of 14 months (range 3–70 months).

**Statistical analysis**

Continuous variables, unless otherwise stated, were expressed as mean ± standard deviation or median (25th–75th percentile) as appropriate. Continuous variables were compared using unpaired Student t test or the Wilcoxon rank sum test as appropriate. Shapiro-Wilk test was used to check for normality of distribution. Categorical variables were compared with the Pearson χ² test, or Fisher exact test in case of expected frequencies <5. Survival was plotted by the Kaplan-Meier method, and comparisons were made with the log-rank test. Multivariate relative risks (RR) and 95% confidence intervals (CI) were estimated using Cox proportional hazard models. All tests were 2-sided, and a probability value of <.05 was considered significant. Statistical analysis was performed using the STATA version 14.2 statistical package (Stata, College Station, TX).

**Results**

We included 205 patients (aged 50 ± 17 years), with a median of 3 syncopal episodes (interquartile range 1–4), 167 (81%) with and 38 (19%) without prodromes. Tilt testing was performed in all patients and was positive in 87 (42%): 27 (31%) had a type I (mixed) response, 12 (14%) had a type 2 (cardioinhibitory) response, and 48 (55%) had a type 3 (vasodepressor) response.

The median follow-up period for the entire study population was 14 months (range 3–70 months). During the follow-up period 60 patients experienced recurrence of syncope. The actuarial total syncope recurrence rate was 22% (95% CI, 16%–29%) at 1 year and 38% (95% CI, 30%–48%) at 2 years. Clinical characteristics of patients with and without recurrence of syncope are presented in Table 1. Patients with syncope recurrence had a higher prevalence of history of pre-syncope, a significantly higher percentage of positive TTT, and smaller LV end-diastolic and end-systolic dimensions.

In regard to the electrocardiographic parameters, VLV in frontal leads was present in 92 patients (45%). The lead that displayed the low voltage was aVL in most patients with VLV (55%). Other leads that displayed VLV were aVF (14%), lead I (14%), lead III (12%), lead II (4%), and aVR (1%).

The QRSmin and QRS voltage sum were significantly lower and the prevalence of isolated VLV in frontal plane leads was significantly higher in patients with syncope recurrence when compared with patients without recurrence of syncope (Table 2).

VASIS type 1 (mixed response) and type 3 (vasodepressor) responses to TTT were significantly more frequent in patients with VLV when compared to patients without VLV in frontal leads. Twenty patients with VLV (22%) vs 7 patients without VLV (6%) had VASIS type 1 (P = .001), and 38 patients with VLV (41%) vs 10 patients without VLV (9%) had VASIS response type 3 (P < .001). No significant differences between patients with VLV and without VLV were found for the VASIS response type 2 (cardioinhibitory).

The actuarial total syncope recurrence rates at 1 year and 2 years were 32% (95% CI 23%–44%) and 59% (95% CI 46%–73%), respectively, in patients with VLV in frontal plane leads, while in patients without VLV in frontal plane the corresponding recurrence rates were lower: 14% (95%
CI 8%–24%) at 1 year and 21% (95% CI 13%–24%) at 2 years. By log-rank test, patients with isolated VLV in frontal leads demonstrated significantly higher recurrence of syncope than those without isolated VLV (Figure 3).

To determine if the presence of isolated VLV in the frontal leads was an independent marker of survival, we performed multivariate analysis using Cox proportional hazards models (Table 3). This analysis determined that the presence of isolated VLV in frontal leads predicted increased syncope recurrence independent of the history of presyncope and the LV end-diastolic diameter during the follow-up period. History of >3 syncopal episodes did demonstrate predictive value for recurrent syncope in univariate Cox regression analysis. The same variable maintained predictive value (RR = 1.8, 95% CI 1.02–3.18, P value = .040) in a bivariate model that also included history of presyncope and syncope (RR = 2.51, 95% CI 1.25–5.05, P value = .009). However, history of >3 syncopal episodes did not retain independent predictive value when included in multivariate models together with VLV in frontal plane.

### Discussion

This study revealed that isolated very low QRS voltage in the frontal leads predicts recurrence of NMS independent of clinical factors that predict recurrence of syncope in such patients. The presence of isolated VLV in frontal leads was associated with a 3-fold increase of the risk of recurrent syncope independent of the predictive value of other clinical variables. The VLV occurred in a limited number of frontal plane leads, while the majority of the leads displayed voltage in normal range, although slightly lower in the group with syncope recurrence when compared with the group with no recurrence.

The mechanism responsible for the isolated low QRS voltage, which occurs in a frontal plane lead approximately perpendicular to the QRS axis, is not known.

Low QRS voltage is usually caused by conditions that either impair voltage generation or alter voltage transmission from the myocardium to the skin electrodes. This applies, however, to cases that fulfill the classical definition of low voltage. In our study we found reductions in voltage, which do not fulfill these classical criteria because the low voltage was not present in all leads. Low voltage on the surface ECG is classically defined as peak-to-peak QRS voltage of less than 5 mm (0.5 mV) in all frontal leads and less than 10 mm (1 mV) in all precordial leads.

Reduction in QRS voltage may be noted only in the limb leads and not in the precordial leads.

Reduction of QRS voltage, which may or may not fulfill criteria for low voltage, can follow reductions in intracardiac...
volumes (e.g., in association with hemorrhage or hypovolemia) via the Brody effect. According to Brody’s theory, any change in intracavitary blood mass resistivity should affect cardiac forces’ transmission to the body surface. The Brody effect accentuates the contributions of dipoles that are situated within the myocardium near the endocardium and oriented perpendicular to the local surface (endocardium). There are data, however, correlating changes in QRS voltage to changes in the intravascular and intracardiac volume. Changes in the intravascular and intracardiac volume have been involved in the etiopathogenesis of NMS.

Possible mechanism for isolated reduction in voltage

The isolated low-amplitude QRS complexes found in our study in patients with NMS do not fit the typical low-voltage criteria because they were not present in all frontal leads. There is no clear explanation for this finding. The isolated low-voltage QRS complexes present in some frontal leads do not seem to be occurring in the setting of a decrease in transmission of voltage from the heart to the surface ECG electrodes, as might be seen in emphysema or obesity, which usually produce low voltage in all leads.

There are findings in our study that could help in formulating a mechanistic hypothesis. The lead with lowest voltage was found to be nearly perpendicular to the QRS axis in all patients. It is possible that cancellation of forces in a direction that is perpendicular to the QRS axis might result in low voltage in some frontal plane leads and not others. Opposing LV walls may be in closer proximity in patients with NMS because of ventricular underfilling and the smaller ventricular dimensions found in this syndrome, and this could result in greater cancellation of forces along an axis that is perpendicular to the long axis of the ventricle (Figure 4). The ECG recorded from the surface of the body represents the net uncancelled potential difference between pairs of electrodes.

It has been estimated that during ventricular activation cancellation disposes of 66%–90% of the electrical information in the frontal plane leads. The ECG is the result of electrical forces that are the residuals of cancellation. Increased cancellation and the resulting reduction in voltage in leads that are perpendicular to the long axis of the ventricle may be related to the specific ventricular geometry seen in patients with NMS.

Table 2 Electrocardiographic parameters in patients with and without syncope recurrence

<table>
<thead>
<tr>
<th>ECG parameters</th>
<th>With recurrence of syncope N = 60</th>
<th>Without recurrence of syncope N = 145</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS lead 1 (mV)</td>
<td>0.70 ± 0.34</td>
<td>0.78 ± 0.32</td>
<td>.110</td>
</tr>
<tr>
<td>QRS lead 2 (mV)</td>
<td>1.12 ± 0.53</td>
<td>1.26 ± 0.54</td>
<td>.152</td>
</tr>
<tr>
<td>QRS lead 3 (mV)</td>
<td>0.74 ± 0.51</td>
<td>0.87 ± 0.47</td>
<td>.082</td>
</tr>
<tr>
<td>QRS lead aVR (mV)</td>
<td>0.92 ± 0.36</td>
<td>0.97 ± 0.34</td>
<td>.341</td>
</tr>
<tr>
<td>QRS lead aVL (mV)</td>
<td>0.45 ± 0.34</td>
<td>0.55 ± 0.31</td>
<td>.041</td>
</tr>
<tr>
<td>QRS lead aVF (mV)</td>
<td>0.86 ± 0.56</td>
<td>0.96 ± 0.50</td>
<td>.207</td>
</tr>
<tr>
<td>QRSmin frontal leads (mV)</td>
<td>0.28 ± 0.16</td>
<td>0.40 ± 0.17</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>QRSmax frontal leads (mV)</td>
<td>1.21 ± 0.53</td>
<td>1.32 ± 0.49</td>
<td>.137</td>
</tr>
<tr>
<td>Very low voltage (&lt;0.3 mV) in frontal leads</td>
<td>43 (72%)</td>
<td>49 (34%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Frontal leads QRS voltage sum (mV)</td>
<td>4.79 ± 2.04</td>
<td>5.37 ± 1.79</td>
<td>.044</td>
</tr>
<tr>
<td>QRS lead V1 (mV)</td>
<td>0.93 ± 0.42</td>
<td>1.06 ± 0.44</td>
<td>.055</td>
</tr>
<tr>
<td>QRS lead V2 (mV)</td>
<td>1.23 ± 0.69</td>
<td>1.39 ± 0.62</td>
<td>.180</td>
</tr>
<tr>
<td>QRS lead V3 (mV)</td>
<td>1.27 ± 0.73</td>
<td>1.42 ± 0.65</td>
<td>.142</td>
</tr>
<tr>
<td>QRS lead V4 (mV)</td>
<td>1.39 ± 0.61</td>
<td>1.51 ± 0.64</td>
<td>.217</td>
</tr>
<tr>
<td>QRS lead V5 (mV)</td>
<td>1.29 ± 0.50</td>
<td>1.36 ± 0.55</td>
<td>.418</td>
</tr>
<tr>
<td>QRS lead V6 (mV)</td>
<td>1.13 ± 0.41</td>
<td>1.16 ± 0.44</td>
<td>.693</td>
</tr>
<tr>
<td>QRS min precordial (mV)</td>
<td>0.76 ± 0.33</td>
<td>0.81 ± 0.31</td>
<td>.280</td>
</tr>
<tr>
<td>QRS max precordial (mV)</td>
<td>1.68 ± 0.71</td>
<td>1.83 ± 0.65</td>
<td>.131</td>
</tr>
<tr>
<td>Presence of very low voltage (&lt;0.3 mV) in the precordial leads</td>
<td>4 (7%)</td>
<td>4 (3%)</td>
<td>.236</td>
</tr>
<tr>
<td>Precordial lead QRS voltage sum (mV)</td>
<td>7.28 ± 2.78</td>
<td>7.91 ± 2.49</td>
<td>.113</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>85 ± 13</td>
<td>91 ± 16</td>
<td>.011</td>
</tr>
</tbody>
</table>

ECG = electrocardiogram.

Figure 3 Kaplan-Meier survival curves of cumulative syncope-free survival according to the presence of very low voltage (VLV) in frontal plane leads.
Other predictors of syncope recurrence
The results of the present study showed that patients with a higher burden of syncope are more likely to have recurrent NMS. The number of syncopal episodes as well as the presence of presyncope in addition to syncope predicted NMS recurrence in univariate analysis. The presence of presyncope in addition to syncope (≥1 episode of syncope and ≥1 episode of presyncope) maintained its predictive value in multivariate analysis as well. This finding is consistent with previous findings in the literature. Grimm and colleagues\textsuperscript{23} showed that recurrent NMS was more frequent in patients with lifetime syncope burden of ≥2 episodes when compared with history of 1 syncopal episode alone. Sheldon and colleagues\textsuperscript{24} demonstrated that the most powerful predictor of

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (0.99-1.01)</td>
<td>.942</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.80 (0.48-1.34)</td>
<td>.407</td>
</tr>
<tr>
<td>Positive TTT</td>
<td>2.11 (1.26-3.55)</td>
<td>.005</td>
</tr>
<tr>
<td>Type 1 mixed response</td>
<td>2.07 (1.14-3.78)</td>
<td>.017</td>
</tr>
<tr>
<td>Type 2A or 2B cardioinhibitory</td>
<td>0.37 (0.05-2.69)</td>
<td>.328</td>
</tr>
<tr>
<td>Type 3 pure vasodepressor</td>
<td>2.13 (1.26-3.59)</td>
<td>.004</td>
</tr>
<tr>
<td>QRSmin frontal leads</td>
<td>0.65 (0.53-0.80)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Presence of isolated very low voltage frontal leads ≤0.3 mV</td>
<td>4.22 (2.39-7.44)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>History of presyncope and syncope</td>
<td>2.85 (1.29-6.27)</td>
<td>.009</td>
</tr>
<tr>
<td>No. syncopal episodes</td>
<td>1.03 (0.99-1.08)</td>
<td>.117</td>
</tr>
<tr>
<td>History of &gt;3 syncopes</td>
<td>2.67 (1.60-4.47)</td>
<td>.001</td>
</tr>
<tr>
<td>LVEDD</td>
<td>0.91 (0.87-0.96)</td>
<td>.001</td>
</tr>
<tr>
<td>LVESD</td>
<td>0.93 (0.88-0.98)</td>
<td>.016</td>
</tr>
</tbody>
</table>

CI = confidence interval; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; RR = relative risk.

Figure 4 Possible mechanism for the isolated very low QRS voltage (VLV) in frontal plane leads. In this case of a patient with neurally mediated syncope and small left ventricular (LV) cavity, an isolated VLV is present in lead aVL (A). It is possible that the small LV cavity brings opposite LV walls in closer proximity, leading to more cancellation of electrical forces along a direction that is close to parallel to lead aVL and perpendicular to the long axis of the ventricle. This leads to a depolarization vector that has at all times an orientation close to parallel to the long axis of the left ventricle (B: Vectorcardiogram with a very flat QRS loop) and to cancellation of the component perpendicular to the long axis and leads to isolated very low voltage in aVL (C: Frontal plane section of the LV on computer tomography scan).
recurrence of vasovagal syncope in patients with positive TTT was the logarithm of the number of preceding syncopal spells. Baron-Esquivias and colleagues revealed a higher recurrence rate of syncope in patients with ≥5 previous episodes of syncope when compared with patients with <5 previous episodes of syncope.

Another finding in our study was the predictive value for the end-diastolic LV dimension associated with recurrent NMS. Smaller LV dimensions were previously shown to play a role in the pathogenesis of NMS. Reduced LV volume during initial upright TTT was associated with a subsequent positive tilt response in patients with unexplained syncope.

**Tilt table testing**

VASIS type 1 and type 3 TTT response predicted syncope recurrence in univariate analysis. However, none of these variables maintained their predictive value for syncope recurrence in multivariate Cox models. Our results are in agreement with previous studies indicating that TTT has a low predictive value for syncope recurrence.

The rate of positive TTT results for our protocol using isoprenaline was 42%. This value is significantly lower than the rate of positive TTT of the “Italian protocol,” which uses nitroglycerin. TTT protocols using isoprenaline were previously shown to have a lower rate of positive tests than the protocols that use nitroglycerin.

In the study by Graham and colleagues on patients with unknown syncope, the rates of positive tilt tests were 52% for isoprenaline TTT and 68% for the TTT using nitroglycerin.

**Limitations**

There is no gold standard for the diagnosis of NMS. The diagnosis was predominantly clinical, based on European Society of Cardiology criteria. We cannot exclude the inclusion of patients with an underlying cause of syncope other than neurally mediated. However, the clinical presentation was characteristic of NMS, with a low probability of including syncope patients with other etiologies. A majority of the patients included into this study were referred by primary care physicians and general cardiologists, which may cause a patient selection bias. Our study population was relatively small. However, despite this limitation, the differences between groups of patients were sizeable and statistically significant. The beat-to-beat blood pressure, parameters of peripheral resistance, and stroke volume, which could have possibly given more insight into the pathogenesis of the VLV, were not recorded at the time of the TTT.

**Conclusion**

Isolated very low QRS voltage in the frontal leads predicts recurrence of NMS independent of clinical factors that predict recurrence of syncope in such patients. This phenomenon, possibly reflecting abnormalities in the ventricular geometry and electrical activation, may help generate new prognostic tools and insights into the pathogenesis of NMS.

**References**

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