JACC: ADVANCES VOL. 2, NO. 2, 2023

EDITORIAL COMMENT

Spatial Ventricular Gradient

A Measure of Global Electrical Heterogeneity*

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In 1934, Wilson et al[1] conducted careful experiments on dogs' hearts, aiming to test the theory that the time integral of electrocardiographic (ECG) potential was zero for different conduction paths. To their surprise, they observed that the algebraic sum of QRS and T areas on ECG deviates from zero by a constant residue value for various conduction paths. They called the residue *ventricular gradient* (VG), although, in a strictly mathematical sense, VG is not truly a gradient. Soon after, numerous limitations of a single frontal plane ECG became apparent and widely recognized, and the ECG field adopted a 3-dimensional (3D) representation of heart vector-vectorcardiogram. In 1954, several groups (Burch et al[2] and Simonson et al[3]) introduced the notion of *spatial ventricular gradient* (SVG) as a 3D vector. In 1957 Burger published a mathematical proof that demonstrated the SVG is theoretically independent of the initial site of stimulation and points toward the area of the myocardium with the shortest duration of the excited state.[4] Comprehensive theoretical studies showed that SVG depends on the action potential area, shape, and duration heterogeneity.[5] The theoretical basis of the SVG was verified experimentally in 1959.[6] Independence of the SVG from the myocardial activation sequence was later reaffirmed in other studies.[7-11] Notably, all fundamental studies of SVG emphasized the importance of SVG's vectorial properties. As a 3D vector, SVG is characterized by its direction in 3D space (azimuth and elevation), and magnitude. The SVG is the main component of the comprehensive *global electrical heterogeneity* phenotype, which also includes the SVG's scalar value (sum absolute QRST integral) and spatial QRS-T angle.[12-14]

In this issue of *JACC: Advances*, Rosas Diaz et al[15] for the first time reported an association between SVG magnitude and risk of anthracycline cardiotoxicity. The authors conducted large retrospective cohort study of patients treated with anthracyclines. Baseline ECG was recorded within 6 months prior to the first dose of chemotherapy. All patients underwent careful follow-up with echocardiogram performed within 12 months after the first anthracycline dose, and the primary outcome of incident heart failure/cardiomyopathy was well justified. The authors should be praised for careful statistical analysis, which included comprehensive adjustment for cardiovascular risk factors and cumulative anthracycline dose, assessment of competing risk of death from any cause, and several sensitivity analyses. Notably, SVG measurements included an important step of detection of the origin of the heart vector, as first described by Perez-Alday et al.[16] The findings of Rosas Diaz et al[15] are clinically important. In competing risk analysis, a larger SVG magnitude was robustly associated with reduced risk of incident heart failure/cardiomyopathy. The direction of SVG magnitude association with the cardiovascular outcome is consistent with previous studies of SVG.[14] The authors very well outlined the potential future applications of SVG use in cardio-oncology as a pretreatment cardiac risk stratification tool in patients with cancer. Obviously, future prospective randomized controlled trials have to demonstrate the benefits of risk stratification based on SVG metrics before the SVG can be recommended for wide implementation into clinical practice.

One particular limitation of the study deserves special comment. In addition to the SVG magnitude, Rosas Diaz et al[15] reported 3 planar, 2-dimensional components of the SVG: ventricular gradients on X, Y, and Z orthogonal ECG lead. The authors attempted to interpret the magnitude of a

*Editorials published in *JACC: Advances* reflect the views of the authors and do not necessarily represent the views of *JACC: Advances* or the American College of Cardiology.

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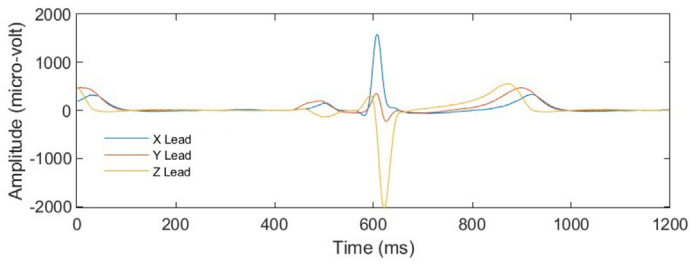
ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2023.100270

FIGURE 1 Orthogonal ECG X, Y, and Z Leads in Time-Coherent Median Beat



Representative examples of X (blue), Y (red), and Z (yellow) waveforms in a time-coherent median normal sinus cardiac beat. Open code software algorithms for time-coherent median beat construction and spatial ventricular gradient measurements are provided at https://github.com/Tereshchenkolab/Origin and https://github.com/Tereshchenkolab/Global-Electrical-Heterogeneity.

VG on one of the orthogonal leads (X, Y, and Z) as a proxy for the direction of SVG. **Figure 1** illustrates the issue with such an approach. Note that the areas under the QRST waveform above the baseline (zero voltage value) carry positive values, and areas below the baseline carry negative values. To calculate the VG on leads X, Y, and Z, positive and negative areas under the QRST waveform are summed. Overall, the VG magnitude on any single orthogonal XYZ ECG lead reflects the amount of electrical heterogeneity in that particular lead (X, Y, or Z). However, considering electrical heterogeneity on only 1 lead, independently, one by one (as was done by the authors in this study) ignores the degree of heterogeneity on 2 other orthogonal leads and complicates the interpretation of the individual XYZ lead VG findings. The magnitude of VG on any given single orthogonal lead (X, Y, or Z) only indirectly reflects the direction of the SVG vector. Unfortunately, the authors missed an opportunity to report the SVG vector direction (azimuth and elevation). For consistency of the research on SVG, it is essential to uniformly report the SVG magnitude, azimuth, and elevation to accumulate the required data for its future implementation into clinical practice.

In summary, the study by Rosas Diaz et al[15] provided critical new data supporting the importance of vectorcardiographic measurements. Notably SVG measurements are reproducible not only in sinus rhythm but also in atrial fibrillation and ventricular pacing, as demonstrated in a large prospective study.[17] Future randomized controlled trials are needed to test risk stratification of cardiotoxicity in the cardio-oncology field using SVG biomarkers. Considering the promising capability of the SVG to discriminate 2 competing risks of developing heart failure versus dying from progressing malignancy and the low cost of ECG recording, future use of SVG biomarkers in cardio-oncology can deliver value-based care to our patients.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was partially supported by R01 and R56 HL118277 to Dr Tereshchenko.

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KEY WORDS electrocardiogram, global electrical heterogeneity, vectorcardiogram