Validation of the Ventricular Gradient Comparing Sinus Beats and Ectopic Beats

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Abstract

Introduction. Wilson assumed that the ventricular gradient (VG) is independent of the ventricular activation order. We sought to validate this tenet by intra-individual comparison of the VG of sinus and ectopic beats, thus assessing both the effects of altered ventricular conduction and of restitution (caused by varying ectopic prematurity).

Methods. We studied standard diagnostic ECGs of 118 patients with accidental extrasystoles, who had either normally conducted supraventricular ectopic beats (SN, N=6), aberrantly conducted supraventricular ectopic beats (SA, N=20), or ventricular ectopic beats (V, N=92). We computed the ventricular gradient vectors of the predominant beat, VGp, of the ectopic beat, VGe, the VG difference vector, VGpe, and compared their sizes.

Results. The VGe vectors of the SA and V ectopic beats were significantly larger than the VGp vectors. The VGpe vectors were three times larger than the difference in size of the VGe and VGp vectors, demonstrating differences in the VGp and VGe spatial directions. Ectopic prematurity had no influence on these results.

Discussion. Electrotonic interactions during repolarization form the likely explanation of our findings. Because of this electrophysiological mechanism, the concept of a conduction-independent ventricular gradient is untenable and cannot be used in ECG diagnostics.

1. Introduction

The ventricular gradient (VG), defined as the integral of the ECG amplitude over the QT interval, has intrigued many investigators ever since it was introduced by Wilson et al. in 1931 (1). Originally defined for separate ECG leads, the VG evolved into a three-dimensional concept when vectorcardiography emerged: the spatial ventricular gradient (2). Already from the beginning, the VG was thought to be independent of the intraventricular conduction order, only depending on "local variations in the excitatory process" (1, 3), *i.e.*, on action potential heterogeneity. Hence, VG was considered as an individual intrinsic property of the ventricular myocardium. In 1957, Burger mathematically derived a formula for the VG, showing that it was proportional to the volume integral of the action potential duration gradients over the heart (4, 5):

$$\vec{G} = \int_{QT} \vec{H} \cdot dt = -\int_{vol} \vec{\nabla}(h \cdot \tau) \cdot dv$$

$\vec{G}$ = spatial ventricular gradient (VG)
$\vec{H}$ = heart vector
h = resting potential (maximal diastolic potential)
τ = action potential duration

As this equation does not figure the excitation order of the heart, VG could be useful in ECG diagnostics. When, in a patient, the ECG changes while the VG remains the same, these changes should have been caused by differences in the excitation order but not by changes in the intrinsic electrophysiological properties of the cardiac myocytes. However, when both the ECG and the VG change, the electrophysiological properties of the myocardium must have changed too. This property of the VG could, e.g., be helpful to detect acute ischemia in patients with a new left bundle branch block (BBB). If the new BBB is caused by the acute ischemia, not only the ECG but also the VG of this patient should have changed due to ischemia-based action potential changes. If the new BBB is caused by a local defect in the conduction system that is unrelated to acute ischemia, the VG is expected to remain unchanged.

Since decades the concept of conduction-independency of the VG has met criticisms. Simonson et al. (6) did not agree with Wilson et al. (3) that the VG was "reasonably constant in spite of the greatly different pathways of excitation and grossly different patterns and electrical axes". They calculated that the amount of variability in Wilson's experiments was 25 percent of the mean, and therefore should not have been interpreted as "a small variability" (3). Angle (7) determined the VGs in the ECGs with intermittent right BBB as published by Wilson et al. (8) and by White (9), and in the ECGs with intermittent left BBB as published by Segers and Boyadjian (10). The VGs in the complexes exhibiting BBB were about half the size of the VGs in the normally conducted complexes in right BBB, and about two thirds the size of the VGs in the normally conducted complexes in left BBB.

Calculations in the above studies were done in the frontal plane. Berkun et al. (11) investigated conduction independency of the VG in 3D. In 1966, Cosma et al. (12)

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stated that a 3D approach of the VG requires time-integral calculations in an orthonormal vectorcardiographic lead system. They compared the VG of normal sinus beats with the VG of premature ventricular contractions in patients with various pathology and concluded that the VG did not remain constant when the ventricular activation changes.

Other investigators were more positive about the presumed independence of the ventricular activation order. Lux et al. (13, 14) investigated this using body surface potential mapping in dogs. They concluded that "QRST iso-area maps were shown to be independent of ventricular activation sequence with the exception of features which are explicable on the basis of electrotonic interaction during ventricular repolarization" (15): "it appears that the influence of activation order on recovery properties should be considered in evaluating the significance of a given value of the ventricular gradient" (16).

Another mechanism that may affect VG is restitution: the relationship between the duration of a cardiac action potential and the length of the preceding diastolic interval. When studying the VG in the setting of ectopic beats, it should be taken into account that not only the ectopic ventricular activation order is different from that of the normal beat, but also the preceding diastolic interval (in supraventricular as well as in ventricular ectopic beats). Premature beats have shorter action potential durations, but the amount of shortening is known to be not homogeneously distributed over the heart: epicardial action potentials shorten more with prematurity than endocardial action potentials do (17). In this way, inhomogeneous restitution alters the VG of ectopic beats.

For clinical use, a robust measure of the recovery properties of the heart is crucially important. Independence of ventricular activation order would render such a measure useful for intrapatient comparison of ECGs with and without conduction disorders. In our current study, we addressed the dependence of the VG on ventricular activation order and on restitution by analyzing the differences between the VGs of predominant and ectopic beats in standard 10-second 12-lead ECG recordings with a spontaneous supraventricular or ventricular ectopic beat.

2. Methods

We searched the historical ECG database of the Leiden University Medical Center (LUMC) over a period of ten successive months for technically sound digital standard 10-second 12-lead ECGs of patients who were 18 years or older, who showed sinus rhythm and contained at least one spontaneous supraventricular or ventricular ectopic beat.

The ECGs were analyzed and generally characterized by the Glasgow Royal Infirmary (GRI) software (18), thus labelling each ECG as normal or abnormal. We additionally classified the GRI detected abnormalities as long QT, axis deviations, BBBs, intraventricular conduction disorders, hypertrophy, old infarctions, pericarditis, ST abnormalities, or low QRS voltage.

The ECGs were additionally analyzed by the Leiden ECG Analysis and Decomposition Software (LEADS) (19). Briefly, LEADS combines automated analysis and human interaction to identify the heartbeats of interest in an ECG recording, and to verify and when necessary to adjust the essential landmarks in time (onset of the QRS complex and end of the T wave, together defining the interval for the computation of the VG). Initially, LEADS computes a vectorcardiogram (VCG) by multiplying the ECG by the Kors transformation matrix (20). Then, heartbeats are detected in the VCG-derived spatial velocity signal (19). Next, ectopic beats are excluded, thus focusing on the analysis of the predominant QRST complex. Before averaging the predominant beats, the baseline is corrected by cubic spline interpolation through the PQ segments immediately preceding the predominant QRS complexes.

For the purpose of this study, ectopic beats had to be analyzed as well. To facilitate the analysis of a separate ectopic beat, a special experimental version of the LEADS program was developed, in which the ectopic beats were baseline-corrected with the baseline as calculated from the surrounding predominant beats in the ECG recording.

From the variables produced by LEADS, we calculated the prematurity of the ectopic beat (the ratio of the coupling interval of the ectopic beat and the mean interval between consecutive predominant beats). From the VG vectors of the predominant and the ectopic beats, $\overrightarrow{VG_p}$ and $\overrightarrow{VG_e}$, we computed two measures of difference:

1. the magnitude of the difference vector between the VGs of the ectopic and predominant beats: $|\overrightarrow{\Delta VG_{ep}}|$
2. the magnitude of the difference between the VG magnitudes of the ectopic and predominant beats: $\left||\overrightarrow{VG_e}| - |\overrightarrow{VG_p}|\right|$

Finally, we divided the ectopic beats into 3 categories: supposed supraventricular origin and normal conduction (SN), supposed supraventricular origin and aberrant conduction (SA), and supposed ventricular origin (V).

To compare $\overrightarrow{VG_p}$ and $\overrightarrow{VG_e}$, we calculated the means and standard deviations of the $\overrightarrow{VG_p}$ and $\overrightarrow{VG_e}$ magnitudes, and tested the difference of the means by a two-sided paired T test. Additionally, we computed the mean and standard deviation of the VG difference vector magnitude, $|\overrightarrow{\Delta VG_{ep}}|$. Values were computed for all patients together, and for the subgroups of patients with ectopic beats of the SN, SA and V categories. Finally, we statistically compared the values of these subgroups by two-sided unpaired T tests, except for the comparison of $|\overrightarrow{\Delta VG_{ep}}|$, for which a one-sided unpaired T test was used and performed linear regressions.

3. Results

Table 1 shows the anthropomorphic characteristics of the study group. Cardiovascular diagnoses are described in

Table 2; an average of 2.2 cardiovascular conditions was present per patient. Table 3 shows the ECG qualification by the GRI software. The majority of the ECGs (72.0%) was interpreted as abnormal or borderline abnormal. Table 4 gives the results of the comparison of the VG magnitudes of the predominant and the ectopic beats, and the magnitude of the VG difference vectors for the SN, SA and V ectopic beats. Figure 1 shows the influence of prematurity of the ectopic beats on the VG difference vectors.

Sex (% male)	66.1
Age (years)	64±14 [24-92]
Height (cm)	175.4±9.6 [148-199]
Weight (kg)	85.5±17.4 [43-154]
BMI (kg/m²)	27.7±4.8 [18.5-47.7]

Table 1. Anthropomorphic characteristics of the study group N=118). Data are displayed as mean±SD [range]. BMI = body mass index.

Diagnosis	n	%
Coronary atherosclerotic disease	49	41.5
Healed myocardial infarction	28	23.7
Chronic heart failure	15	12.7
Cardiomyopathy	13	11.0
Systemic/pulmonary hypertension	60	50.8
Hypertrophy (ventricular/atrial)	2	1.7
Valvular disease	34	28.8
Congenital heart disease	6	5.1
Rhythm disorders	45	38.1
Conduction disorders	14	11.9
	266	225

Table 2. Cardiovascular diagnoses. On the average, 2.2 cardiovascular conditions were present per patient.

Interpretation	**n**	**%**
Normal	2	1.7
Borderline normal	31	26.3
Borderline abnormal	17	14.4
Abnormal	68	57.6
	118	100.0

Table 3. Automated GRI classification of the ECGs.

4. Discussion

We investigated the dependence of the VG on activation order and on restitution, by analyzing standard diagnostic ECGs with a spontaneous ectopic beat, measuring intraindividual differences between the VGs of predominant and ectopic beats in 118 patients (Table 1) with various cardiovascular pathology (Table 2) and with, for the greater part, abnormal ECGs (Table 3). Prematurity varied widely (0.43–1.03; Figure 1), thus covering almost the entire electrophysiologically possible range.

	$\lvert\overrightarrow{VG_p}\rvert$ (mV·ms)		$\lvert\overrightarrow{VG_e}\rvert$ (mV·ms)		***P* values**	$\lvert\overrightarrow{\Delta VG_{ep}}\rvert$ (mV·ms)	
	Mean	SD	Mean	SD		Mean	SD
All (N=118)	47.78	24.62	53.72	25.03		19.94	9.76
SN (N=6)	57.01	27.46	59.5	32.77	0.66	17.83	10.83
SA (N=20)	48.45	31.69	54.3	27.89	0.04	18.87	6.13
V (N=92)	47.03	22.85	53.22	24.12	<0.001	20.31	10.37
	***P* values**		***P* values**			***P* values**	
SA vs. SN	0.56		0.70			0.76	
V vs. SN	0.31		0.55			0.57	

Table 4. Means and standard deviations of the magnitudes of the ventricular gradient vectors of the predominant beat ($\lvert\overrightarrow{VG_p}\rvert$), of the ectopic beat ($\lvert\overrightarrow{VG_e}\rvert$), and of the difference vector ($\lvert\overrightarrow{\Delta VG_{ep}}\rvert$). Statistical comparisons were done with unpaired (columns) and paired (rows) two-sided T tests. SN = patients with a normally conducted supraventricular ectopic beat; SA = patients with an aberrantly conducted supraventricular ectopic beat; V = patients with a ventricular ectopic beat.

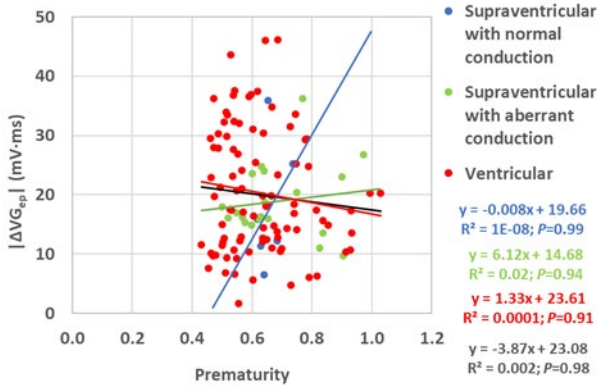

Figure 1. Magnitudes of the ventricular gradient difference vectors as a function of prematurity for patients with normally conducted supraventricular ectopic beats (SN; N=6), aberrantly conducted supraventricular ectopic beats (SA; N=20), and ventricular ectopic beats (V; N=92). Four linear regressions were computed of the VG difference vectors of these three groups, and of the entire study group (All; N=118). All correlation coefficients were very low, and none of the regression lines had a slope that was statistically significantly different from zero.

Ectopic VG vector magnitudes were significantly larger than predominant VG magnitudes, for SA and V, but not for SN ectopic beats (Table 4). VG difference vectors were larger than the differences between the predominant and ectopic VG magnitudes, signalling predominant-ectopic differences in spatial VG orientation (Table 4). The magnitudes of the VG difference vectors were uncorrelated with the prematurity of the ectopic beats (Figure 1).

From the times in which the concept of the VG was formulated it was considered important because of its presumed independency of ventricular activation order. In this way, the VG could help to diagnose ECG changes in a given subject as either changes in ventricular conduction, or changes in the electrophysiological properties of the ventricular myocardium. Later, additional use of the VG in risk assessment was proposed (for an overview, see the publication by Waks and colleagues (21)).

We addresssed the premise that VG is an individual constant, independent of ventricular activation order. We showed that VG can change considerably with ventricular activation order, although prematurity does not play a major role in this effect. These findings can be explained by electrotonic interactions during repolarization that depend on the ventricular activation order (15).

As a final remark, it should be stated that invalidation of Wilson's premise of a conduction-independent VG does not imply that the VG has no diagnostic potential. VG changes occurring in a clinical setting in which ventricular activation order is presumably not altered may indicate pathology-associated action potential changes. An example are the VG changes as observed in pulmonary hypertension, in which right-ventricular action potentials are changing due to mechano-electrial feedback as a consequence of elevated right-ventricular pressures (22).

References

[1] Wilson FN, Macleod AG, Barker PS. The T deflection of the electrocardiogram. Trans Assoc Am Phys. 1931;46:29-38.

[2] Burch GE, Abildskov JA, Cronvich JA. The spatial vectorcardiogram and mean spatial ventricular gradient in normal pregnant women. Circulation. 1954;9:381-7.

[3] Wilson FN, Macleod AG, Barker PS, Johnston FD. The determination and significance of the areas of the ventricular deflections of the electrocardiogram. Am Heart J. 1934;10:46-61.

[4] Burger HC. A theoretical elucidation of the notion ventricular gradient. Am Heart J. 1957;53:240-6.

[5] Draisma HH, Schalij MJ, van der Wall EE, Swenne CA. Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. Heart Rhythm. 2006;3:1092-9.

[6] Simonson E, Schmitt OH, Dahl J, Fry D, Bakken EE. The theoretical and experimental bases of the frontal plane ventricular gradient and its spatial counterpart. Am Heart J. 1954;47:122-53.

[7] Angle WD. The ventricular gradient vector and related vectors. Am Heart J. 1960;59:749-61.

[8] Wilson FN, Rosenbaum FF, Johnston FD. Interpretation of the ventricular complex of the electrocardiogram. Advances in Internal Medicine. New York: Interscience Publisher, Inc.; 1947.

[9] White PD. Heart disease. New York: The Macmillan Co.; 1951.

[10] Segers M, Boyadjian N. Étude critique du concept du gradient ventriculaire. Arch mal coeur. 1949;42:522.

[11] Berkun MA, Donoso E, Grishman A, Kesselman RH. The spatial ventricular gradient: intermittent Wolff-Parkinson-White syndrome, intermittent left bundle branch block and ventricular premature contractions. Circulation. 1956;13:562-72.

[12] Cosma J, Levy B, Pipberger HV. The spatial ventricular gradient during alterations in the ventricular activation pathway. Am Heart J. 1966;71:84-91.

[13] Lux RL, Urie PM, Burgess MJ, Abildskov JA. Variability of the body surface distributions of QRS, ST-T and QRST deflection areas with varied activation sequence in dogs. Cardiovasc Res. 1980;14:607-12.

[14] Abildskov JA, Urie P, Lux R, Burgess MJ, Wyatt R. Body surface distribution of QRST area. Adv Cardiol. 1978;21:59-64.

[15] Abildskov JA. Effects of activation sequence on the local recovery of ventricular excitability in the dog. Circ Res. 1976;38:240-3.

[16] Abildskov JA, Burgess MJ, Millar K, Wyatt R. New data and concepts concerning the ventricular gradient. Chest. 1970;58:244-8.

[17] Litovsky SH, Antzelevitch C. Rate dependence of action potential duration and refractoriness in canine ventricular endocardium differs from that of epicardium: role of the transient outward current. J Am Coll Cardiol. 1989;14:1053-66.

[18] Macfarlane PW, Devine B, Latif S, McLaughlin S, Shoat DB, Watts MP. Methodology of ECG interpretation in the Glasgow program. Methods Inf Med. 1990;29:354-61.

[19] Draisma HHM, Swenne CA, Van de Vooren H, Maan AC, Hooft van Huysduynen B, Van der Wall EE, et al. LEADS: an interactive research oriented ECG/VCG analysis system. Computers in Cardiology. 2005;32:515-8.

[20] Kors JA, van Herpen G, Sittig AC, van Bemmel JH. Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. Eur Heart J. 1990;11:1083-92.

[21] Waks JW, Tereshchenko LG. Global electrical heterogeneity: A review of the spatial ventricular gradient. J Electrocardiol. 2016;49:824-30.

[22] Kamphuis VP, Haeck ML, Wagner GS, Maan AC, Maynard C, Delgado V, Vliegen HW, Swenne CA. Electrocardiographic detection of right ventricular pressure overload in patients with suspected pulmonary hypertension. J Electrocardiol. 2014;47:175-82

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