Detection of Incipient Left Ventricular Hypertrophy in Mild to Moderate Arterial Hypertension with Normal Electrocardiogram and Echocardiogram. A New Use for Signal-Averaged Electrocardiography

Paulo Ginefra, Eduardo C. Barbosa, Paulo R. Benchimol Barbosa, Alfredo S. Bomfim, Silvia H. Boghossian, Angelo A. Salgado, Flavia G. Brasil, Elizabete A. Freitas, Francisco M. Albanesi Filho

Rio de Janeiro, RJ - Brazil

Objective - To assess signal-averaged electrocardiogram (SAECG) for diagnosing incipient left ventricular hypertrophy (LVH).

Methods - A study with 115 individuals was carried out. The individuals were divided as follows: GI - 38 healthy individuals; GII - 47 individuals with mild to moderate hypertension and normal findings on echocardiogram and ECG; and GIII - 30 individuals with hypertension and documented LVH. The magnitude vector of the SAECG was analyzed with the high-pass cutoff frequency of 40 Hz through the bidirectional four-pole Butterworth high-pass digital filter. The mean quadratic root of the total QRS voltage (RMST) and the two-dimensional integral of the QRS area of the spectro-temporal map were analyzed between 0 and 30 Hz for the frequency domain (Int FD), and between 40 and 250 Hz for the time domain (Int TD). The electrocardiographic criterion for LVH was based on the Cornell Product. Left ventricular mass was calculated with the Devereux formula.

Results - All parameters analyzed increased from GI to GIII, except for Int FD (GI vs GII and RMST log (GI vs GIII). Int TD showed greater accuracy for detecting LVH with an appropriate cutoff ≥8 (sensitivity of 55%, specificity of 81%). Positive values (≥8) were found in 56.5% of the GII patients and in 18.4% of the GI patients (p < 0.0005).

Conclusion - SAECG can be used in the early diagnosis of LVH in hypertensive patients with normal ECG and echocardiogram.

Keywords: signal-averaged electrocardiogram, left ventricular hypertrophy, arterial hypertension

In recent decades, several studies have been dedicated to the electrocardiographic diagnosis of left ventricular hypertrophy based on the criteria related to deviation of the QRS electrical axis, to voltage and duration of the ventricular complex (R and S waves of the precordial electrocardiogram), to the time of inscription of the intrinsicoid deflection in the left precordial leads, and also to the polarity and configuration of the ST segment and T wave in several leads. These criteria were used alone or in association, comprising, according to some authors, scores of points to increase the accuracy of the method for diagnosing left ventricular hypertrophy. Many of these studies, which are a small sample of the huge relation of communications about the subject, are also based on autopsy findings, allowing the correlation of electrocardiographic data with anatomic data. However, the entire literature refers to the already established left ventricular hypertrophy, which exists and is consequent to the underlying disease, and whose electrocardiographic diagnostic criteria are based on the already established consensus.

In the study of left ventricular hypertrophy, in addition to the conventional electrocardiogram, the echocardiogram has shown great accuracy not only in detecting left ventricular dimensions, but also in quantifying the thickness of the walls. Since the introduction of echocardiography as a diagnostic method, several studies of correlation with the conventional electrocardiogram have been reported in the literature. A consensus about the greater accuracy of the echocardiogram for detecting left ventricular hypertrophy as compared with that of the electrocardiogram seems to exist, with sensitivity and specificity values of 93% and 95%, respectively, while the conventional 12-lead electrocardiogram does not reach values greater than 55% and 84%, respectively.
However, neither the electrocardiogram nor the echocardiogram are accurate for detecting probable left ventricular hypertrophy consequent to the first alterations in myocardial fibers related to the initial process of protein synthesis and replication of the sarcomeres 19,20, which are subclinical and not detected with conventional techniques. On the other hand, the signal-averaged electrocardiogram is a technique with variables for assessing the existence of electrical potentials of very low voltage and high frequency, in microvolts, and it can record them almost at the cellular level. After performing 1,878 signal-averaged electrocardiograms in our laboratory in healthy individuals and children and adults with different heart diseases from 1995 until the end of this study, the experience obtained by our team allowed proposing that the technique be applied to the investigation of other parameters, in addition to those usually studied to stratify the risk of atrial and ventricular tachyarrhythmias, because this has been the major objective of numerous studies about that technique in the literature. Based on the functions and characteristics of the signal-averaged electrocardiogram, at first we thought that the QRS duration of the magnitude vector, one of its variables in the time domain, was useful to detect ventricular hypertrophy in its initial phase, the so-called incipient left ventricular hypertrophy, which had no repercussion on the electrocardiogram and on other noninvasive methods. But the first observations in some patients with mild to moderate hypertension showed that parameter, based only on the vector’s duration, did not change, and, therefore, we began to use its integral, which is the product of time by amplitude, corresponding to the vector’s area.

Aiming at investigating the possible presence of electrical potentials resulting from incipient left ventricular hypertrophy, we took as a model a group of patients with mild to moderate arterial hypertension and with normal electrocardiograms and echocardiograms, who, for validation, were compared with a control group of healthy individuals and with another group of individuals with documented systemic arterial hypertension. In this comparison, signal-averaged electrocardiographic variables in the time and frequency domains were used, and the micropotentials and the electrical signal energy of the magnitude vector were analyzed to detect the possible alternations in the myocardial status in the initial phase of arterial hypertension (incipient left ventricular hypertrophy). So far, we know of no other study with this design reported in the literature. In the area of signal-averaged electrocardiography, the studies about arterial hypertension refer only to the already established left ventricular hypertrophy present in several underlying heart diseases and with repercussions in other noninvasive examinations.

**Methods**

Our study comprised 115 individuals (69 females and 46 males) divided into 3 groups: group I (control) – comprising 38 individuals (mean age of 35.4±14.8 years, 21 females) with no history of systemic arterial hypertension, normal blood pressure, and normal electrocardiographic and echocardiographic findings; group II – comprising 47 patients (mean age of 53±12.6 years, 32 females) with mild to moderate systemic arterial hypertension, and normal electrocardiographic and echocardiographic findings; and group III – comprising 30 patients (mean age of 56.0±13.18 years, 16 females) with severe systemic arterial hypertension, and signals of left ventricular hypertrophy on the electrocardiogram and echocardiogram.

All patients had their blood pressure values and complementary tests recorded during outpatient clinic follow-up, and all of them underwent clinical examination prior to the procedures. The control group was formed by young individuals < 40 years (mean age of 35.4±14.8), with no previous history of arterial hypertension, and normal clinical and complementary examinations. In this control group, the individuals under the age of 27 years were resident physicians, nursing staff, and staff at our institution, of both sexes, and this was the reason why they were not paired with the other 2 groups, whose mean age was more elevated.

After consent, all patients underwent conventional 12-lead electrocardiography, single- and two-dimensional echocardiography, and signal-averaged electrocardiography in the time and frequency domains.

Electrocardiography was performed with the ECAPS 12 Nihon Kohden device with 3 channels and automatic processing of the measurements in real time. The tracing analysis comprised the determination and total duration of QRS (mean of all complexes recorded), the voltages of the R wave in aVL and S wave in V3, the voltages of the S wave in V1 and R wave in V6, and the analysis of the ST segment and the T wave for assessing the presence or absence of left ventricular hypertrophy. The only electrocardiographic criterion for left ventricular hypertrophy adopted was that most currently used, the so-called Cornell Product (CP). The Cornell voltage (CV) is obtained by adding the voltages of the R wave in aVL and of the S wave in V3, being CV = 35 mm in men and = 25 mm in women. The CP is the product of CV by the total duration of QRS (mean of the 12 leads), ie, CP=CV multiplied by the duration of QRS. Its normal value should be smaller than 2440 mm ms. Values above that indicate left ventricular hypertrophy.9,10

On echocardiography, the following parameters were analyzed: left ventricular diastolic (LVD) and systolic (LVs) diameters, thickness of the interventricular septum (IVS), and thickness of the left ventricular posterior wall (LVPW). Left ventricular mass (M) was calculated with the Devereux formula 16: M = 1.04 [(LVD + IVS + LVPW) - LVD] - 13.6; where 1.04 and 13.6 are constants, and left ventricular mass up to 215 g was considered normal.

On signal-averaged electrocardiography, the Art-Coronix device (ART Inc., Texas, USA), Predictor II model, was used with recording in the 3 orthogonal leads (X, Y, and Z) according to the methodology recommended by the American Heart Association and the European Society of Cardiology 21, which was used in our laboratory 22. A mean
of 300 beats with a sampling frequency of 2000 Hz were programmed to obtain a final noise reduction of 0.3 µV. For analysis in the time domain (TD), each lead was treated with a bidirectional four-pole Butterworth high-pass digital filter, with cutoffs of 40 to 250 Hz, and the 3 X, Y, and Z leads were combined in the magnitude vector through the formula: √(x² + y² + z²).

Prior to statistical analysis, the values of the Cornell Product and the variables of the signal-averaged electrocardiogram underwent logarithmic transformation (log) to normalize the asymmetric distributions of probability 23. This procedure not only statistically normalizes the distribution, but also reduces data variability, concentrating them around the mean.

The parameters studied in the time domain were the duration of the filtered QRS (DQRS), the integral of the magnitude vector (Int TD), and the mean total quadratic root of the amplitude of the magnitude vector (RMST). In the frequency domain (FD), not only the 4 routine variables recommended by Kelen et al 24 were determined, but also mainly the two-dimensional integral of the area of the time-frequency map of ventricular activation between 0 and 30 Hz (Int FD) 24 were determined.

Results

On conventional electrocardiography, the QRS complex configuration, voltage, and duration and the characteristics and polarity of the ST segment and T wave were normal in groups I and II. In those groups, the Cornell Product was also normal with values of 992.3±464.2 mm x ms in group I and 1516.3±602.5 mm x ms in group II. In group III, however, the amplitude of the S and R waves and the characteristics of the ST segment and T wave were altered with the appearance of left ventricular hypertrophy, but the Cornell Product was abnormal only in 12 (40%) patients with a mean value of 3166±543.8 mm x ms (tab. I); the remaining patients in group III had normal Cornell Product values.

Likewise, on echocardiography, in group I, the mean values of the thickness of the interventricular septum and of the left ventricular posterior wall were 0.86±0.1 cm and 0.85±0.1 cm, respectively, and, in group II, they were 0.89±0.08 cm and 0.9±0.09 cm, respectively, which are normal values for both groups. In group III, however, the mean values of thickness of the interventricular septum and of the posterior wall were 1.26±0.18 cm and 1.17±0.16 cm, respectively, characterizing hypertrophy in those structures (tab. I).

On signal-averaged electrocardiography, the 3 parameters analyzed had their values increased from group I (healthy individuals) to group III (patients with systemic arterial hypertension and electro- and echocardiographic evidence of left ventricular hypertrophy) with p<0.005 (fig. I). Comparing groups II and III, only the parameter integral TD showed a statistically significant difference (1.92±0.26 versus 2.13±0.28) with p<0.005. With an appropriate cutoff point ≥ 8, the integral TD showed the best accuracy to detect ventricular hypertrophy with sensitivity of 55% and specificity of 81%. The integral TD ≥ 8 was present in 56.5% of group II individuals and in 18.4% of group I individuals (p=0.0005). In regard to RMST, no significance was observed in those 2 groups as well (tab. II and fig. I).

These data suggest that the integral TD is the most accurate parameter of the signal-averaged electrocardiogram to capture the energy increase in the electrical signal, and this increase may be attributed to electric alterations in the myofibrils, which is called incipient myocardial muscular hypertrophy.

Discussion

Left ventricular hypertrophy is one of the complications of systemic arterial hypertension, and its presence has been associated with an increase in the incidence of heart failure, coronary artery disease, myocardial infarction, cardiac arrhythmias, and sudden death 25-26.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>GI</th>
<th>p</th>
<th>GII</th>
<th>p</th>
<th>GIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMST log</td>
<td>4.53 ± 0.3</td>
<td>&lt;0.005</td>
<td>4.76 ± 0.3</td>
<td>NS</td>
<td>4.53 ± 0.3</td>
</tr>
<tr>
<td>Int TD log</td>
<td>1.74 ± 0.28</td>
<td>&lt;0.005</td>
<td>1.92 ± 0.26</td>
<td>&lt;0.005</td>
<td>2.13 ± 0.28</td>
</tr>
<tr>
<td>Int FD log</td>
<td>10.72 ± 0.53</td>
<td>&lt;0.005</td>
<td>11.24 ± 0.67</td>
<td>NS</td>
<td>11.25 ± 0.59</td>
</tr>
</tbody>
</table>

G – group; log – logarithm; NS – nonsignificant.

Table II – Increasing values of the 3 parameters of RMST, Int TD, and Int FD from GI to GII. The integral of the magnitude vector in the time domain (Int TD) between GII and GIII has the greatest values (p<0.005). Data in the graphic also indicate increasing values of the 3 parameters between GI and GII (p<0.005). In regard to GII and GIII, the values are lower in GII.
Fig. 1 - Examples of magnitude vectors in each group studied. Note that all variables in the time (left) and frequency (right) domains are increased (arrows) from GII to GIII, indicating an increase in the electrical signal energy between GII and GI and between GIII and GII, because of the myocardial changes resulting from the initial left ventricular overload occurring in GII.
That is why its early detection is desirable, to obtain its regression with the adequate use of certain antihypertensive drugs.27,28

The identification of hypertensive patients with electrocardiographic evidence of left ventricular hypertrophy has not been very frequent in medical practice; on the other hand, on echocardiography, more than half of the patients in different stages of the disease have been identified29-32, and their diagnosis with that technique has been considered a factor in a poor prognosis by several authors.33

On echocardiography, left ventricular hypertrophy is usually found in 20% to 30% of nonselected patients and those with mild to moderate arterial hypertension31,34, which means that the method does not identify left ventricular hypertrophy in 70% to 80% of the patients in those phases of the disease. The diagnostic accuracy of echocardiography in hypertensive patients with severe ventricular hypertrophy observed in autopsy studies reaches 93% of sensitivity and 95% of specificity in this highly selected group15,18.

Conventional electrocardiography has been considered a less accurate method than echocardiography for detecting well-established left ventricular hypertrophy. When the left ventricular hypertrophy found in anatomicopathological studies is considered, the electrocardiographic sensitivity and specificity are 55% and 84%, respectively, according to some authors.35. And when echocardiography is used to identify the left ventricular hypertrophy condition, the electrocardiographic sensitivity ranges from 16% to 89% according to the electrocardiographic criterion adopted, and the Cornell Product has the best performance. This lack of correlation between the electrocardiographic and the echocardiographic findings is due to the fact that electrocardiography is a linear method of recording cardiac electrical activity, and it undergoes variations depending on the patients’ biotypes, position of the electrodes, orientation, sum or annulment of instantaneous vectors, etc. On the other hand, echocardiography is a method of direct and morphological observation and does not depend on electrical factors, unlike electrocardiography.

However, some electrocardiographic diagnostic criteria for left ventricular hypertrophy are acceptable in practice, such as those proposed by Romhilt and Estes.5. These criteria analyze several parameters at the same time, and, therefore, constitute a point-score system that increases the sensitivity of the method. Currently, a team at Cornell University has been using the Cornell Product, based on the correlation between left ventricular mass and the voltages and duration of the QRS complex9,10.

Although the Cornell Product values in groups I and II were normal, they were higher in group II as compared with those in group I, indicating that the myocardial metabolic conditions of group II patients with mild to moderate systemic arterial hypertension are at least more obvious than those of group I healthy individuals. In group III, only 40% of the patients had abnormal Cornell Product values, showing that, although this electrocardiographic index incorporates the mass value, it did not have sensitivity to detect left ventricular hypertrophy in the remaining 60% of patients.

In the present study, we used the left ventricular mass obtained on echocardiography (Devereux formula) and the Cornell Product obtained on electrocardiography as determinants of the presence of left ventricular hypertrophy, therefore selecting the 3 groups studied.

Group III comprised patients with severe systemic left ventricular hypertrophy and positive electrocardiographic and echocardiographic findings for left ventricular hypertrophy. Group II comprised patients with mild to moderate systemic arterial hypertension and no change on the electrocardiogram and echocardiogram.

Theoretically, the signal-averaged electrocardiogram allowed a more accurate assessment in group II based on the electrical signal energy detected by the system as compared with the conventional electrocardiogram. In the latter, opposite vectors nullify each other; on the other hand, on the signal-averaged electrocardiogram, the vectors are decomposed and are added, and the electrical signal energy in group II can be more precisely quantified.

Few studies have been carried out using signal-averaged electrocardiography to detect hypertrophy in patients already diagnosed with left ventricular hypertrophy on echocardiography.

The objective of our study was to assess signal-averaged electrocardiographic data related to quantification of the electrical signal energy of the ventricle in hypertensive patients with hypertrophy detected on electrocardiography and echocardiography and to compare them with those of healthy individuals and patients with confirmed left ventricular hypertrophy.

Thus, we used the time domain (TD) and frequency domain (FD) variables of signal-averaged electrocardiography to quantify the electrical signal energy (in our case, the energy released by the magnitude vector) provided by the integral, which is the product of the voltage of the vector by the duration of the vector, representing its total area. This increased its accuracy in relation to the other variables. Thus, the integral in the time domain (Int TD) analyzed and quantified the energy of the vector in a band between 40 and 250 Hz in a linear way, and the integral in the frequency domain (Int FD) did that in a two-dimensional way, evaluating in a certain time (ms), the frequency lines recorded between 0 and 30 Hz. Of the 2 integrals, the Int TD was more sensitive as compared with the Int FD and with the other variables of the method. This shows that the integral TD is more accurate in detecting the energy released by the magnitude vector, increased and quantified at the level of micropotentials and resulting from a metabolic phenomenon not detected on echocardiography and surface electrocardiography.

The values of the 3 parameters analyzed (RMST log, Int TD log, and Int FD log) were greater in group II as compared with those in group I, with statistical significance, and those values were also greater in group III as compared with those in group II, with statistical significance in at least 1 parameter (Int TD). This serves as evidence that the method is useful for detecting incipient left ventricular
hypertrophy and that patients with mild to moderate systemic arterial hypertension may have some degree of hypertrophy, although hypertension may not be detected on echocardiography and conventional electrocardiography. Although incipient left ventricular hypertrophy may have no short-term and medium-term prognostic implications, its progressive character may influence the survival of patients in the long run. Therefore, starting appropriate antihypertensive therapy in the early stages of left ventricular hypertrophy is highly desirable, because its consequent regression may prevent future complications, including severe arrhythmic events. We suggest that the events that we called incipient left ventricular hypertrophy should be investigated by other authors.

References