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Left Ventricular Hypertrophy: An allometric comparative analysis of different ECG markers

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Abstract. Allometry, in general biology, measures the relative growth of a part in relation to the whole living organism. Left ventricular hypertrophy (LVH) is the heart adaptation to excessive load (systolic or diastolic). The increase in left ventricular mass leads to an increase in the electrocardiographic voltages. Based on clinical data, we compared the allometric behavior of three different ECG markers of LVH. To do this, the allometric fit $AECG = \delta + \beta$ (VM) relating left ventricular mass (estimated from ecocardiographic data) and ECG amplitudes (expressed as the Cornell-Voltage, Sokolow and the ECG overall voltage indexes) were compared. Besides, sensitivity and specifity for each index were analyzed. The more sensitive the ECG criteria, the better the allometric fit. In conclusion: The allometric paradigm should be regarded as the way to design new and more sensitive ECG-based LVH markers.

1. Introduction

Left ventricular hypertrophy (LVH) is the heart way to adapt to overloads, either during diastolic or systolic periods. This adaptation consists of increasing the diameter of the cardiac fibers and, consecuently, of left ventricular mass. Such augmented mass directly affects the electrocardiographic signal by raising its voltage amplitudes. We address the following question here: does this increase in amplitude keep an allometric relationship with the increase in left ventricular (LV) mass? To figure this out, a comparison of the allometric adjustment of different LVH indexes was carried out.

Scaling of many biological processes can be described by the allometric equation, $Y = a(B_M)^b$, where Y is the biological process, B is the body or organ mass and a and b are scaling constants. In general, the weights of most individual organs scale as a constant fraction of body mass (i.e., the body mass exponent, b, equals 1.0). Biological rates (heart rate, respiratory rate) scale as b close to 0.25. Finally, volume rates (the product of volume and rate), such as cardiac output, ventilation and oxygen uptake, vary as b around 0.75. These emergent patterns provide insights into body-size dependent "principles of design" that seem to dictate several aspects of design and function across species among all mammals [1,2,3].

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Noujaim *et al* [4] assumed that the heart behaves as a set of "fractal-like" networks tending to minimize propagation time across the conducting system while ensuring a hemodynamically optimal atrioventricular activation sequence. With the potential relationship given above and, subsequently, based on previously published values of PR interval, heart rate, and body masses of 541 mammals, they reported as best fit the equation $PR = 53(B_M)^{0.24}$.

The existence of many different criteria for diagnosing LVH makes clinical application more complex. The sensitivity of the LVH indexes based on ECG is generally quite low (usually less than 50%), while the specificity is quite high (often in the range of 85% to 90%) [5,6,7]. Published studies are currently insufficient to indicate whether any of the more recently proposed criteria are clearly superior to the others or are simply redundant. For these reasons, the aim of this work was to provide insight into new clues and theoretical support to help researchers find more sensitive markers of LVH.

1. Materials and Methods

1.1. Patient population

According to the Penn Convention and using the Deveraux equation [8], LV mass was assessed in 36 patients, from which, 23 out of 36 showed ecocardiographic mass index greater than 259 g and 166 g for men and women, respectively, leading to LVH diagnosis. The average age of the studied population was composed of 16 men (75.44±8.13 years old) and 20 women (72.75±13.54 years old). Pathologies were varied, since recruitment was done on outpatients of the General Hospital *Instituto de Investigaciones Médicas Dr. A. Lanari*, belonging to University of Buenos Aires (UBA). Patients with intraventricular conduction diseases (IVCD) were ruled out, since both LVH and IVCDs alter QRS patterns, therefore, the existence of an IVCD may impact the accuracy of ECG criteria for LVH [7].

1.2. ECG criteria for LVH

We compared the allometric adjustment of three ECG markers for LVH, i.e., Cornell index, ECG total 12-lead voltage and Sokolow index. They are widely used in clinical practice. These indexes were calculated as follows:

- **Cornell (voltage) index:** There are two versions of this index, one concerning voltage only and the other one combining QRS voltage and duration. We used here only the voltage version that combines the amplitude of the S wave in V₃ lead and the amplitude of R wave in aVL lead [7,9].
 - Men: $S_{V3} + R_{aVL} > 2.8 \text{ mV} (28 \text{ mm})$
 - Women: $S_{V3} + R_{aVL} > 2,0 \text{ mV} (20 \text{ mm})$
- Total 12-lead voltage: Total 12-lead voltage, measured as the sum of all S and R peaks of all 12 leads> 175 mm [7,10].
- Sokolow index: who in 1949 introduced the widely used criterion based on the sum of the amplitude of the S wave in V₁ lead plus the amplitude of R wave in V₅ or V₆ leads. The cut-off point for this index is >/= 3,5 mV (35 mm) [7,11]. We have chosen V₆ lead for our analysis.
 - \circ S_{V1}+R_{V6}>= 3,5 mV (35 mm)

For the ECG studies, we have used a standard 12-lead ECG device and obtained 10 second-recordings. The device had a sampling rate of 400 Hz and 12 bits resolution. From the

ECG recordings, peak amplitudes were averaged out from all the beats contained in the entire recording.

1.3. Left ventricular mass calculation

In the late 80s, Levy and coworkers published a landmark paper evaluating a subset of individuals without known cardiovascular risk factors in the Framingham Cohort [8]. These authors calculated LV mass both with the ASE (American Society of Echocardiography) convention and Troy equation [12]:

$$LV mass(Troy) = 1.05 ([LVIDD + PWTD + IVSTD]^{3} - [LVIDD]^{3}) g.$$
(1)

Where:

LVIDD = Left Ventricular Internal Diameter in Diastole PWTD = Posterior Wall Thickness in Diastole IVSTD = Interventricular Septum Thickness in Diastole

and with the Penn Convention and Devereux equation [13]:

LV mass(Deveraux) =
$$1.04$$
 ([LVIDD + PWTD +IVSTD]³- [LVIDD]³) -13,6 g (2)

In this work, the Penn Convention and Devereaux equation were chosen. The authors proposed normal limits for LV mass for men and women, based on cut points at two standard deviations above the mean [8,14].

1.4. Allometric equation

Allometry, in general biology, measures the relative growth of a part in relation to the whole living organism. The term was first used by Snell, in 1891 [15], to express the mass of a mammal's brain as a function of the body mass. The growth velocity of a component 'y' is related to the growth velocity of another component (or the whole organism) 'x' in a constant way. This was clearly described by von Bertalanffy in 1957 [16]. Thus, the relative rate of change of a given event 'y' is proportional to the relative rate of change of body mass or body weight 'x', i.e.,

$$\frac{dy/dt}{y} = B\frac{dx/dt}{x}$$
(3)

After integration and some easy algebraic manipulation, equation (3) becomes

$$\ln y = A + B \ln x$$

or

$$y = Ax^{B}$$
⁽⁴⁾

Originally, 'y' was the weight of an organ (heart, stomach, other) and 'x' was body weight or mass. The parameters A and B require numerical estimation by an appropriate procedure usually using empirical information. By the same token, let us say that the amplitude of the ECG (we use *Aecg* in a general form, since *Aecg* will be cuantified as the ECG criteria for LVH) follows a relationship with the number of ventricular hypertrophic fibers, and therefore, the ventricular mass (*Vm*). Thus, eq. (4) will be reformulated as in (5):

$$Aecg = \alpha (Vm)^{\beta} \tag{5}$$

After taking logarithms of both sides, the latter equation becomes

$$\ln Aecg = (\ln \alpha + \beta \ln \gamma) + \beta (\ln \Delta_{Vm})$$
(6)

which can be reduced to

$$AECG = \delta + \beta(VM) \tag{7}$$

We define AECG as ECG voltage or amplitude, where $\delta = \ln \alpha + \beta \ln \gamma$, $VM = \ln \Delta Vm$ and $AECG = \ln Aecg$. The straight line, equation (5), in log-log plot with the parameters β and δ would represent the increase in ECG amplitude as function of the amount of hypertrophic fibers.

1.5. Numerical procedure

To calculate the two constants δ and β and later on apply the mathematical expression in equation (7), linear regression was implemented in order to evaluate the allometric fit on a log-log plot gathering the variables ventricular mass and LVH index. Notice that δ represents the intercept to the origin and β is the slope of the regression line when plotted on log-log coordinates. When $\beta < 1$, the relative weight of the ECG criteria (fraction of total ventricular mass) is greater in small than large hypertrophy. Also, sensitivity and specificity was estimated from our set of data by calculating the following equations:

$$Sensitivity = TP/(TP+FN)$$
(8)

 $Specificity = TN/(TN+FP), \tag{9}$

where *TP* are the true positive, *FP* the false positive and *TN* the true negative cases, all of them confirmed by ecocardiographic analysis. More specifically, ecocardiographic mass calculation, as described above, and the criteria of a cardiologist were set as the gold standard for LVH diagnosis.

2. Results

Using the equation $AECG = \delta + \beta$ (VM) in log-log representation, the fitting procedure produced coefficients for every LVH index, displayed in Table 1. Moreover, graphic results for the allometric adjustments on log-log plots are showed in Figure 1. Linear regression and determination coefficients r are also displayed. Note that the ECG criteria for LVH that correlated best with ventricular mass in an allometric fit was the Voltage-Cornell index (r=0.7229), followed by the Total Voltage index (r=0.5292) and last, with a very low fit the Sokolow index (r=0.2769) with a slope deviation from zero not significant.

Table 1. Coefficients β and δ and goodness of fit *r* for all three LVH indexes.

	β	δ	r
Voltage-Cornell	$0,89 \pm 0,14$	$-0,90 \pm 0,33$	0,72
Total voltage	$0,\!42 \pm 0,\!11$	$1,1 \pm 0,26$	0,52
Sokolow	$0,\!24 \pm 0,\!14$	$0,72\pm0,33$	0,27



Figure 1: Linear regressions for the allometric fits of ECG-based LVH markers: Cornell index, total 12-lead voltage index and Sokolow index.

Notice as well, that all the slopes β in the adjustment are positive and smaller than 1. This means that indexes are inversely proportional to the amount of hypertrophy in the heart. This is, the greater the amount of hypertrophic fibers, the lesser the growth of the LVH index. Slopes greater or even equal to 1 would be more desirable in order not to lose sensitivity with the hypertrophy extent.

Table 2 shows the sensitivity and specificity as reviewed from the bibliography and as estimated from our set of data. In all cases, notice how the sensitivity suffered when calculated from a reduced set of samples.

	Sensitivity from bibliography	Specificity from bibliography	Estimated Sensitivity	Estimated Specificity	References
Voltage- Cornell	42 %	96 %	35 %	100 %	Casale 1985 [7]
Sokolow	22 %	100 %	13 %	100 %	Sokolow 1949 [9]
Total voltage	17.2 %	95 %	17 %	100 %	Siegel 1982 [8]

Table 2. Sensitivity and specificity collected from bibliography and estimated from our pool of data,23 patients with and 13 without LVH ecocardiographically confirmed.

3. Discussion

The results show that sensitivity goes along with allometric behavior when searching for LVH markers based on ECG. However, certain constraints should be regarded. For instance, the population in study is quite homogeneous in terms of age, presenting mainly the same type of LVH. Thus, the analysis herein accomplished holds for the elderly only. It is important to notice that patients with intraventricular conduction diseases (IVCD) were excluded from the study in order not to confuse the symptoms, since both LVH and IVCD lead to similar changes in QRS.

Another limitation of the study is that not all the QRS-based indexes of LVH were analyzed. Nevertheless, the results found here encourage a more complete study including all

electrocardiographic indexes of LVH over a larger and more heterogeneous sample population.

One point to mention is the slope β of the linear regressions in the allometric fit. All of them resulted positive and smaller than 1. This means that the greater the amount of hypertrophic fibers, the lesser the growth of the LVH marker. This leads to a loss of sensitivity with hypertrophy extent. Therefore, if more sensitive markers are required, β tending to 1 would be desired.

Interestingly, the Voltage-Cornell index, which showed the best allometric fit, is the one that best sensitivity achieved among the studied indexes. Voltage-Cornell index has a sensitivity of 42%, as collected from the bibliography [8] and 35% as estimated from our pool of data (see Methods, section 2.5. Numerical procedures).

Finally, even though the Cornell index was designed for different LVH cut-off points (132 g/m^2 for men and 109 g/m^2 for women) as used here, it adapted well to the new definition, postulating itself as the most robust ECG marker of LVH.

4. Conclusions

The voltage increase in ECG would follow an allometric relation with left ventricular mass. This fact should guide the search of new and more sensitive markers of hypertrophy by taking into account the allometric law. Moreover, slopes of the regression lines (or constants β) resulted all positive and smaller than one. This means that ECG-based indexes for LVH are inversely proportional to the amount of hypertrophy in the heart. Slopes greater or even equal to one would be more desirable in order not to lose sensitivity with hypertrophy extent.

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