Inverse allometry: foundations for a bioinspired LVH-prediction model

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Abstract. 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) that leads to an increase in left ventricular mass, which in turn, raises the electrocardiographic voltages. If this mass increase followed an allometric law, then it would be possible to design a bioinspired model based on the allometric equation to predict LVH. In this work, we first investigated the validity of this hypothesis and then proposed an LVH marker based on the inverse allometry model. 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 echocardiographic data) and ECG amplitudes (expressed as the Cornell-Voltage, Sokolow and the ECG overall voltage indexes) were compared. Besides, sensitivity and specificity for each index were analyzed. The more sensitive the ECG criteria, the better the allometric fit. Finally, the Receiver Characteristic Curve (ROC) of an allometric model proposed here was computed. 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 amplitude. We address two questions here. Firstly: 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. Secondly: can the allometric model be the foundation for more sensitive bioinspired LVH markers?

Allometry, in general biology and physiology, has been recently reassessed with some new insights as, for example, the relationship between organ and animal size [1], organ and biological times such as heart rate, volumes and capacities

such as cardiac output [2], ECG-PR interval and animal size [3] and finally, electrocardiographic parameters in ischemia and number of cardiac diseased fibres [5, 4].

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%) [6][7][8]. 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 is to provide insight into new clues and theoretical support to help researchers find more sensitive markers of LVH.

2 Materials and Methods

2.1 Patient Population

According to the Penn Convention and using the Deveraux equation [14], LV mass was assessed in 36 patients, from which, 23 out of 36 showed echocardiographic 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 17 men (75.44±8.13 years old) and 19 women (72.75±13.54 years old). Pathologies varied, since recruitment was done on outpatients of a general hospital. 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 [10].

2.2 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 [10, 11].
  - Men: $S_{V3} + R_{aVL}$ >2,8 mV (28 mm)
  - Women: $S_{V3} + R_{aVL}$ >2,0 mV (20 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 (8, 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) (8, 11). We have chosen V6 lead for our analysis.
  - 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.

2.3 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 [10]. These authors calculated LV mass both with the ASE (American Society of Echocardiography) convention and Troy equation [13]:

$$LV_m(Troy) = 1.05 * ([LVID_d + PWT_D + IVST_d]^3 - LVID_d^3) \quad (1)$$

Where: $LVID_d$ = Left Ventricular Internal Diameter in Diastole PWT_d = Posterior Wall Thickness in Diastole $IVST_d$ = Interventricular Septum Thickness in Diastole and with the Penn Convention and Devereux equation [15]:

$$LV_m(Dev) = 1.04 * ([LVID_d + PWT_d + IVST_d]^3 - LVID_d^3) - 13,6g \quad (2)$$

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 [9, 15].

2.4 Allometric equation

The term allometry was first used by Snell, in 1891 [16], 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 [17]. 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.,

$$(dy/dt)/y = B(dx/dt)/x \quad (3)$$

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

$$y = Ax^B \quad (4)$$

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 quantified as the ECG criteria for LVH) follows a relationship with the number of ventricular hypertrophic fibres, and therefore, the ventricular mass (Vm). Thus, equation 4 can be reformulated as,

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

After taking logarithms of both sides, the latter equation becomes

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

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(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 fibres.

2.5 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 β ¡1, the relative weight of the ECG criteria is greater in small than large hypertrophy. Also, sensitivity and specificity was estimated from our set of data by calculating the following equations: $Sensitivity = TP/(TP + FN)$ and $Specificity = TN/(TN + FP)$, where TP are the true positive, FP the false positive and TN the true negative cases, all of them confirmed by echocardiographic analysis. More specifically, echocardiographic mass calculation, as described above, and the criteria of a cardiologist were set as the gold standard for LVH diagnosis.

2.6 ROC curves

We set δ=1 and β=1 and calculated the Receiver Operating Characteristic (ROC) curves for the simplified allometric model log(y) = log(m) and plotted the Sensitivity against the 1-Specificity values for the different possible cut-off points. Thereafter, the optimal cut-off point in the ROC curve was computed as the point nearest the top left-hand corner. This selection maximizes the sensitivity and specificity sum, when it is assumed that the 'cost' of a false negative result is the same as that of a false positive result [18].

3 Results

3.1 Allometry and sensitivity of electrocardiographic LVH markers

Using the equation AECG = δ + β (VM) in log-log representation, the fitting procedure produced coefficients for every LVH index. 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. The best correlation was offered by the Voltage-Cornell index (r=0.7229), followed by the Total Voltage index (r=0.5292) and last, by Sokolows (r=0.2769), the latter obviously very low.

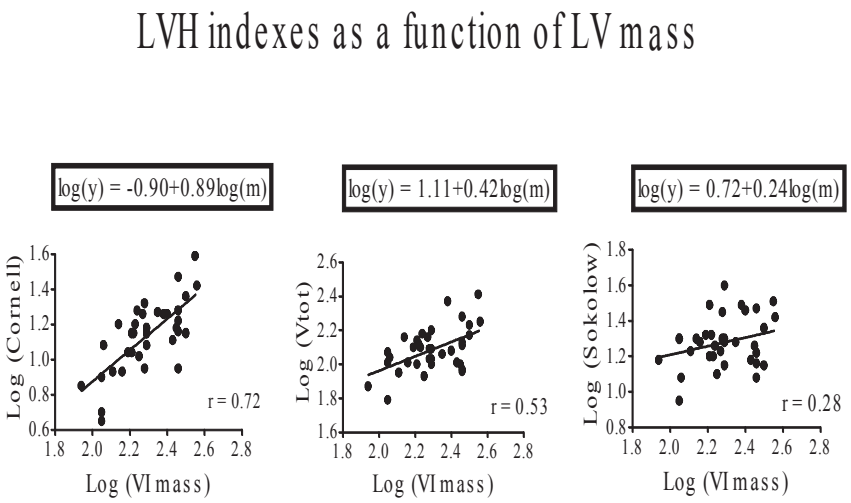

Fig. 1. Linear regressions for the allometric fits of ECG-based LVH markers: Cornell index (left panel), total 12-lead voltage (middle panel) index and Sokolow index (right panel).

Notice as well, that all the slopes β in the adjustment are positive and smaller than 1. This means that indexes will increase along with the amount of hypertrophy up to a certain saturation level. This is, there will be a point at which even though the amount of hypertrophic fibres increases, the LVH index will remain almost constant. Slopes greater or even equal to 1 would be more desirable in order not to lose sensitivity with the hypertrophy extent. Table 1 shows the sensitivity and specificity as reviewed in 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.

3.2 Theoretical allometric model

Finally, the theoretical allometric model was computed on the left ventricular mass data available by setting the coefficient $\delta = 0$ and $\beta = 1$. Afterwards, the

Table 1. Mean ± SD of SVD indexes for healthy subjects (PTB Database) and ischemic patients (STAFF-III Database), $p<0.005$

	Sensitivity	Specificity	δ	β	r
Voltage-Cornell	42%	96%	-0.90	0.89	0.72
Sokolow	22%	100%	1.11	0.42	0.53
Total Voltage	17.2%	95%	0.72	0.24	0.28

ROC curve of this theoretical model and the remaining ECG-based indexes were calculated in order to compare their hability to predict LVH. Also, the area under the curves (AUC) were calculated. Figure 2 shows the great potential of the allometric model to predict LVH, displaying an AUC = 0.96, clearly outstanding from the others. AUC values for the LVH indexes were as follows: Theoretical model (AUC=0.96), Cornell (AUC=0.74), Total Voltage (AUC=0.64) and Sokolow (AUC=0.59).

4 Discussion and conclusions

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 under study was quite homogeneous in terms of age, presenting mainly the same type of hypertrophy. 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 can 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. Interestingly, the Voltage-Cornell index showed the best allometric fit, with a sensitivity of 42%, as collected from the bibliography [10] and 35%, as estimated from our data pool. 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, which means that the greater the amount of hypertrophic fibres, the lesser the growth of the LVH marker, leading to a loss of sensitivity with hypertrophy extent. Therefore, if more sensitive markers are required, β tending to 1 would be desired. It is important to note that even though the latter index was designed for different

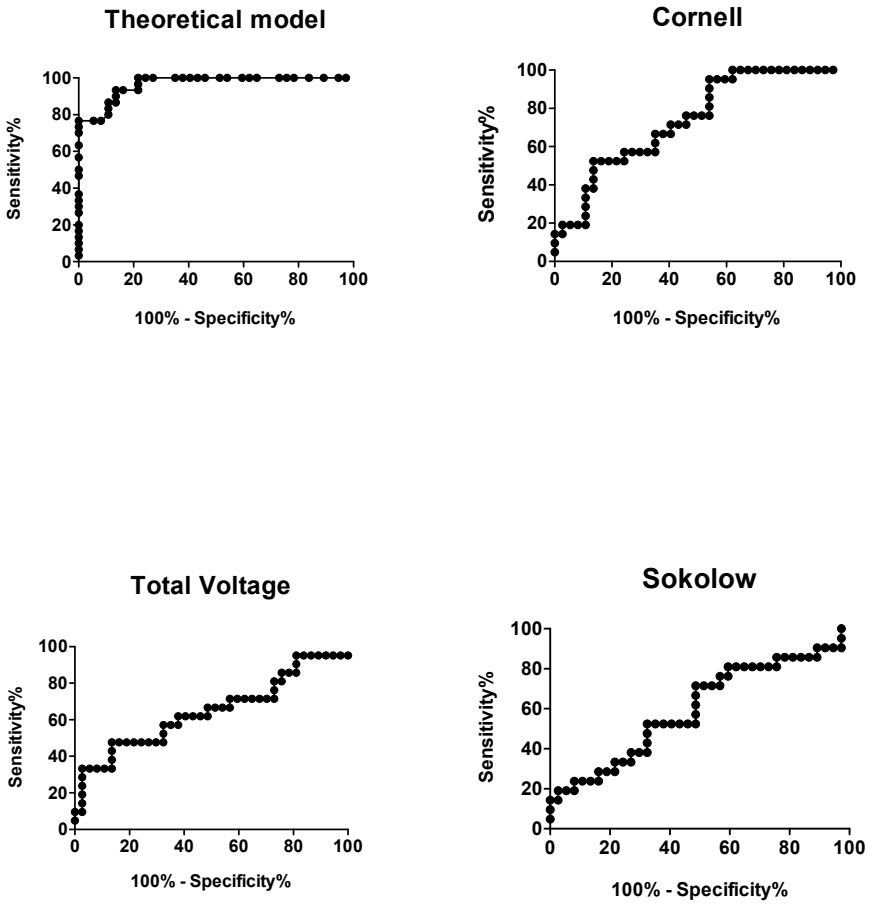

Fig. 2. ROC curve for the theoretical allometric model (upper left panel, AUC=0.96), the Cornell index (upper right panel, AUC=0.74), Total Voltage index (lower left panel, AUC=0.64) and Sokolow index (AUC=0.59)

LVH cut-off points (132 g/m2 for men and 109 g/m2 for women) as used here, it adapted well to the new definition, postulating itself as the most robust ECG marker of hypertrophy. Finally, the voltage increase, as expressed in the electrocardiographic indexes studied here followed 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 constant β) resulted all positive and smaller than one, leading to ECG-based indexes showing a saturation for high hypertrophy levels. To overcome this, a theoretical model with $\beta = 1$ was proposed, and an AUC of 0.96 was found, proving the power of the allometric model to predict LVH.

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References

[1] Lindstedt SL, Schaeffer PJ.: Use of allometry in predicting anatomical and physiological parameters of mammals. Laboratory Animals, 2002, 36:1-19

[2] Lindstedt SL, Miller B, Buskirk S: Home range, time, and body size in mammals Ecology, 1986, 67(2):413-418

[3] Noujaim SF, Lucca E, Muoz V, Persaud D, Berenfeld O, Meijler FL and Jalife J.: From mouse to whale: A universal scaling relation for the PR interval of the electrocardiogram of mammals. Circulation, 2004, 110:2801-8

[4] Bonomini MP, Arini PD, Gonzalez G, Buchholz B, Valentinuzzi ME: The allometric model in chronic myocardial infarction Theoretical Biology and Medical modeling, epub. Abril 2012, 9:15

[5] Probability of ventricular fibrillation: allometric model based on the ST deviation Bonomini MP, Arini PD, Valentinuzzi ME. Biomed Eng Online, 2011, Jan 13;10:2

[6] MacFarlane PW, and Lawrie TD: Press P, editor. Comprehensive Electrocardiography: Theory and Practice in Health and Disease. Oxford, United Kingdom, 1998

[7] Hsieh BP, Pham MX and Froelicher VF : Prognostic value of electrocardiographic criteria for left ventricular hypertrophy Am Heart J., 2005, 150(1):161-7

[8] Hancock W, Deal B, Mirvis D, Okin P, Kligfield P and Gettes L Recommendations for the standardization and interpretation of the electrocardiogram Journal of the American College, 2009, 53(11)

[9] Casale P DR, Kligfield P, Eisenberg RR, Miller DH, Chaudhary BS and Phillips MC Electrocardiographic detection of left ventricular hypertrophy: development and prospective validation of improved criteria J Am Coll Cardiol., 1985, 6:572-80

[10] Levy D SD, Garrison RJ, Anderson KM, Kannel WB and Castelli WP: Echocardiographic criteria for left ventricular hypertrophy: the Framingham Heart Study Am J Cardiol., 1987, 59:956-60

[11] Siegel RJ, Roberts RW: Electrocardiographic observations in severe aortic valve stenosis: correlative necropsy study to clinical, hemodynamic, and ECG variables demonstrating relation to 12-lead QRS amplitude to peak systolic transaortic pressure gradient Am Heart J, 1982, 103(2):210-21
[12] Sokolow M, and Lyon TP: The ventricular complex in left ventricular hypertrophy as obtained by unipolar and limb leads Am Heart J., 1949, 38(2):273-94
[13] Troy BL, Pombo J, and Rackley CE: Measurement of left ventricular wall thickness and mass by echocardiography Circulation, 1972, 45(3):602-11
[14] Devereux RB, and Reichek N: Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method Circulation, 1977, 55(4):613-8
[15] Foppa M DBaRL. Echocardiography-based left ventricular mass estimation. How should we define hypertrophy? Cardiovasc Ultrasound, 2005, 3:3-17
[16] Snell O.: Die Abhngigkeit des Hirngewichtes von dem Krpergewicht und den geistigen Fhigkeiten (Dependence of brain weight on body weight and the intellectual capacity) Arch Psychiatr u Nervenkr, 1891, 23:436-46
[17] Von Bertalanffy L: Quantitative laws in metabolism and growth Quaterly Review Biology., 1957, 32(3)
[18] Altman DG.: Statistics in medical journals: developments in the 1980s. Stat Med. 1991 Dec;10(12):1897-913