Evaluation of the Relation between Changes in R-wave Amplitude and LV Mass and Dimensions in a Model of "Reversed Hypertrophy"

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Abstract

Electrocardiographic (ECG) diagnosis of left ventricular (LV) hypertrophy, based on the so-called voltage criteria, suffers from low sensitivity, so that the dominant cardiac factors influencing the QRS voltage have not been fully elucidated. Our aim was to evaluate the correlation between changes in R-wave amplitude (R-AMP) and LV mass and size in a model of "reversed hypertrophy", such as that induced by 5-days head-down (6°) bed rest (HDBR). ECG Holter-24h and echocardiographic imaging were obtained before (PRE) and on the last day (HDT5) of HDBR in 11 male subjects (age 21÷41 years).The R-AMP derived from the vectorcardiogram was correlated with the echo-derived LV mass, end-diastolic (EDV), systolic (ESV) and stroke (SV) volumes. Linear regression between R-AMP and ESV (y=.013R+26, r2=.31) was found significant (p<.05), while regression with LV mass (y=.195R+83, r2=.19, p=.04) was weaker. Further studies using electrophysiologic models could better elucidate the phenomenon.

1. Introduction

The QRS changes found in left ventricular (LV) hypertrophy include increased QRS amplitude, increased QRS duration, and deviation of the electric axis in the frontal plane to the left. Nevertheless, electrocardiographic (ECG) diagnosis of LV hypertrophy is based mainly on the so-called voltage criteria, i.e. the increased amplitude of the QRS complex [1]. However, it is well known that the ECG criteria of LV hypertrophy have low sensitivity, and the correlation between the QRS amplitude and LV mass is poor [2]. Moreover, recent cardiac modeling studies [3] have shown that LV mass is not the major determinant of QRS voltage, but yet the dominant cardiac factors influencing the QRS voltage and morphology have not been fully elucidated.

In order to improve knowledge about the effect of LV remodelling on QRS voltage, our aim was to evaluate the correlation between changes in R-wave amplitude (R-AMP) and LV mass and dimensions in a model of "reversed hypertrophy", such as that induced by 5-days head-down (6°) bed rest (HDBR). The HDBR is known to represent a model of chronic circulatory unloading, simulating sustained exposure to microgravity and related cardiac deconditioning. Changes in LV mass and volume take place soon after entering into HDBR, due to short-term volume regulatory mechanisms activated resulting in loss of plasma volume.

2. Methods

2.1. Subjects

Twelve healthy men aged 33±7 (range, 21 to 41 years; body mass index, 23.7±2.1 kg/m^2, maximal oxygen uptake 39±6 ml*kg^{-1}*min^{-1}) were selected for this study. Each subject gave their informed consent to participate in the protocols which were approved by the Institutional Review Board of the "Comité de Protection des Personnes Sud Ouest et Outre Mer I" and by the French Drug Agency (Agence Française de Sécurité Sanitaire pour les Produits de Santé).

2.2. Bed rest study design

Strict bed rest was performed at -6º head-down tilt position for a total of 5 days. Subjects were housed in the Institut de Médecine et de Physiologie Spatiales (MEDES) facility at the University Hospital of Rangueil, Toulouse, France.

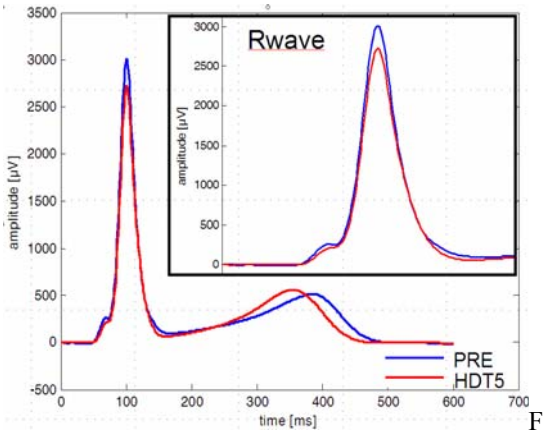

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Figure 1. Example of the averaged waveform derived from the vectorcardiogram relevant to 1000-1009 ms duration bin of one subject before (PRE) and during bed rest (HDT5).

As part of the European Space Agency BR strategy, subjects were enrolled in a cross-over design with a wash-out period of about 1.5 months between three consecutive campaigns, with one control (CTRL) and two artificial gravity (AG) treatment groups applied each day during HDBR: AG1, with AG for 30' continuously, and AG2, with AG for 30' intermittently (6 periods of 5' each), both obtained with a short-arm centrifuge producing a 1g gravity level at the level of the heart.

In this study, only results obtained while subjects were in the CTRL group will be presented. Before the beginning and after the end of each 5-days HDBR, subjects were evaluated during 5 days of ambulatory period, during which lying in bed during the day was prohibited.

2.3. Data acquisition

Plasma volume was measured two days before HDBR and during HDBR in the last day (HDT5), using the optimized CO-rebreathing method (SpiCO®, Blood tec GbR, Bayreuth, Germany). Also blood volume was derived.

The ECG signals used for this study were acquired using a 12-lead Holter 24-h high-fidelity (1000 Hz) digital recorder (H12+, Mortara Instrument Inc., Milwaukee, WI) with beginning of the acquisition 6 days before the start of the HDBR (PRE), and on the last day of HDBR (HDT5).

A single expert operator performed all the transthoracic echocardiographic acquisitions using a iE33 ultrasound equipment (Philips Medical Systems). All participants underwent standard 2D, as well as real-time 3D echocardiographic (RT3DE) examination. RT3DE datasets were acquired using wide-angled acquisitions in which four to seven wedge-shaped sub-volumes (93°x21°) were obtained over consecutive cardiac cycles during a breath-hold with ECG gating. Image acquisition was performed 5 days before the start of HDBR (PRE) and in the last day of HDBR (HDT5), with the subject in supine left decubitus position.

2.4. ECG signal processing

Only the RR values classified as in sinus rhythm (H-scribe and SuperECG software, Mortara Instrument Inc., Milwaukee, WI, USA) were included in the following analysis. First, the RR intervals were classified as day-time (from 6:30 to 23:00) and night-time (from 23:00 to 06:30), to apply the next steps to the analysis of the night period only, to avoid misinterpretation due to daily movements or subject's involvement.

From the 12-lead ECGs, the inverse Dower matrix transformation was applied to obtain the orthogonal leads X, Y, Z, from which the vectorcardiogram was computed.

A selective beat averaging technique [4-5] was used to obtain averages of P-QRS-T complexes preceded by the same stable heart rate in the range from 900 to 1200 ms, with 10 ms bin amplitude. After beats realignment according to the R wave peak and filtering with a low-pass FIR filter (15 Hz), a simple averaging operation was applied, thus obtaining a mean template for each bin, from which the isoelectric line (defined by a stationary point between S- and T-waves and by a relative minimum after 800 ms) was subtracted. Then, a procedure for the automated detection of the R-apex was applied.

2.5. Image analysis

Analysis was performed by an investigator blinded to the subject identity, epoch of acquisition and group assignment. LV mass was computed by the area-length method from end-diastolic 2D images, while LV end-diastolic (EDV) and end-systolic (ESV) volumes, stroke volume (SV) and ejection fraction (EF) were computed from 3D echo datasets (QLab 8, Philips).

Table 1. Results echocardiographic examinations and plasma volume.

	PRE	HDT5
Heart rate (bpm)	64±6	64±10
LV mass (g)	137±23*	109±21
3D EDV (ml)	147±25*	120±25
3D ESV (ml)	58±13*	45±11
3D SV (ml)	88±16*	75±17
3D EF (%)	60±5	62±5
BMI (kg/m^2)	24.0±2.1*	23.6±2.1
Plasma volume (l)	3.7±.4*	3.2±.2
Blood volume (l)	6.0±.6*	5.6±.4

*: $p<.05$ PRE vs HDT5

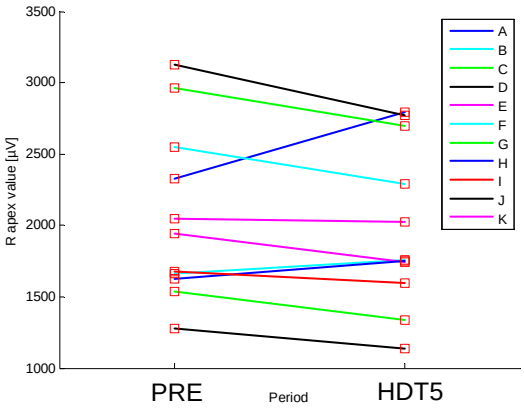

Figure 2. Individual results for R-AMP computed from the vectorcardiogram as median value in the range 900-1200 msec duration bin, before (PRE) and during bed rest (HDT5).

2.6. Statistical analysis

Data are expressed as mean±standard deviation, unless otherwise specified. A paired Student t-test or Wilcoxon Signed-rank test ($p<0.05$) was applied to test for differences between PRE and HDT5 in the computed parameters. To evaluate correlation between changes in LV dimensions and R-AMP, HDT5 measurements (i.e., affected by 5-d chronic unloading) were considered as the reference values, to be compared with PRE measurements (i.e., "reversed hypertrophy" model). For each subject, the change in R-AMP was considered as the median value of variation in the range 900-1200 msec. For each parameter, linear regression was computed and coefficient of determination (r^2) obtained, if significant.

3. Results

For technical reasons, both ECG and echo measurements were available at PRE and HDT5 in only 11 of the 12 subjects.

Considering HDT5 as the reference value in the model of reversed hypertrophy, on the average R-AMP was 6.9% larger at PRE than at HDT5 ($p<.05$), passing from 1991±576 μV to 2066±605 μV. More precisely, in 8/11 subjects this trend was confirmed, while in 3/10 subjects R-AMP was found greater at HDT5.

Also for echo parameters, when HDT5 was assumed as the baseline, at PRE the heart appeared more hypertrophic, with a significant increase in LV mass of 19.7%, and a corresponding dilated ventricle with an increase in EDV by 21%, in ESV by 30% and in SV by 20%. This was the result of the higher amount of circulating plasma and blood volume at PRE compared to HDT5, reflected in an increased preload (Table 1).

Linear regression computed over absolute values obtained at both PRE and HDT5 showed higher and more significant correlation in ESV, lower for EDV and weaker for LV mass, while for SV it was not significant (Table 2).

Table 2. Linear regression of echo-derived absolute measurements with R-AMP.

		r^2	p
LV mass	Y=.0195R+83	.187	.045
3D EDV	Y=.0235R+86	.233	.023
3D ESV	Y=.0130R+26	.311	.007
3D SV	Y=.0105R+60	.119	n.s.

Once considering the 8/11 subjects with R-AMP lower in HDT5 than PRE, significant direct correlation with the change in R-AMP was found for the change in ESV, while no correlation was present with the change in LV mass or EDV. Interestingly, negative correlation was found with the change in SV (see Table 3). Conversely, when correlation was computed on all subjects (Table 4), an inverse linear relation was found both for EDV and SV, with the latter highly significant and able to explain about 90% of variability in changes in R-AMP.

4. Discussion and conclusions

Five-days HDBR resulted in significant decreases in LV mass and size, presumably in response to the decreased physiological loading and dehydration caused by the elimination of the head-to-foot hydrostatic gradient [6]. Previous studies evidenced this effect, both after bed rest or spaceflight, by reporting a decrease in LV mass following the adaptation of EDV. However, by observing in astronauts after 9-16 days spaceflight that the reduction of about 10% in LV mass and EDV at landing was completely reversed three days later, these changes could be interpreted as due to dehydration instead than cardiac atrophy [7]. Observations of about 4% loss in LV mass explained as loss of cardiac interstitial volume during the dialysis session, together with decrease in LV EDV and

Table 3. Linear regression of changes in echo and R-AMP (Δ=PRE-HDT5) measurements in 8/11 subjects with Δ>0.

		r^2	p
LV mass	ΔY=.0063ΔR+22	.003	n.s.
3D EDV	ΔY=.0015ΔR+86	.0006	n.s.
3D ESV	ΔY=.0419ΔR+4	.511	.046
3D SV	ΔY=-.0404ΔR+15	.504	.048

Table 4. Linear regression of changes in echo and R-AMP (Δ=PRE-HDT5) measurements in 11 subjects.

		r^2	p
LV mass	ΔY=-.0273ΔR+30	.231	n.s.
3D EDV	ΔY=-.0454ΔR+30	.627	.004
3D ESV	ΔY=.004ΔR+13	.02	n.s.
3D SV	ΔY=-.049ΔR+13	.898	<.0001

ESV, corroborates this hypothesis [8].

Conditions causing changes in LV chamber size cause alterations in ECG waveform amplitude in humans. In LV volume overload states, increases in both T and R wave amplitude have been observed, but no explanation has been proposed [9]. Using a mathematical model, Brody suggested that intracardiac blood, a highly conductive mass, augments the electrocardiographic surface potential if the progress of myocardial excitation is radial to the blood mass [10]. Studying the relation between LV size and R-AMP by changing preload (but not LV mass) or position of the heart in the chest, R-wave amplitude in leads V5 and V6 were reported as varying directly with LV dimensions [11]. However, other studies [12] reported a significant increase in QRS voltages inversely proportional to acute changes in LV dimensions.

In our hypothesis, baseline values before HDBR should have been related to higher R-AMP, while reduced LV mass and size at HDBR to lower R-AMP. As in Table 2, this relation in absolute values, hence weak, was confirmed, in agreement with the findings of Aittomäki and Salrnenperä [13], hence 3/11 subjects had increased R-AMP at HDT5. However, when focusing on differences measured between PRE and HDT5, the strongest relationship found was of negative correlation with changes in SV, while confirming the lack of correlation with changes in LV mass.

The discrepancy between LV mass and QRS voltage is currently perceived as a limitation of electrocardiography in LV hypertrophy diagnosis. However, there may be important diagnostic information hidden in this apparent discrepancy. In this respect, mathematical modeling could help in elucidating the phenomenon.

Our results could have suffered from several confounding factors: 1) the amplitude of R-wave was computed from the vectorcardiogram, while previous studies focused on V5 and V6 as main leads to observe changes in ECG amplitude; 2) electrodes position between PRE and HDT5 might slightly have changed; 3) echo and ECG were not acquired simultaneously, and R-AMP was obtained by averaging of the night period; 4) 5-days HDBR elicits both reduction in LV preload and dehydration of LV mass, with combined effects on R-AMP.

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References

[1] Schillaci G, Battista F, Pucci G. A review of the role of electrocardiography in the diagnosis of left ventricular hypertrophy in hypertension. J Electrocardiol 2012;45(6):617–623

[2] Krittayaphong R, Nomsawadi V, Muenkaew M, Miniphan M, Yindeengam A, Udompunturak S. Accuracy of ECG criteria for the diagnosis of left ventricular hypertrophy: a comparison with magnetic resonance imaging. J Med Assoc Thai 2013; 96 Suppl 2:S124-32.

[3] Bacharova L, Estes H, Bang L, Rowlandson I, Schillaci G, Verdecchia P, Macfarlane PW. The first statement of the Working Group on Electrocardiographic Diagnosis of Left Ventricular Hypertrophy. J Electrocardiol 2010;43(3):197-9.

[4] Badilini F, Maison-Blanche P, Childers R, Coumel P. QT interval analysis on ambulatory electrocardiogram recordings: a selective beat averaging approach. Med Biol Eng Comput 1999;37:71–79.

[5] Caiani EG, Pellegrini A, Bolea J, Sotaquira M, Almeida R, Vaïda P. Impaired T-wave amplitude adaptation to heart-rate induced by cardiac deconditioning after 5-days of head-down bed-rest. Acta Astronautica 2013;91:166-172

[6] Kozàkovà M, Malshi E, Morizzo C, Pedri S, Santini F, Biolo G, Pagani M, Palombo C. Impact of prolonged cardiac unloading on left ventricular mass and longitudinal myocardial performance: an experimental bed rest study in humans. J Hypertens 2010; 29(1):137-43.

[7] Summers RL, Martin DS, Meck JV, Coleman TG. Mechanism of spaceflight-induced changes in left ventricular mass. Am J Cardiol 2005;95:1128-1130

[8] Hunold P, Vogt FM, Heemann UW, Zimmermann U, Barkhausen J. Myocardial mass and volume measurement of hypertrophic left ventricles by MRI-study in dialysis patients examined before and after dialysis. J Cardiovasc Magn Reson 2003;5(4):553-61.

[9] Cabrera E, Monroy JR. Systolic and diastolic loading of the heart. II. Electrocardiographic data. Am Heart J 1952;43:669

[10] Brody DA: A theoretical analysis of intracavitary blood mass influence on the heart-lead relationship. Circ Res 1956;4:731

[11] Feldman T, Borow KM, Neumann A, Lang RM, Childers RW. Relation of electrocardiographic R-wave amplitude to changes in left ventricular chamber size and position in normal subjects. Am J Cardiol 1985; 55(9):1168-74.

[12] Vancheri F, Barberi O. Relationship of QRS amplitude to left ventricular dimensions after acute blood volume reduction in normal subjects. Eur Heart J 1989;10(4):341-5

[13] Aittomäki JV, Salrnenperä MT. Association between R-wave amplitude of the electrocardiogram and myocardial function during coronary artery bypass grafting. J Cardiothor Vasc Anesthesia 1997;11: 856-860

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