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ORIGINAL ARTICLE

Biological, electrical and echocardiographic indices versus cardiac magnetic resonance imaging in diagnosing left ventricular hypertrophy

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The aim of this study was to compare the diagnostic performance of N-terminal pro-brain natriuretic peptide (NT-proBNP), electrocardiographic (ECG) criteria and transthoracic echocardiography (TTE) versus cardiac magnetic resonance imaging in detecting left ventricular hypertrophy (LVH). The study included 42 hypertensive subjects with mean ± s.d. age 48.1 ± 12.3 years, 57.1% men, 24-h ambulatory blood pressure 144/89 mm Hg, left ventricular ejection fraction >50%, without symptoms of heart failure, and not taking any drugs that interfere with hormonal regulation. The accuracies of the methods in detecting LVH were compared at two diagnostic LVH cutoffs: low, 83 g m^{-2} in men and 67 g m^{-2} in women; and high, 96 g m^{-2} in men and 81 g m^{-2} in women. With the low and high LVH cutoffs, the areas under the receiver-operating characteristic curves and the optimal values for NT-proBNP were 0.761, 0.849, 200 and 421 pg ml^{-1}, respectively. An NT-proBNP level under 30 pg ml^{-1} ruled out LVH with 100% sensitivity. The optimal values and literature-based values of NT-proBNP allowed a correct classification of 73–81% of the subjects. In 80–90% of the cases, the diagnostic accuracy of NT-proBNP was close to that of ECG criteria but lower than that of TTE criteria. Interestingly, combining ECG criteria and NT-proBNP level improved the diagnostic performance to be at least comparable to that of TTE: the percentages of correctly classified subjects were 73–95% *vs.* 67–86%, respectively. Of note, the range considers both diagnostic LVH cutoffs. The simultaneous use of ECG criteria and NT-proBNP plasma levels seemed to be powerful enough to detect LVH in most hypertensive subjects.
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Keywords: cardiac magnetic resonance imaging; hypertension; left ventricular hypertrophy; NT-proBNP; transthoracic echocardiography

INTRODUCTION

Left ventricular hypertrophy (LVH) has frequently been shown to be a powerful prognostic marker in hypertensive subjects.[1–3] Among the numerous diagnostic tools that can be used to detect LVH, the electrocardiographic (ECG) criteria are easily available and generally have a high specificity but a low sensitivity (90% and 30%, respectively).[4] Transthoracic echocardiography (TTE) improves LVH detection to levels of sensitivity and specificity near 90%[5] but presents many limits, among which are an overestimation of the left ventricular mass (LVM), poor reproducibility, high cost and result unavailability in more than 10% of hypertensive subjects for technical reasons.[6–8] Cardiac magnetic resonance imaging (CMR) is currently the gold standard for assessing LVM. This technique provides high-resolution images with excellent reproducibility.[9–11] However, CMR is neither readily available nor cost-effective for LVM assessment in the routine evaluation of hypertensive subjects.

The use of N-terminal pro-brain natriuretic peptide (NT-proBNP) may be an alternative method to detect LVH in hypertensive subjects. Indeed, NT-proBNP plasma level is correlated with the TTE LVM index (LVMI).[12,13] In addition, NT-proBNP has been compared with CMR in one study;[14] its diagnostic value for LVH seemed sufficient, but the study included only 27 participants.

As the respective values of NT-proBNP, ECG and TTE in assessing LVH are currently unknown, the objective of the present study was to compare the diagnostic accuracies of these three methods with each other and to the accuracy of CMR, the reference method. The value of combining these markers was also tested.

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METHODS

Participants

From June 2007 to September 2008, the study included 42 subjects referred to our center for the evaluation and treatment of hypertension. The exclusion criteria were the following: history or current symptoms of heart failure, left ventricular ejection fraction <50% on echocardiography, aortic or mitral regurgitation of grade 3 or 4, atrial fibrillation, pulmonary fibrosis, cirrhosis, use of a pacemaker, presence of a metal implant, claustrophobia, pregnancy and age under 18 years.

The study was approved by the local ethics committee and by the Comité de Protection des Personnes de Lyon Sud-Est IV. All enrolled participants gave written informed consent.

Protocol

Before the hypertension work-up, any drugs likely to interfere with hormone regulation were withdrawn before admission (6 weeks for spironolactone and 2 weeks for diuretics, beta-blockers or renin-angiotensin system inhibitors) and were replaced with alpha-blockers, centrally acting drugs or calcium antagonists according to the current guidelines.[15] Over 2 days of a hospital stay, all of the participants filled out a questionnaire (morphometric characteristics, cardiovascular risk factors, symptoms and so on) and underwent a physical examination and various biological tests (including plasma NT-proBNP), a 24-h recording of ambulatory blood pressure (BP), a 12-lead ECG and a CMR.

The body surface area (BSA) was calculated using the Dubois and Dubois formula; that is, $BSA = 0.20247 \times (height)^{0.725} \times (weight)^{0.725}$.

The electrical LVH criteria were defined as follows: a Sokolow–Lyon index (amplitude of leads SV1 + RV5 or RV6) >3.5 mV, a Cornell voltage criterion (R wave in aVL lead (RaVL) + SV3, with 8 mm added in women) >2.8 mV and a Cornell product >2440 mm ms (Cornell voltage criterion × QRS duration).[16–18] The amplitude of RaVL was also tested with a threshold of 6 mm.[19,20]

The plasma NT-proBNP concentration was assessed after one night in the supine position using an ELISA kit (Roche Diagnostics, Meylan, France; range 5–35 000 pg ml^{-1}). Considering the previously published reference values for NT-proBNP in men and women in different age classes,[21–23] all values under the 97.5th percentile for a given sex and age were considered to be in the normal range.

Two-dimensional images, M-mode and Doppler recordings were obtained from a Vivid Five ultrasound device (GE Vingmed Ultrasound, Horten, Norway). The thickness of the IVS (interventricular septum), that of the posterior wall, and the LVD (diameter of the left ventricle) were assessed according to the Penn convention.[24] Each parameter was recorded over three consecutive heart beats, ignoring other data. The LV dimensions were determined from M-mode images and used to calculate LVM using the formula of Devereux: $LVM = 1.04[(IVS + LVD + PW)^3 - LVD^3] - 13.6$. The LVMI was defined in two different ways: (i) indexation to the BSA (TTE LVMI^{BSA}) according to the European Society of Cardiology—European Society of Hypertension guidelines with the following LVH criteria: TTE LVMI^{BSA} >125 g m^{-2} in men and >110 g m^{-2} in women;[15] and (ii) indexation of height to the allometric power of 2.7 (TTE LVMI$^{2.7}$) with the following LVH criterion: TTE LVMI$^{2.7}$ >51 g m$^{-2.7}$ in both sexes.[25] Diastolic dysfunction was diagnosed when patients had an increased E/e′ ratio >15 (average of three measurements of septal and lateral e′) as mentioned in the current European Society of Cardiology—European Society of Hypertension guidelines.[26]

CMR was performed using a 1.5T magnet (Magnetom Symphony Maestro Class, Siemens, Erlangen, Germany). Electrocardiogram-gated, breath-hold segmented, cine true fast imaging (True-FISP) was performed in long-axis views (four- and two-chamber views) and finally in short-axis views. On each short-axis slice, the endocardial and epicardial contours were manually traced at end diastole. LVM was derived using Simpson's method: after summation of the discs, the LVM was calculated by subtracting the endocardial volume from the epicardial volume at end diastole and multiplying the result by 1.05 g cm^{-3}. Two previously described LVH cutoff values were considered: a low value of 83 g m^{-2} in men and 67 g m^{-2} in women[27] and a high value at 96 g m^{-2} in men and 81 g m^{-2} in women.[28]

Statistical analyses

The qualitative variables are summarized as the mean ± s.d., except those with skewed distributions, which are expressed as median values (boundaries of the interquartile ranges). Categorical variables were expressed as percentages. Student's paired or unpaired *t*-tests and nonparametric ANOVA (Mann–Whitney's *U*-test) were used to compare continuous variables between groups. The χ^2-test was used to compare dichotomous variables.

The correlations between variables were assessed with a linear regression analysis (Pearson's coefficient of correlation '*r*'). A logarithmic transformation was applied to NT-proBNP, Sokolow–Lyon index, Cornell voltage criterion, Cornell product, RaVL lead, TTE LVMI$^{2.7}$, TTE LVMI^{BSA} and CMR LVMI values because of their skewed distributions. To test the independent association between NT-proBNP and CMR LVMI, a multiple linear regression analysis included the variables that had statistically significant correlations with NT-proBNP in univariate analyses.

To estimate the global accuracy of NT-proBNP, ECG indexes and TTE LVMI in diagnosing CMR LVH, an empirical receiver-operating characteristic (ROC) curve was built. To test the negative and positive predictive values, we used for NT-proBNP (i) our optimal values, (ii) values above the 97.5th percentile of the reference distribution according to age and sex[21–23] and (iii) the NT-proBNP threshold proposed by Morillas *et al.*[14] (35 pg ml^{-1}). For ECG criteria and TTE LVMI, we used values previously reported in the literature (see the Protocol paragraph above). The area under the ROC curve (AUC) was estimated using the Mann–Whitney test and was compared with 50%. Various AUCs were compared using the χ^2-test.

RESULTS

Baseline characteristics

There were 42 participants included in this study: 28 with essential hypertension, 10 with primary aldosteronism (6 adenomas and 4 adrenal hyperplasias) and 4 with secondary hyperaldosteronism (2 fibromuscular dysplasias and 2 atheromatous renal artery stenosis). The participants' baseline characteristics are summarized in Table 1. Using the low CMR LVMI cutoff values (83 g m^{-2} in men and 67 g m^{-2} in women), 16 subjects (12 men and 4 women) were classified as having LVH. These subjects had higher NT-proBNP levels, 24-h ambulatory BPs, Sokolow indexes, Cornell voltages, Cornell products, RaVL amplitudes and TTE LVMs than subjects classified without LVH. Using the high CMR LVMI cutoff values (96 g m^{-2} in men and 81 g m^{-2} in women), only nine men were classified as having LVH and showed the same differences *vs.* subjects classified without LVH regarding NT-proBNP levels and ECG indices (data not shown). NT-proBNP levels and age were not significantly different between women and men (123 (54–183) *vs.* 59 (30–158) pg ml^{-1}, $P = 0.286$ and 46.8 ± 12.9 *vs.* 49 ± 12 years, $P = 0.525$, respectively).

A reliable measurement of LVM by TTE was obtained in 37 subjects (88%). As expected, LVM was statistically overestimated by TTE compared with CMR (206 *vs.* 120 g; $P < 0.001$).

Using TTE LVMI$^{2.7}$ >51 g m$^{-2.7}$ as a cutoff, nearly half of the subjects were classified as having LVH (17 subjects, 49.6%). The same number was found using TTE LVMI^{BSA}; however, as expected, ECG criteria detected fewer LVH subjects: 9 (22.5%) had a Sokolow–Lyon index >3.5 mV, 8 (20%) had a Cornell voltage criterion >2.8 mV, 10 (25%) had a Cornell product >2440 mm ms and 14 (33%) had a RaVL >0.6 mV.

Correlations between CMR LVMI and other parameters

As shown in Table 2, considering the entire cohort, NT-proBNP, ECG criteria and TTE LVMI were all statistically correlated with CMR LVMI. Pearson's correlation coefficient between CMR LVMI and NT-proBNP was higher than that between CMR LVMI and the Sokolow–Lyon index. The best correlation with CMR LVMI was that

Table 1 Baseline characteristics of the participant hypertensive subjects

Characteristics	*All* (N = *42*)	*CMR LVH* (N = *16*)	*No CMR LVH* (N = *26*)	P-*value*
Demographic characteristics				
Mean age (years)	48.1 ± 12.3	49.8 ± 11.1	47.0 ± 13.1	0.479
Ratio of women/men (%)	42.9/57.1	25.0/75.0	53.9/46.1	0.067
Body surface area (m^2)	1.85 ± 0.20	1.91 ± 0.21	1.81 ± 0.19	0.107
Height (m)	1.68 ± 0.10	1.70 ± 0.09	1.68 ± 0.10	0.487
BMI ($kg\,m^{-2}$)	25.2 (23.0–29.6)	27.6 (24.4–31.5)	24.7 (21.9–29.3)	0.133
24-h ambulatory blood pressure				
SBP (mm Hg)	144 (126–163)	176 (147–201)	131 (125–144)	<0.001
DBP (mm Hg)	89 (79–96)	103 (92–122)	81 (77–89)	<0.001
Heart rate (b.p.m.)	71.7 ± 10.3	72.3 ± 9.8	71.3 ± 10.8	0.778
Medical history				
Current smoking (%)	15.6	12.5	19.2	0.570
Diabetes (%)	7.1	11.5	0.0	0.159
Biochemical assays				
NT-proBNP ($pg\,ml^{-1}$)	79 (31–166)	155 (48–373)	61 (27–117)	0.005
eGFR ($ml\,min^{-1}$)	95.6 ± 27.9	89.9 ± 18.8	99.7 ± 32.0	0.273
LDL cholesterol (g^{-l})	1.24 ± 0.33	1.30 ± 0.31	1.20 ± 0.33	0.353
HbA1c (%)	5.3 ± 0.4	5.4 ± 0.4	5.3 ± 0.4	0.666
ECG				
Sokolow–Lyon index (mV)	2.4 (1.7–3.2)	2.6 (1.8–4.8)	2.3 (1.5–2.9)	0.105
R wave in aVL lead (mV)	0.5 (0.2–0.9)	1.0 (0.6–1.5)	0.3 (0.2–0.6)	<0.001
Cornell voltage criterion (mV)	1.8 (1.4–2.4)	2.8 (2.0–3.1)	1.6 (1.4–2.0)	<0.001
Cornell product (mm ms)	1627 (1185–2543)	2680 (1798–2872)	1393 (992–1706)	<0.001
Cardiac imaging				
TTE left ventricular mass (g)	206 (145–350)	364 (276–393)	153 (131–206)	<0.001
TTE LVEF (%)	61.6 ± 11.0	59.3 ± 12.1	63.0 ± 10.3	0.322
CMR left ventricular mass (g)	120 (100–167)	217 (158–286)	101 (87–122)	<0.001
CMR LVEF (%)	64.7 ± 9.1	62.0 ± 8.4	66.3 ± 9.3	0.137
Anti-hypertensive treatment	1.4 ± 0.9	1.8 ± 1.1	1.2 ± 0.7	0.065

Abbreviations: BMI, body mass index; b.p.m., beats per minute; CMR, cardiac magnetic resonance imaging; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; TTE, transthoracic echocardiography.
Unless otherwise stated, the values are expressed as mean ± s.d. or median (interquartile range).
LVH was defined with the following cutoff values: $83\,g\,m^{-2}$ in men and $67\,g\,m^{-2}$ in women.

Table 2 Correlations between LVMI CMR and various left ventricular mass indexes

	All (N = *42*)		*Men* (N = *24*)		*Women* (N = *18*)		*BMI < 25* (N = *19*)		*BMI > 25* (N = *23*)	
Index	r	P-*value*	r	P-*value*	r	P-*value*	r	P-*value*	r	P-*value*
NT-proBNP	0.595	<0.001	0.802	<0.001	0.115	0.648	0.660	0.002	0.574	0.004
Sokolow–Lyon index	0.462	0.002	0.515	0.010	−0.018	0.942	0.363	0.126	0.539	0.008
Cornell voltage	0.539	<0.001	0.758	<0.001	0.124	0.624	0.567	0.011	0.533	0.009
Cornell product	0.606	<0.001	0.730	<0.001	0.344	0.162	0.660	0.002	0.585	0.003
RaVL	0.571	<0.001	0.643	<0.001	0.306	0.217	0.610	0.006	0.554	0.006
TTE LVMI	0.780	<0.001	0.904	<0.001	0.371	0.157	0.869	<0.001	0.763	<0.001
TTE $LVMI^{2.7}$	0.692	<0.001	0.891	<0.001	0.259	0.332	0.851	<0.001	0.672	<0.001

Abbreviations: BMI, body mass index; CMR, cardiac magnetic resonance imaging; LVM, left ventricular mass; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-brain natriuretic peptide; *r*, Pearson's coefficient of correlation; RaVL, amplitude of R wave in aVL lead; TTE, transthoracic echocardiography.
A logarithmic transformation was applied to all variables. Correlations between variables were assessed with a linear regression analysis.

of TTE LVMI. Correlations between NT-proBNP and CMR LVMI or TTE LVMI are illustrated in Figure 1. A subanalysis by sex showed higher correlation coefficients in men than that in women. Conversely, a subanalysis by body mass index class showed few differences between subjects with body mass index $<25\,kg\,m^{-2}$ and subjects with body mass index $>25\,kg\,m^{-2}$. To further confirm our data, we performed two sensitivity analyses: one after exclusion of patients with diastolic dysfunction and the other after exclusion of patients with CMR left ventricular ejection fraction <60%. NT-proBNP remained significantly correlated with CMR LVMI after exclusion of patients with diastolic dysfunction and left ventricular ejection fraction <60% ($N=38$, $r=0.532$, $P=0.001$; $N=30$, $r=0.495$, $P=0.005$, respectively).

Because of potential confounders, the relationship between NT-proBNP and CMR LVMI was also studied in a multivariate analysis that included the variables found significantly associated with NT-proBNP in univariate analyses, that is, 24-h ambulatory systolic BP ($r=0.559$; $P<0.001$) and active renin ($r=0.638$; $P<0.001$). In this analysis too, NT-proBNP remained statistically and independently correlated with CMR LVMI (used here with log-transformed values, $r=0.324$, $P=0.042$).

ROC curves

The characteristics of the ROC curves are summarized in Table 3. With the low CMR LVMI cutoff values, the AUC for NT-proBNP was 0.761 (95% confidence interval, 0.609–0.911; $P=0.005$, Figure 2a). An NT-proBNP level $<30\,pg\,ml^{-1}$ ruled out LVH with 100% sensitivity, whereas a level above $380\,pg\,ml^{-1}$ predicted LVH with 100% specificity. The best diagnostic value of NT-proBNP was obtained with $200\,pg\,ml^{-1}$; this optimal level classified 76.2% of the subjects correctly with 43.5% sensitivity, 96.2% specificity, 87.5% positive predictive value and 69.4% negative predictive value. In comparison with other ECG criteria, the Sokolow–Lyon index had the worst diagnostic value. The largest AUC was that of TTE $LVMI^{BSA}$.

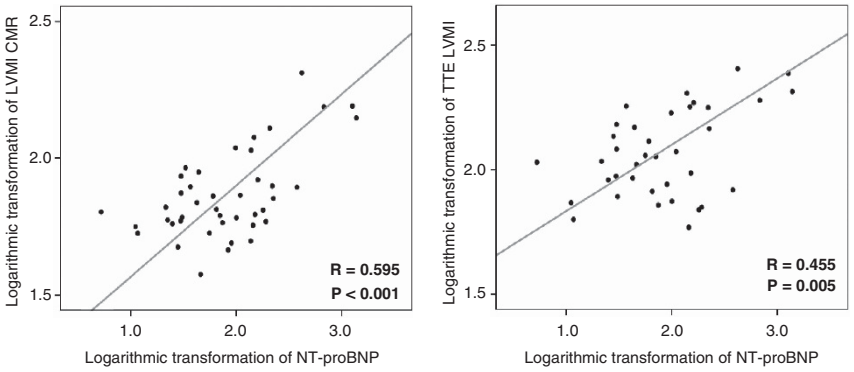

Figure 1 Pearson's correlations between NT-proBNP and LVMI. LVMI, left ventricular mass index; CMR, cardiac magnetic resonance; TTE, transthoracic echocardiography; CMR, cardiac magnetic resonance imaging; NT-proBNP, N-terminal pro-brain natriuretic peptide. A full color version of this figure is available at *Hypertension Research* online.

Table 3 Performance characteristics of various indices according to the two diagnostic CMR LVH cutoffs

Index	*AUC (95% CI)*	P-*value*	*Optimal value*	*Specificity*	*Sensitivity*
Low LVH cutoff[a]					
NT-proBNP	0.760 (0.609–0.911)	0.005	$200\,pg\,ml^{-1}$	0.962	0.562
Sokolow–Lyon index	0.650 (0.467–0.834)	0.105	3.9 mV	1	0.625
RaVL	0.864 (0.750–0.979)	<0.001	0.65 mV	0.885	0.750
Cornell voltage	0.874 (0.753–0.995)	<0.001	2.2 mV	0.962	0.688
Cornell product	0.875 (0.748–1.000)	<0.001	2099 mm ms	1	0.750
TTE LVMI	0.941 (0.860–1.000)	<0.001	$126\,g\,m^{-2}$	0.913	0.929
TTE $LVMI^{2.7}$	0.923 (0.848–1.000)	<0.001	$60.4\,g\,m^{-2.7}$	0.870	0.929
High LVH cutoff[b]					
NT-proBNP	0.849 (0.714–0.983)	<0.001	$421\,pg\,ml^{-1}$	1	0.444
Sokolow–Lyon index	0.855 (0.692–1.000)	<0.001	4.0 mV	1	0.667
RaVL	0.897 (0.792–1.000)	<0.001	1.0 mV	0.909	0.778
Cornell voltage	0.919 (0.800–1.000)	<0.001	2.7 mV	0.970	0.889
Cornell product	0.960 (0.878–1.000)	<0.001	2700 mm ms	1	0.889
TTE ILVMI	0.948 (0.877–1.000)	<0.001	$190\,g\,m^{-2}$	1	0.625
TTE $LVMI^{2.7}$	0.931 (0.846–1.000)	<0.001	$76.1\,g\,m^{-2.7}$	0.931	0.750

Abbreviations: AUC, area under curve; CI, confidence interval; CMR, cardiac magnetic resonance imaging; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMI, left ventricular mass index; RaVL, amplitude of R wave in aVL lead; TTE, transthoracic echocardiography.
[a]$83\,g\,m^{-2}$ in men and $67\,g\,m^{-2}$ in women.
[b]$96\,g\,m^{-2}$ in men and $81\,g\,m^{-2}$ in women.

The AUC of NT-proBNP was not significantly different from the AUCs of the electrical LVH indexes ($P=0.292$ for Sokolow–Lyon index, $P=0.221$ for RaVL, $P=0.178$ for Cornell voltage and $P=0.203$ for Cornell product). The AUCs of TTE $LVMI^{BSA}$ and $LVMI^{2.7}$ were significantly different from that of NT-proBNP ($P=0.036$ and $P=0.032$, respectively).

With the high CMR LVMI cutoff values, the AUC for NT-proBNP increased up to 0.849 (95% confidence interval, 0.714–0.983; $P<0.001$, Figure 2b) and the optimal level was 421 pg ml^{-1}. This level correctly classified 88.1% of the subjects with 44.4% sensitivity, 100% specificity, 100% positive predictive value and an 86.8% negative predictive value. With the high CMR LVMI cutoff values, the AUCs and the optimal values were higher than that with the low CMR LVMI cutoff values for all ECG and TTE criteria (Table 3), and the AUC for NT-proBNP was not significantly different from the AUCs found for the electrical LVH indexes and TTE criteria ($P=0.928$ for Sokolow–Lyon index, $P=0.475$ for RaVL, $P=0.250$ for Cornell voltage, $P=0.057$ for Cornell product, $P=0.055$ for $LVMI^{BSA}$ and $P=0.091$ for $LVMI^{2.7}$).

After the exclusion of patients with diastolic dysfunction or CMR left ventricular ejection fraction <60%, the areas under the curves were slightly truncated both for NT-proBNP and ECG criteria, possibly because of the reduced number of patients remaining eligible for analysis (Supplementary Table S1; Supplementary Data).

Predictive values of the diagnostic methods

Table 4 displays the negative and positive predictive values as well as the rates of correctly classified subjects with each LVH criterion and according to each of the above-mentioned CMR LVMI cutoffs values. For each tool, we tested three NT-proBNP thresholds: the optimal value obtained with our ROC curves, Morillas' cutoff and the reference value obtained in a normal population;[21–23] (Supplementary Table S2; Supplementary Data). The optimal value and the reference value (above the 97.5th percentile for age and sex) of NT-proBNP

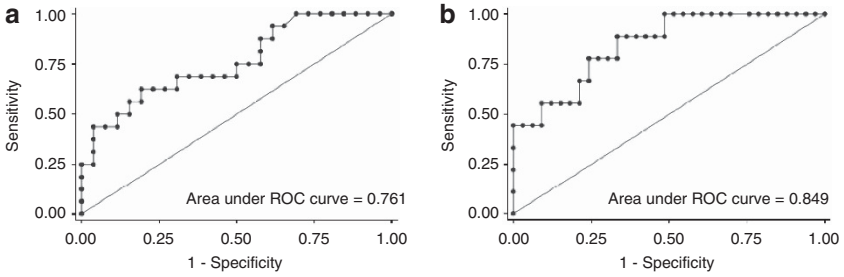

Figure 2 ROC curves for NT-proBNP as a diagnostic test for LVH as assessed by CMR. Panel **a** corresponds to the low LVH cutoff (83 g m^{-2} in men and 67 g m^{-2} in women) and panel **b** to the high LVH cutoff (96 g m^{-2} in men and 81 g m^{-2} in women). CMR, cardiac magnetic resonance imaging; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVH, left ventricular hypertrophy. A full color version of this figure is available at *Hypertension Research* online.

Table 4 Predictive values of various LVH criteria according to the low and high CMR LVH cutoffs values

LVH criteria	*Positive predictive value*	*Negative predictive value*	*Rate of correctly classified patient*	*AUC*
Low cutoff values[a]				
NT-proBNP >200 pg ml^{-1}	87.5% (7/8)	73.5% (25/34)	76.2% (32/42)	0.760
NT-proBNP >35 pg ml^{-1}	46.7% (14/30)	83.3% (10/12)	57.1% (24/42)	0.760
Reference values of NT-proBNP	66.7% (10/15)	77.7% (21/27)	73.8% (31/42)	0.760
Sokolow–Lyon index >3.5 mV	66.7% (6/9)	69.7% (23/33)	69.0% (29/42)	0.650
Cornell voltage >2.8 mV	100% (8/8)	76.5% (26/34)	80.9% (34/42)	0.874
Cornell product >2440 mm ms	100% (11/11)	83.4% (26/31)	88.1% (37/42)	0.875
RaVL >0.6 mV	80.0% (12/15)	85.2% (23/27)	83.3% (35/42)	0.864
TTE LVMI >51 g m$^{-2.7}$	68.4% (13/19)	94.4% (17/18)	81.1% (30/42)	0.944
TTE LVMI >110 g m^{-2} in women, >125 g m^{-2} in men	76.4% (13/17)	95.0% (19/20)	86.4% (32/42)	0.921
High cutoff values[b]				
NT-proBNP >421 pg ml^{-1}	100% (4/4)	86.8% (33/38)	88.1% (37/42)	0.849
NT-proBNP >35 pg ml^{-1}	26.7% (8/30)	91.7% (11/12)	45.2% (19/42)	0.849
Reference values of NT-proBNP	53.3% (8/15)	96.3% (26/27)	81.0% (34/42)	0.849
Sokolow–Lyon index >3.5 mV	66.7% (6/9)	90.9% (30/33)	85.7% (36/42)	0.855
Cornell voltage >2.8 mV	87.5% (7/8)	94.1% (32/34)	92.9% (39/42)	0.919
Cornell product >2440 mm ms	72.7% (8/11)	96.8% (30/31)	90.5% (38/42)	0.960
RaVL >0.6 mV	53.3% (8/15)	96.3% (26/27)	80.9% (34/42)	0.897
TTE LVMI >51 g m$^{-2.7}$	36.8% (7/19)	100% (18/18)	67.6% (25/42)	0.931
TTE LVMI >110 g m^{-2} in women, >125 g m^{-2} in men	41.2% (7/17)	100% (20/20)	73.0% (27/42)	0.948

Abbreviations: AUC, area under curve; CMR, cardiac magnetic resonance imaging; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMI, left ventricular mass index; RaVL, amplitude of R wave in aVL lead; TTE, transthoracic echocardiography.
[a] >83 g m^{-2} in men and >67 g m^{-2} in women.
[b] >96 g m^{-2} in men and >81 g m^{-2} in women.

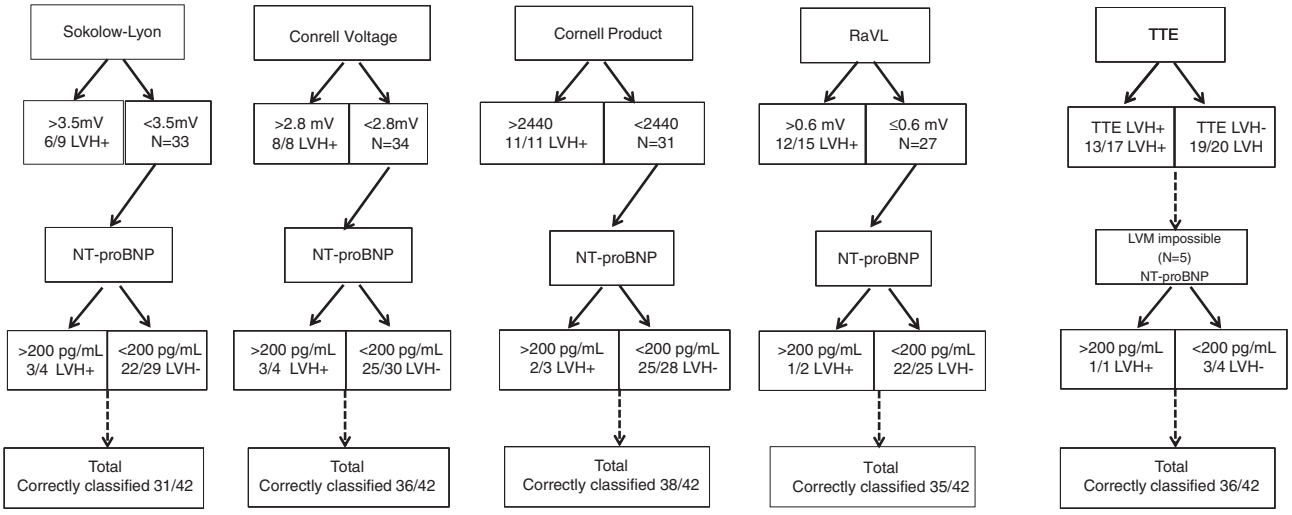

Figure 3 Imaging strategy (ECG or TTE first, and then NT-proBNP) to diagnose left ventricular hypertrophy with the low LVH cutoff of 83 g m^{-2} in men and 67 g m^{-2} in women. ECG, electrocardiograph; LVH, left ventricular hypertrophy; LVM, left ventricular mass; NT-proBNP, N-terminal pro-brain natriuretic peptide; RaVL, amplitude of R wave in aVL lead; TTE, transthoracic echocardiography.

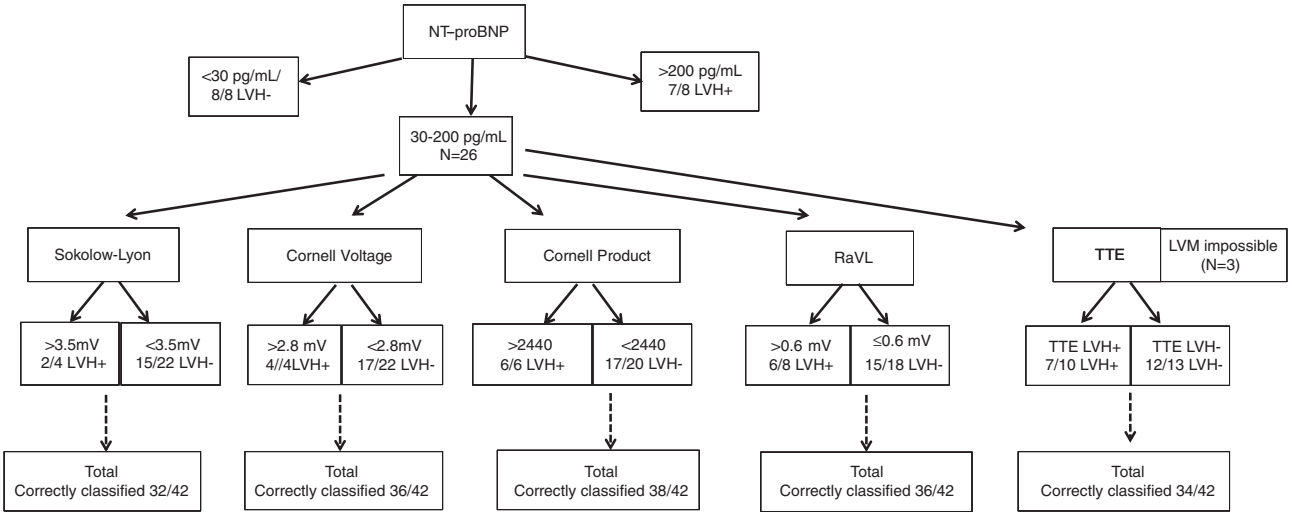

Figure 4 Biological strategy (NT-proBNP first, and then ECG or TTE) to diagnose left ventricular hypertrophy with the low LVH cutoff 83 g m^{-2} in men and 67 g m^{-2} in women. ECG, electrocardiograph; LVH, left ventricular hypertrophy; LVM, left ventricular mass; NT-proBNP, N-terminal pro-brain natriuretic peptide; RaVL, amplitude of R wave in aVL lead; TTE, transthoracic echocardiography.

correctly classified 73% and 88% of the subjects, respectively. In comparison, Morillas' cutoff of 35 pg ml^{-1} correctly classified only 45.2% and 57.1% of the subjects according to the low and high CMR LVH cutoffs values, respectively. We also observed that the diagnostic accuracies of the Cornell voltage and the Cornell product were relatively close to that of TTE (80–90%). The usual TTE LVMI^{BSA} and LVMI$^{2.7}$ cutoffs overestimated the prevalence of LVH regardless of the LVH cutoff values used for diagnosis.

We therefore tested two strategies to diagnose LVH with the low CMR LVMI cutoff: (i) ECG or TTE first and then NT-proBNP (imaging strategy, Figure 3); and (ii) NT-proBNP first and then ECG or TTE (biological strategy, Figure 4). The results obtained with the high cutoff are shown as Supplementary Data (Supplementary Figures S1 and S2). Whatever the strategy and the cutoff level, the rate of correctly classified subjects (except with the Sokolow–Lyon index) tended to be higher than that found using TTE criteria alone (83–95% *vs.* 67–86%, respectively).

DISCUSSION

This study confirmed the satisfactory performance of NT-proBNP against the gold standard of CMR in diagnosing LVH in hypertensive subjects. It demonstrated that the performance of the ECG + NT-proBNP combination was not much different from that of TTE in diagnosing LVH in a population of hypertensive subjects without heart failure.

The present study found an association between NT-proBNP and CMR LVMI. Some studies have previously demonstrated a correlation between BNP[29–32] or NT-proBNP[12] and TTE LVMI, but others have not.[33,34] These contradictory results may be explained by the influence of the renin-angiotensin system on the plasma levels of natriuretic peptides.[35] Indeed, renin-angiotensin inhibitors, diuretics and drugs that lower blood volume usually decrease natriuretic peptide concentrations.[36] This was confirmed in a substudy of LIFE that showed an increase in NT-proBNP levels in the group treated with atenolol but a decrease in the group treated with losartan.[37]

At the time of the biological and imaging analyses in this study, none of the participants were receiving drugs that interfere with the renin-angiotensin system. This is one of the major strengths of the study.

The results shown herein are in agreement with those obtained by Morillas *et al.*[14] in a cohort of 27 hypertensive subjects; these authors have reported an AUC of 0.867 of NT-proBNP and a correlation of 0.589 with CMR LVMI. They mentioned a negative predictive value of 100% for the diagnosis of LVH at NT-proBNP levels $<35\,pg\,ml^{-1}$. In this study, we found a similar performance with a threshold of $30\,pg\,ml^{-1}$. However, the best diagnostic value of NT-proBNP was obtained with $200\,pg\,ml^{-1}$, whereas Morillas *et al.*[14] reported a much lower value of $35\,pg\,ml^{-1}$ using a CMR cutoff of $83\,g\,m^{-2}$ in men and $67\,gm^{-2}$ in women for LVH detection. In our cohort, the latter cutoff values were not able to predict LVH reliably (<58% of correctly classified subjects, whatever the CMR LVMI cutoff). This difference may be explained by a lower proportion of women in the study by Morillas *et al.*[14] compared with our study (15% *vs.* 43%, respectively). Indeed, at any given age, NT-proBNP normal values are slightly higher in women than that in men.[21–23] Another potential explanation for the use of a lower threshold by Morillas *et al.*[14] would be the assessment of subjects using diuretics or renin-angiotensin system inhibitors (unprovided data). Another choice for the NT-proBNP threshold is the literature reference values.[21–23] Here, using these reference values led to 74–81% good classification.

The worst correlations observed in women were between CMR LVMI and each of ECG criteria, TTE LVMI and NT-proBNP. This can be explained by a narrow range of LVMI values and a small prevalence of LVH in women. Indeed, a previous study regarding TTE LVMI in a larger cohort demonstrated a better predictive value of NT-proBNP in detecting LVH in women than in men.[12] In that study, the optimal value of NT-proBNP was $109\,pg\,ml^{-1}$. This lower NT-proBNP threshold is in agreement with the overestimation usually found with TTE-estimated LVMs.[6]

As demonstrated here and in previous reports, the main limits in TTE assessment of LVM are poor reproducibility and lack of LVM measurement for technical reasons in ~10% of hypertensive subjects who consult a general practitioner.[19] In this regard, NT-proBNP and ECG criteria are likely to offer better interobserver and intraobserver reproducibility and are available to all patients. We have recently demonstrated that beyond the diagnosis of LVH, NT-proBNP has a powerful ability to predict mortality,[38] and potentially allows for a more integrative approach to stratify the risk in hypertension and other conditions such as subclinical heart failure, afterload excess and arterial stiffness.[35]

BP is a major determinant of NT-proBNP level.[12,35] This may be a limitation for its practical use because BP is highly variable. However, we performed a multivariate analysis including 24-h ambulatory BP monitoring as a potential confounder; despite this adjustment, NT-proBNP was still associated with CMR LVMI. Moreover, we previously showed that the conditions of measurement, namely, ambulatory *vs.* standardized, and as a consequence, the related small BP changes, had very limited effects on NT-proBNP levels.[38] Consequently, we believe that even if NT-proBNP is associated with BP, the effect of small BP variations on its diagnostic value should be limited. In clinical practice, NT-proBNP could be the general practitioner's first approach to detect LVH in hypertensive subjects. All general practitioners are not equipped to perform ECG measurements; therefore, detecting LVH is not frequent. According to Spranger *et al.*,[39] only 11% of subjects with newly diagnosed hypertension were ordered to have an ECG. The Sokolow–Lyon index is likely the most popular, but we demonstrate here that its performance in detecting LVH is lower than that of NT-proBNP. In subjects with NT-proBNP values within the gray zone (30–$200\,pg\,ml^{-1}$), the interpretation of ECG by a trained practitioner (especially with Cornell Voltage, Cornell product and RaVL) allowed reaching rates >85% of correct LVH classifications. The cardiologist may use NT-proBNP as a second step in subjects without electrical LVH signs. In the diagnosis of LVH, combining ECG and NT-proBNP offers a performance close to that of TTE. Finally, NT-proBNP may be used in subjects who already have had a TTE that could not precisely evaluate LVH.

Limits

This study has the limits inherent to single-center, small-sample-size series: a low statistical power and a partial recruitment bias; one-third of the subjects were referred to our reference center for hypertension because of secondary hypertension. Another limit concerns NT-proBNP; it is likely that it represents a criterion of LVH in subjects without heart or kidney failure.[40] Unfortunately, we were not able to test the effect of renal failure on the diagnostic value of NT-proBNP as most of patients have preserved renal function. Nevertheless, in such a setting, false positive cases would correspond to high-risk conditions and lead to close control of BP.

CONCLUSIONS

This study confirms the good correlation between NT-proBNP and LVH as assessed by the current gold standard of CMR. Moreover, it shows that ECG criteria plus NT-proBNP offers a similar predictive value to that of TTE in detecting LVH. To optimize the detection of LVH with NT-proBNP, physicians should consider a threshold close to $200\,pg\,ml^{-1}$ or refer to the normal values for sex and age. For cost-effectiveness reasons, our results suggest performing TTE only in hypertensive subjects with murmur, cardiac symptoms or impaired renal function. Taken together, ECG criteria and NT-proBNP plasma levels seem to be powerful enough for risk stratification in subjects with hypertension.

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