The relation between QRS amplitude and left ventricular mass in patients with hypertension identified at screening

Ljuba Bacharova, Oleg V. Baum, Galina A. Muromtseva**, Leonid A. Popov*, Vyatcheslav B. Rozanov**, Victor I. Voloshin*, Oleg M. Voroshnin*, Elena A. Zhavoronkova***

International Laser Center, Bratislava, Slovak Republic

*Institute of Theoretical and Experimental Biophysics RAS, Pushchino, Russia,

**National Center for Preventive Medicine, Moscow, Russia

ABSTRACT

Objective: The aim of this study was to analyze the relationship between QRS amplitude and left ventricular mass (LVM) in hypertensive patients identified by screening, with the focus on those without left ventricular hypertrophy (LVH).

Methods: The entire study group consisted of 189 healthy subjects (average 39.6 years) and 54 subjects with hypertension (average 52.4 years). The LVH-free subgroup consisted of 159 normal subjects and 30 hypertensive patients. Electrocardiograms were recorded and the magnitude of the maximum QRS spatial vector magnitude (QRSmax) was calculated from the RaVF, RV5 and SV2 amplitudes. The LVM was estimated echocardiographically. The specific potential of myocardium (SP) was calculated as a ratio of QRSmax to LVM.

Results: Contrary to higher LVM values in hypertensive subjects (240.2±58.7g and 191.5±48.3 g, respectively), the QRSmax values (1.9±0.5 mV and 2.0±0.6 mV, respectively) and SP values ($8.3\pm2.5*10^{-3}$ mV/g and $11.3\pm4.4*10^{-3}$ mV/g, respectively) were significantly lower as compared to healthy subjects in the entire study group. Also in the LVH-free subgroup the SP values were significantly lower in hypertensive patients ($8.70\pm2.83*10^{-3}$ mV/g and $10.98\pm4.79*10^{-3}$ mV/g, respectively). The lower values of QRSmax and SP could not be explained by the differences in age and body mass index between the hypertensive patients and normal subjects.

Conclusion: We showed that the SP provides a more sensitive parameter for the evaluation of early hypertrophic remodeling as compared to separated evaluation of LVM and QRS voltage already in subjects with no signs of cardiac target organ involvement according to current clinical classification. *(Anadolu Kardiyol Derg 2007: 7 Suppl 1; 153-8)*

Key words: hypertension, left ventricular hypertrophy, relative voltage deficit, specific potential of myocardium, target organ damage

Introduction

Left ventricular hypertrophy (LVH) detected either by electrocardiography (ECG) or echocardiography (EchoCG) in patients with high blood pressure (BP) is defined as an indicator of cardiac target organ damage (C-TOD) (1, 2). The early detection of LVH in hypertensive patients is therefore of utmost diagnostic and prognostic importance, since it affects the diagnostic procedure and prognosis, and guides the treatment.

The specific ECG sign of LVH is the increased QRS amplitude over the upper normal limit in defined leads of 12-lead ECG (3, 4), in the case of EchoCG - it is the increase in estimated left ventricular mass (LVM) (5). Patients without either ECG or EchoCG signs of LVH are clinically considered to be without the cardiac target organ damage, i.e. without clinically detectable cardiac involvement. However, it has been documented that structural and electrical remodeling is present already in very early stages of hypertension (6, 7), therefore the assumption that patients without ECG or EchoCG signs of LVH are "without target organ/cardiac damage" is questionable.

In our previous papers (7, 8) we have presented a novel hypothesis on the relative voltage deficit (RVD). This hypothesis assumes that the false negative ECG findings reflect changes in electrical properties of myocardium due to electrical and structural remodeling in the early stage of LVH. The specific potential of myocardium (SP) – a ratio of QRS voltage to LVM – has been recommended as a parameter to quantify the RVD.

The aim of this study was to analyze the relationship between ECG amplitude and LVM in a screened population. We hypothesized that hypertensive patients diagnosed in the cardiovascular screening program exhibit signs of relative voltage deficit, i.e. decreased values of SP and of QRS, as compared to normotensive subjects, and that the RVD is present also in hypertensive subjects without clinically detectable LVH.

Methods

Study population

The study population was selected retrospectively from a screening program database of the National Center for Preventive Medicine, Moscow, Russia. Records of subjects with final clinical diagnoses either "healthy" or "hypertension" were included in the study. The diagnostic conclusions were based on medical history, blood and urine analysis, electrocardiogram, echocardiogram, and, eventually on ultrasonographic examination of abdomen, kidneys, or thyroid gland. The details on the diagnostic procedure are described in details by Shamarin et al (9).

Address for Correspondence: Ljuba Bacharova, MD, PhD, MBA, Assoc. Prof., International Laser Center, Ilkovicova 3, 812 19 Bratislava, Slovak Republic
Phone: +421.2.654 21 575 Fax: +421.2.654 23 244 E-mail: bacharova@ilc.sk

The entire study group represented by 243 medical records consisted of:

1. 189 apparently healthy normotensive subjects (NORM) aged 28 to 64 years, (average 39.6 years). They were free of cardiopulmonary disease or diabetes, and they were not receiving cardiac or antihypertensive medication.

2. 54 subjects with hypertension (HYPER) aged 28 to 70 years (average 52.4 years).

The healthy subjects were leaner and younger than hypertensive patients. The average values of body mass index (BMI) in normotensive subjects were shifted to the upper limit of the category "normal weight", and they were in the category "overweight" in hypertensive patients.

Two subgroups were selected from the entire study population:

I. BMI- and gender-matched subgroup (BMI-M subgroup) (n=36). The hypertensive subjects in this subgroup were significantly older as compared to healthy subjects.

II. The subgroup without left ventricular hypertrophy (LVH-free subgroup), i.e. with both negative ECG and EchoCG findings according the following criteria:

- LVM within normal limits: <145.5g.m^{-1} men, <125.4 g.m^{-1} women (10);
- ECG within normal limits: <3 mV.

These criteria were fulfilled in 159 (84.1%) normal subjects and 30 (55.6%) hypertensive patients (Table 1). The hypertensive subjects in this subgroup were significantly older and had significantly higher values of BMI as compared to normotensive subjects.

The basic demographic data of the entire group the BMI-M and LVH-free subgroups are presented in Table 2.

Table 1. Proportion of subjects with ECG and/or echocardiographic signs of left ventricular hypertrophy using the partition values 145.5 g.m-1 for men and 125.4 g.m-1 for women, respectively, for LVM and 3 mV for QRSmax

		echo LVM	
		-	+
QRS	+	6/3.2%	3/1.6%
		1/1.9%	0
	-	159/84.1%	21/11.1%
		30/55.6%	23/42.6%

Data presented as absolute values/per cent. Values for normal subjects are in brackets. ECG- electrocardiogram, echo- echocardiographic, LVM- left ventricular mass

Electrocardiogram

A 12-lead ECG was recorded using either of the electrocardiographs Karel (ars-EKG 12K, Kardiosis, Turkey) and EKG 12-1.1. (Geolink, Russia/Sweden). The ECGs were evaluated by two specialists, and in the case of disagreement opinion of the third specialist was sought. The magnitude of the approximated maximum QRS spatial vector was calculated from the amplitudes of RaVF, RV5 and SV2, using the formula:

$$QRS\max = \sqrt{RV5^2 + RaVF^2 + SV2^2}$$

Echocardiogram

The EchoCG examinations were provided by either of the echocardiographs Aloka 630 (Japan) and Aquson 128 (USA). The echocardiograms were performed by either of two echocardiographers, complicated and/or unclear findings were consulted by both echocardiographers.

The LV dimensions were measured at end-diastole from standard two-dimensional guided M-mode registration. The left ventricular mass was calculated using Penn convention (11):

LVM=1.04 ([LVIDD+PWTD+IVSTD]3 -[LVIDD]3)–13.6 g

The specific potential of myocardium was calculated as the ratio of QRSmax and LVM:

SP=QRSmax/LVM.

Statistical analysis

Data are presented as mean and standard deviation (SD), or standard error of the mean (SEM), respectively. The differences between the groups were tested using the unpaired t-test or the two factor independent measures ANOVA when appropriate. The association between two variables was evaluated using the Pearson correlation. A probability value of $p<0.05$ was accepted as significant.

Results

The basic statistics on LVM, QRSmax and SP of the entire study group and of the BMI-M and LVH-free subgroups are summarized in Table 3. The correlation coefficients between LVM, QRSmax and SP, and age, BMI and BP in entire study group and LVH-free subgroup are presented in Table 4.

The entire study group

The LVM was significantly higher in hypertensive subjects of the entire study group as compared to healthy subjects. On the contrary, both the QRSmax values and SP values were significantly lower in the hypertensive subjects (Table 3). While the

Table 2. Basic characteristics of the entire study group, the body mass index-matched subgroup (BMI-M) and the subgroup without left ventricular hypertrophy (LVH-free)

		N	Age, years	Gender, M/F	sBP, mmHg	dBP, mmHg	BMI, kg/cm²
Entire study group	Normal	189	39.6±7.0	176/13	124±13	82±7	24.9±3.6
	Hypertension	54	52.4±9.4***	47/7	151±22***	97±12***	28.6±4.29***
BMI-M subgroup	Normal	36	37.9±6.7	34/2	124.8±10.7	82.5±6.4	26.9±3.3
	Hypertension	36	50.7±10.2***	34/2	150.0±24.5***	96.9±13.0***	26.9±3.3
LVH-free subgroup	Normal	159	39.1±6.6	148/11	123±12	81±7	24.7±3.7
	Hypertension	30	50.4±1.0***	25/5	148±22***	96±13***	27.4±3.7***

Data are presented as mean±standard deviation. ***-p<0.001- differences are significant as compared with Normal subjects

BMI- body mass index, dBP- diastolic blood pressure, F- female, M- male, sBP- systolic blood pressure

frequency distribution of LVM in hypertensive patients was shifted up the scale as compared to healthy subjects, the QRSmax values were shifted slightly down the scale (Fig. 1). The shift of the frequency distribution down the scale in hypertensive patients was more pronounced in SP values.

There was no significant correlation between LVM and QRSmax values in the normotensive healthy subjects (r=0.068). Statistically significant correlation between LVM and QRSmax values was found in hypertensive patients (r=0.302), however, the coefficient of determination was low (r^2=0.091).

As is shown in Table 1, only one hypertensive patient (1.9%) had the ECG-LVH and 23 (42.6%) hypertensive patients had echocardiographic signs of LVH, i.e. the cardiac damage according JNC VI and JNC VII was classified in 24 hypertensive patients of the entire study group. Thirty (55.6%) hypertensive patients had QRSmax and LVM values within normal limits, and were classified as free of target organ damage.

The influence of age

As presented in Figure 2, the SP values in particular age categories decreased gradually, the SP values were lower in hypertensive patients as compared to healthy subjects, and this differences was statistically significant (p<0.05).

The LVM values correlated with age in normal subjects, this correlation was relatively weak (r=0.2048), no significant correlation was found between LVM and age in hypertensive patients (Table 4). On the opposite, the QRSmax correlated significantly inversely with age (r=-0.3293) in hypertensive patients, no significant correlation was found between QRSmax and age in normotensive subjects. There was a significant negative correlation between SP values and age in hypertensive patients (r=-0.5092), the correlation was not significant in healthy subjects.

The influence of BMI

The LVM values significantly correlated with BMI both in normal subjects and hypertensive patients, while there was no significant correlation between QRSmax and BMI. The SP values correlated significantly inversely with BMI.

In the BMI-M subgroup, the LVM was higher of by 10% in hypertensive patients as compared to healthy subjects and this difference was statistically significant. The QRSmax values did not differ between hypertensive subjects and hypertensive patients in the BMI-M subgroup, while the SP values were significantly lower in hypertensive patients.

The LVH-free subgroup

The LVM was significantly higher in hypertensive subjects as

Table 3. Basic statistics on left ventricular mass (LVM), maximum QRS spatial vector magnitude (QRSmax) and specific potential of myocardium (SP) of the entire study group, the body mass index-matched subgroup (BMI-M) and the subgroup without left ventricular hypertrophy (LVH-free).

		N	LVM, g	QRSmax, mV	SP, mV/g (values*10-3)
Entire study group	**Normal**	189	191.5±48.3	2.0±0.6	11.3±4.4
	Hypertension	54	240.2±58.7***	1.9±0.5*	8.3±2.5***
BMI-M subgroup	**Normal**	36	203.1±53.3	2.05±0.46	10.98±4.79
	Hypertension	36	229.1±51.1*	1.92±0.58	8.70±2.83**
LVH-free subgroup	**Normal**	159	180.3±37.1	1.97±0.5	11.4±3.8
	Hypertension	30	201.9±36.6**	1.8±0.4	9.2±2.3***

Data are presented as mean±standard deviation. * -p<0.05, **-p<0.01, ***-p<0.001 - differences are significant as compared with Normal subjects

Table 4. Values of correlation coefficients among parameters under study in the entire study group and the subgroup of subjects with ECG and echocardiographic findings within normal limits (LVH-free subgroup)

			Age	BMI	sBP	dBP
Entire study group	**LVM**	Normal	0.2048*	0.4159**	0.3787**	0.3323**
		Hypertension	0.2314	0.4635**	0.2255	0.2129
	QRSmax	Normal	-0.0095	-0.0996	0.0437	-0.0251
		Hypertension	-0.3293*	0.0071	-0.4030**	-0.3188*
	SP	Normal	-0.1658	-0.3527**	-0.2578**	-0.2575**
		Hypertension	-0.5092**	-0.3545**	-0.5964**	-0.4858**
LVH-free subgroup	**LVM**	Normal	0.1371	0.4560**	0.4119**	0.3245**
		Hypertension	0.1620	0.1799	0.3372*	0.2062
	QRSmax	Normal	0.0060	-0.0451	-0.0098	0.0219
		Hypertension	-0.2752*	-0.2193	-0.3492*	-0.3637**
	SP	Normal	-0.1164	-0.3209**	-0.3177**	-0.2182*
		Hypertension	-0.4447**	-0.3327*	-0.6270**	-0.5417**

*-p<0.05, **-p<0.01 - differences are significant as compared with Normal subjects
BMI- body mass index, dBP- diastolic blood pressure, ECG- electrocardiogram, LVH- left ventricular hypertrophy, LVM- left ventricular mass, sBP- systolic blood pressure, SP – specific potential of myocardium

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compared to normotensive subjects also in the LVH-free subgroup. There was no statistically significant difference in QRSmax values between healthy subjects and hypertensive patients, while the SP values were significantly lower in the hypertensive subjects.

There was no significant correlation between LVM and QRSmax in normotensive subjects of the LVH-free subgroup. Statistically significant correlation between LVM and QRSmax was found in the hypertensive patients ($r=0.369$, $r^2=0.136$). Similarly to the entire study group, the QRSmax and SP values correlated significantly inversely with age in hypertensive patients ($r=-0.2752$ and -0.4447, respectively), while no correlation was found between either QRSmax or SP and age in normotensive subjects.

Discussion

The important and novel findings in this study are, first, the lower values of QRSmax and of SP in hypertensive patients as compared to normotensive subjects in the screened population, and second, the lower SP values in the subgroup of hypertensive patients without LVH.

The entire study group

In accordance with our hypothesis, we found the QRS values to be significantly lower in hypertensive patients as compared to normotensive subjects in the entire study group. Our hypothesis was derived from the results of our previous animal studies. We have shown a decrease in QRS voltage in the early stage of LVH in

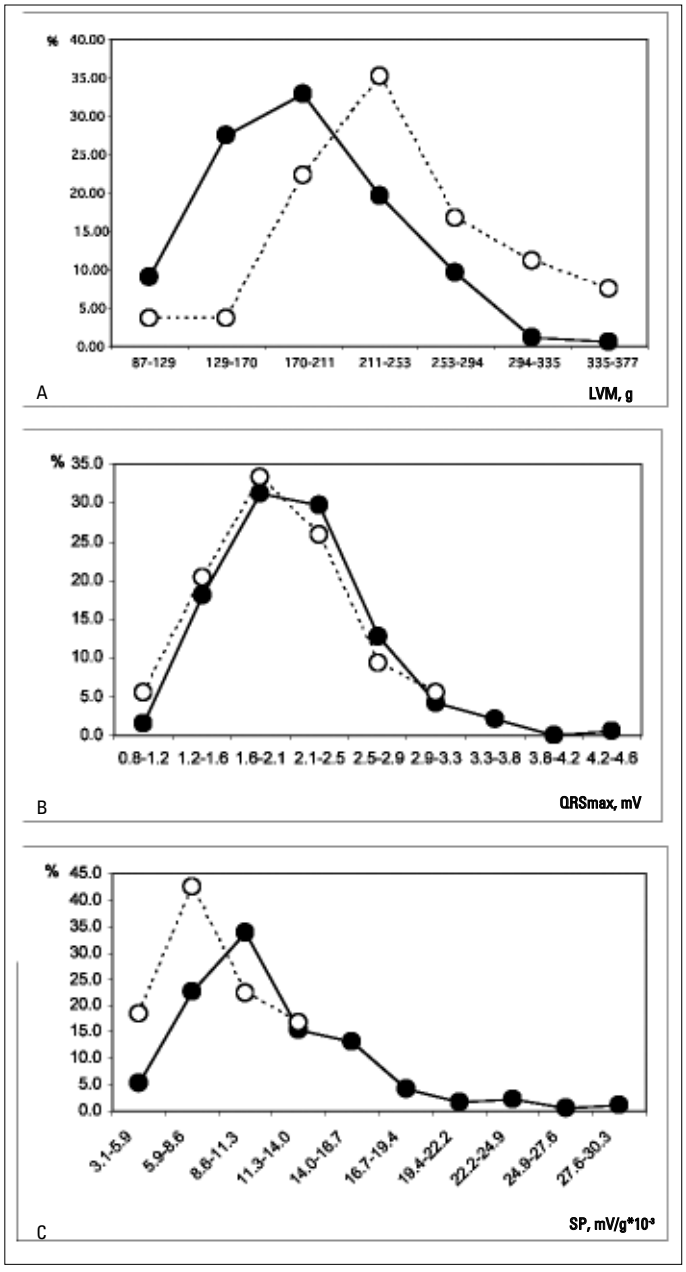

Figure 1. Relative frequency distributions of (A) left ventricular mass (LVM), (B) maximum spatial QRS vector magnitude (QRSmax), (C) specific potential of myocardium (SP) in normal subjects (black dots – full line) and hypertensive patients (circles - dotted line)

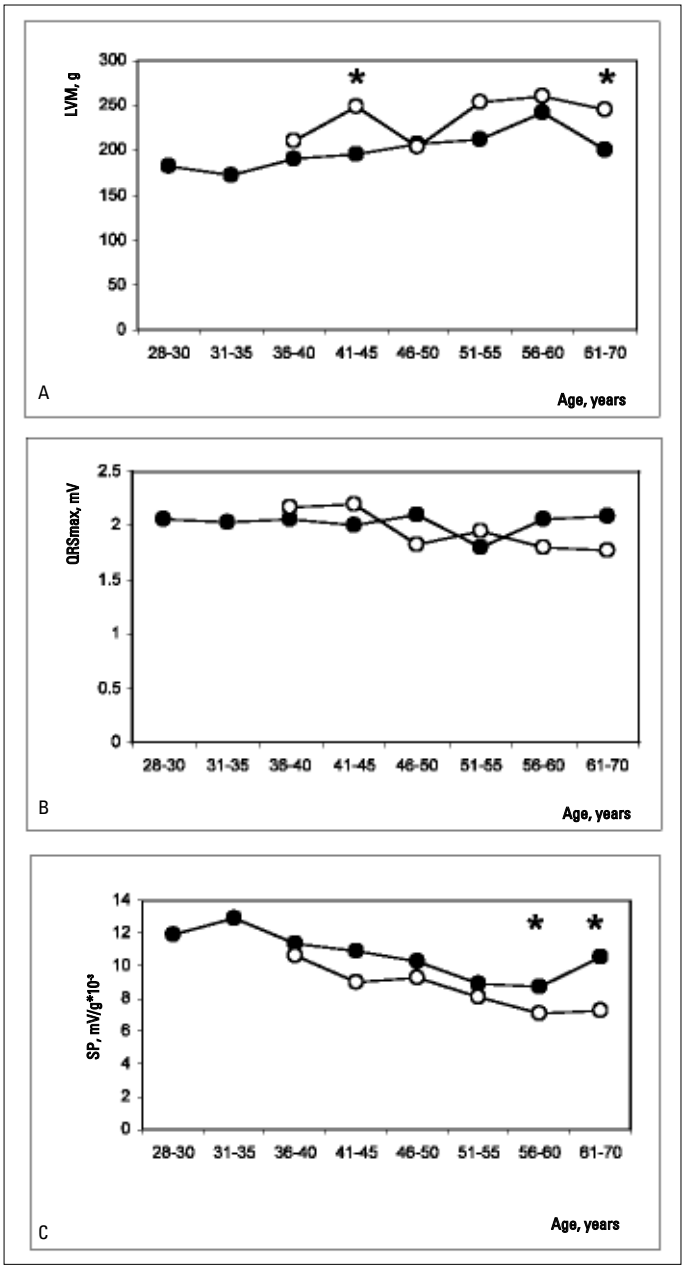

Figure 2. Average values of (A) left ventricular mass (LVM), (B) maximum spatial QRS vector magnitude (QRSmax), (C) specific potential of myocardium (SP) in normal subjects (black dots – full line) and hypertensive patients (circles - dotted line) according with age *-p<0.05

several experimental animal models of volume and pressure overload, as well as in case of the so-called physiological LVH (12-14).

Contrary to the findings in this study, clinical studies report higher QRS values in hypertensive patients (15). Norman and Levy (16) pointed out that the distribution of LVM and ECG voltage values of population-based and clinical sample differ, and that the ranges tend to lessen the extent of overlap in clinical studies. We observed in this study, that the frequency distribution of QRSmax values of healthy subjects and hypertensive patients practically overlapped. We see the explanation in the differences in the selection of the study populations. We assume that newly diagnosed hypertensive patients identified at screening are more likely examined at a relatively earlier stage of hypertension/LVH development as compared to samples of patients recruited from hospital settings, and that the results are probably less modified by previous treatment.

Hypertensive patients in this study were significantly older and had significantly higher values of BMI, that is in agreement with other findings reporting on increased incidence of hypertension by increasing age and BMI (17). According to the traditional understanding of the ECG-LVH diagnostics based on voltage criteria, the results of this study could be therefore influenced by differences in age and BMI between the normal and hypertensive subgroups.

In the general population, the prevalence and incidence of LVH, determined by ECG or EchoCG, increases progressively by age (17, 18). In healthy subjects, the QRS voltage has been documented to decrease with increasing age (19). However, we found no significant correlation between QRS and age in normal subjects, while in hypertensive patients we observed though statistically significant only slight negative correlation.

The hypertensive patients in this study had significantly higher values of BMI. The association of hypertension and obesity has been well documented (17, 20), and obesity has been shown to be independently associated with LVH (21). The prevailing traditional concept in electrocardiographic diagnostics of LVH postulates that obesity has an attenuating effect on ECG amplitudes due to the increased amount of adipose tissue in the chest wall affecting the resistance of the current flow and the distance between the precordial electrode and the heart. Therefore adjusting formulas are recommended for ECG-LVH diagnostics (22, 23).

However, the impact of obesity on QRS voltage is not explicit. There is evidence showing that low voltage is not a significant feature in the ECG of obese subjects (24, 25). Frank et al. (26) found increasing QRS voltage with increasing obesity, and a decrease in QRS voltage was reported in obese subjects after weight loss (24,27). Rautaharju et al. (28) showed that breast tissue appears to have a practically negligible effect on ECG amplitudes in women. Conflicting evidence can be found even in the same study, e.g. high frequency of both low voltage and various markers of LVH in the same group of obese subjects are described (29).

With respect to echocardiographically detected LVH, Iacobellis et al. (30) showed that uncomplicated obesity, including its extreme forms, seems not to be associated with LVH in the absence of glucose intolerance, hypertension, and dyslipidemia. We assume that an important adiposity-related factor affecting the QRS voltage could be the direct effect of adiposity on the heart, modifying its electrical properties as the generator of cardiac electrical field. The direct effect of adiposity on the heart includes the increase in epicardial fat and the infiltration of adipocytes from the epicardial adipose tissue to areas between the myocardial fibers (25, 31), and metabolic and endocrine disorders (32). It was shown, that the BMI is not the main determinant of epicardial fat thickness, or intramyocardial adiposity (33). In electrocardiographic terms, the direct effect of adiposity on the heart - epicardial and intramyocardial adiposity - results in the reduction of the proportion of electrically active myocardial tissue and modification of its electrical properties.

The effect of BMI on the QRSmax voltage in this study was however eliminated in the BMI-matched subgroup. But also, in this subgroup the QRS values were not proportional to the significantly increased LVM in hypertensive patients, on the contrary, they were significantly lower as compared to normotensive subjects.

The values of SP, quantifying the relative voltage deficit, were significantly lower of 36.1% in hypertensive patients as compared to healthy subjects in the entire study group. Also, the SP was found to be significantly lower in hypertensive patients of the BMI-matched subgroups as well as in the particular age groups. These results are in accordance with the hypothesis of this study and in agreement with results of our previous clinical and experimental studies.

In our previous works, we reported lower SP values in hypertensive patients as compared to healthy subjects, contrary to higher QRS values recorded in hypertensive patients (34). In experimental animal studies, we observed lower SP values up to 60% and significantly lower QRS values in rats in the early stages of different models of LVH development (12-14). Since the experimental animal studies are well controlled for age and body weight, these differences cannot be attributed to these factors. According to our understanding (7, 8) the lower SP values quantified the relative voltage deficit due to a complex structural and electrical remodeling in left ventricular hypertrophy.

The subgroup without LVH

Similar relation between LVM and QRSmax as was seen in the entire study population was found also in the LVH-free subgroup, i.e. in the subgroup, which is considered free of cardiac target organ damage according to the current classification (1, 2). The values of the SP were significantly lower of 23.9% in average in hypertensive patients as compared to healthy subjects in the LVH-free subgroup. We assume, that this finding reflects an early hypertrophic structural and electrical remodeling also in this subgroup of patients. This assumption can be supported by findings of Levy et al. (35), who demonstrated a progressive increase in risk associated to LV mass, even at levels not considered as "hypertrophic".

The limitation of the study

The study population was composed mostly of men. The hypertensive patients were older and had higher BMI values. However, since the incidence of hypertension increases with increasing age, and hypertension is frequently associated with obesity, this study sample reflects the representation of hypertensive population in a screening setting.

Conclusion

We showed in this study that LVM was not the major determinant of QRS voltage in hypertensive patients and that the discrepancies between LVM and QRS voltage could not be attributed solely to extracardiac factors – age and BMI. We assume that the following factors modifying the electrical properties of the myocardium should be considered in the

interpretation of the lower QRSmax and SP values in hypertensive patients: (1) hypertrophic electrical and structural remodeling of myocardium; (2) changes of myocardium caused by aging and duration of hypertension; (3) the direct effect of adiposity on the myocardium. Each of these factors could by itself change the electrical properties of myocardium. The combination of these factors is however more pronounced in hypertension.

Using a ratio of QRS to LVM to evaluate the relative voltage deficit in hypertensive patients we found that changes in SP were detected already in the LVH- free subgroup. We assume that SP – the ratio of QRS and LVM - could provide a more sensitive clinical tool for evaluation of the early cardiac involvement due to anatomical and electrical remodeling using available clinical methods. We assume that the lower values of SP reflect a complex structural and electrical remodeling of myocardium present already in subjects with no signs of target organ damage according to current clinical classification.

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