Relation of heart rate to left ventricular dimensions in normotensive, normal-weight children, adolescents and adults

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Aging; Body growth; Cardiac hypertrophy; Heart rate.

Background. **The quantitative relation between body growth and changes in heart rate, and the relationship of heart rate to left ventricular (LV) dimensions, independent of the influence of body size, have been only marginally investigated. Accordingly, we designed this study to investigate the relation between heart rate, body size and LV dimensions in children, adolescents and adults over a broad age span.**

Methods. **Eight hundred and nineteen normotensive, multi-racial, normal-weight individuals (444 males, 375 females, aged 1-85 years) with normal LV systolic function were studied at echocardiography in three centers, using previously reported methods. The resting heart rate was measured on the M-mode echo-tracing or right after the echocardiogram with the subject still in the supine position.**

Results. **In children and adolescents (up to 17 years), the heart rate decreased with increasing body height ($r = -0.51$, $p < 0.0001$) and body weight ($r = -0.42$, $p < 0.0001$), in a similar manner in girls and boys. In adults, the heart rate was higher in women than in men, but it was not independently related to body size. The LV diastolic diameter was higher in males and decreased with increasing heart rate in children and adolescents ($r = -0.45$) as well as in adults ($r = -0.25$, both $p < 0.0001$). This relation was also independent of the effect of body size, sex and race. Similarly, the LV mass increased with decreasing heart rate in children and adolescents ($r = -0.45$), but the association was not confirmed after controlling for body size, sex and race. In adults, heart rate was inversely related to LV mass ($r = -0.21$, $p < 0.0001$), and this relation was also independent of body size, sex, race, age and blood pressure ($p < 0.001$). In women, the relation of heart rate to LV mass/height$^{2.7}$ was less close than in men, due to the greater increase in LV mass with age.**

Conclusions. **The heart rate has an inverse association with the LV chamber diameter and with the LV mass in children-adolescents and in adults. This relation is largely, but not uniquely, mediated by body proportions, especially during body growth.**

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The animal life span may be predetermined by the basic energetics of living cells[1], and this energy-balance might be the basis for the physiological evidence of a close inverse exponential relation between heart rate and life expectancy in mammals[2]. Although in the 20th century human life expectancy is substantially greater than predicted from the heart rate-life expectancy relations in other species of mammals, a high heart rate has been reported to be associated with increased cardiovascular risk[3,4]. Large epidemiological studies have been undertaken to address the influence of the resting heart rate on prevalent and incident cardiovascular diseases[5].

An important physiological determinant of heart rate appears to be body size[2]. In mammals, the heart rate ranges from more than 1000 b/min in shrews[6] to 15 b/min in whales[2]. This inverse relation with body size also occurs in humans. The heart rate begins to decrease in infants a few weeks after birth[7], paralleling changes in body size due to growth. The modulation of heart rate and left ventricular (LV) dimensions is such that cardiac output is maintained at levels which are appropriate for the metabolic demand. However, the quantitative relation between body growth and the magnitude of heart rate, and whether the relation of heart rate to LV dimensions is independent of the influence of body size has been only marginally investigated[8]. Accordingly, this study was designed to explore the interrelations among body growth, body size, heart rate and LV dimensions in a study population of children, adolescents and adults, across a broad age span.

Methods

Participants. Two-dimensional echocardiograms were performed in 819 normotensive, normal-weight individuals (aged 1 to 85 years) in three University Hospitals: 337 adults from New York, NY, USA (202 males, 135 females, age 18 to 85 years, 231 white), 128 adults (50 males, 78 females, age 19 to 69 years, all white) and 108 children and adolescents (66 boys, 42 girls, age 6 to 17 years, all white) from Naples, Italy, 241 children and adolescents (124 males, 117 females, age 1 to 17 years, 161 white) and 5 young adults (2 males, 3 females, 18 to 23 years, 3 white) from Cincinnati, OH, USA. The 337 adults from New York were part of employed populations studied in different surveys in work-site programs or enrolled on a voluntary basis; the adults from Naples were part of a screening program of the departmental staff and other normal volunteers, whereas children were studied in a school site, as part of an epidemiological program among elementary-school children, previously described in detail[9]. Children, adolescents and young adults from Cincinnati were recruited from schools in the Cincinnati area. More information on a substantial portion of this study population has been previously reported[8,10,11].

The eligible participants of the present study were consistently normotensive and normal-weight according to previously reported criteria[8,10,11], and were required to exhibit a LV endocardial shortening (as a measure of LV chamber function) ≥ 25%.

Procedures. Immediately after the echocardiogram, the blood pressure was measured with the patient in the supine position and using mercury sphygmomanometers and cuffs of appropriate size. The heart rate was measured from echocardiographic M-mode tracings or derived from the RR interval on the ECG tracing on at least three cardiac cycles at the time of LV measurements or taken at the radial pulse with the subject in the supine position, immediately after the echocardiogram. The body weight and height were measured on the day of echocardiographic evaluation.

Echocardiography. Two-dimensionally targeted M-mode echocardiograms were performed and read by expert sonographers as previously described in detail[8,10-14]. Measurements of the interventricular septal thickness, posterior wall thickness and LV diameters were taken according to the American Society of Echocardiography recommendations[15]. The LV mass was calculated by the adjusted American Society of Echocardiography method[16].

Statistical analysis. Primary echocardiographic variables were adjusted for a "center effect" using the linear coefficient of regression of the relation of each echocardiographic parameter with a dichotomous independent variable representing the center, in age, gender and body size-matched groups of subjects (20 in each group), according to a procedure previously reported in detail[8,10,11]. Briefly, the variables considered in this preliminary analysis were related to the two centers labeled 1 or 2 (Naples and Cincinnati for children and adolescents; Naples and New York for adults) and adjusted using the linear coefficient of regression (b). Thus the adjusted variable (V_{adj}) was:

$$V_{adj} = V - b\,(x - \mu)$$

where V was the observed value of the dependent variable, x was the dummy variable representing the Center and μ was the average value of the variable representing the Centers (where $\mu = 1.5$ for equal cell-size).

The study population was arbitrarily divided into two groups. One group consisted of children and adolescents up to 17 years old and the other of adults ≥ 18 years of age. This stratification takes into account the estimated period of body growth, already used in previous analyses[8,10,11]. The overall prevalence of non-white participants was 30% in both age strata.

Data are expressed as mean ± SD. Descriptive statistics are presented using χ^2 and exact tests performed using the Monte-Carlo method. Least squares linear regression and partial correlation analysis were used to describe relations between study variables. Differences between regression lines were tested by computing F-statistics of the between-slopes sum of squares. Multiple linear regression analysis was used to study the independent associations of demographics with heart rate and of heart rate with LV diameter or mass, by using body size, sex, race and, when needed, age and systolic blood pressure as covariates. The null hypothesis was rejected at two-tailed $\alpha \leq 0.05$.

Results

Table I shows the demographic characteristics of children-adolescents and adults. There were no gender differences in body mass index, blood pressure and heart rate among children and adolescents. Among adults, women were slightly younger and had a lower average blood pressure and body mass index and a higher heart rate than men (all $p < 0.005$).

Left ventricular geometry. Among children and adolescents, females had lower values of LV mass, mostly due to smaller LV end-diastolic diameters (both $p < 0.05$), with no difference in the relative wall thickness. Adult men had a larger LV internal diameter and a thicker LV wall (either absolute or relative value) than women, yielding higher values of LV mass (all $p < 0.0001$; Table II).

Relation of heart rate to age and body size. *Children and adolescents.* The heart rate was linearly and inversely related to age in children and adolescents (r =

Table I. Characteristics of the study population.

Variable	Males (n=190)	Females (n=159)
1 to 17 years		
Age (years)	9.70 ± 3.3	9.84 ± 3.1
Body mass index (kg/m^2)	18.01 ± 2.8	17.92 ± 3.3
Systolic blood pressure (mmHg)	106.16 ± 7.9	105.68 ± 8.8
Diastolic blood pressure (mmHg)	63.12 ± 9.2	64.14 ± 9.2
Heart rate (b/min)	80.16 ± 13.6	81.12 ± 12.5
	Males (n=254)	Females (n=216)
18 to 85 years		
Age (years)	44.60 ± 12.3	41.33 ± 13.6*
Body mass index (kg/m^2)	24.27 ± 2.1	22.60 ± 2.7*
Systolic blood pressure (mmHg)	120.46 ± 8.5	113.28 ± 12.3**
Diastolic blood pressure (mmHg)	74.48 ± 7.2	70.96 ± 8.3**
Heart rate (b/min)	66.21 ± 11.3	70.10 ± 10.8**

Data are expressed as mean ± SD. * $p < 0.005$; ** $p < 0.0001$.

Table II. Left ventricular (LV) geometry in normotensive children, in adolescents and in adults.

Variable	Males (n=190)	Females (n=159)
1 to 17 years		
Septal thickness (cm)	0.58 ± 0.14	0.57 ± 0.12
LV end-diastolic diameter (cm)	4.13 ± 0.50	3.98 ± 0.47*
Posterior wall thickness (cm)	0.59 ± 0.16	0.58 ± 0.13
LV mass (g)	70.25 ± 31.2	62.83 ± 23.9**
Relative wall thickness	0.29 ± 0.06	0.29 ± 0.06
	Males (n=254)	Females (n=216)
18 to 85 years		
Septal thickness (cm)	0.92 ± 0.12	0.80 ± 0.13§
LV end-diastolic diameter (cm)	5.01 ± 0.4	4.56 ± 0.4§
Posterior wall thickness (cm)	0.85 ± 0.11	0.73 ± 0.11§
LV mass (g)	156.53 ± 32.3	110.82 ± 26.0§
Relative wall thickness	0.34 ± 0.05	0.32 ± 0.05§

Data are expressed as mean ± SD. * $p < 0.005$; ** $p < 0.02$; § $p < 0.0001$.

-0.49; SEE 11.43 b/min; $p < 0.0001$), with similar trends in girls (-1.67 b/min/year) and boys (-2.24 b/min/year; p for difference in trends = 0.14).

Similarly, the heart rate was also inversely related to body height ($r = -0.51$, SEE 11.31 b/min, $p < 0.0001$) or body weight ($r = -0.42$, SEE 11.90 b/min; $p < 0.0001$) with similar trends in girls (-0.28 b/min per cm of increasing height and -0.28 b/min per kg of increasing weight, respectively) and boys (-0.33 b/min per cm of increasing height and -0.41 b/min per kg of increasing weight, both p values for the difference in trends > 0.12).

Adults. The inverse relation of the heart rate to age, observed in children and adolescents, was not significant in adults ($r = -0.09$, $p = 0.07$). However, although less evident than in the younger age-stratum, a weak, inverse relation was found between the heart rate and height ($r = -0.13$, SEE 11.11 b/min; $p = 0.004$). This relation was substantially due to gender differences, not being statistically significant when examined separately in men ($r = 0.03$) and women ($r = -0.07$). Just as for body height, the heart rate was not related to body weight, both in pooled genders ($r = -0.08$) as well as when men and women were considered separately.

Relation of heart rate to left ventricular end-diastolic diameter. *Children and adolescents*. The heart rate was inversely related to the LV internal diameter ($r = -0.45$, SEE 0.44 cm; $p < 0.0001$), with almost identical trends in girls (1.4 mm increase per 10 b/min decrease) and boys (1.9 mm increase per 10 b/min decrease; p for difference in trends > 0.17).

Although substantially reduced, the relation between the heart rate and the LV internal diameter was still significant after controlling for the effect of body size (height and cube root of body weight), sex and race (partial $r = -0.17$, $p < 0.003$).

Adults. The LV internal dimensions increased with decreasing heart rate ($r = -0.25$, SEE 0.42 cm, $p < 0.0001$) similarly in women (0.5 mm per 10 b/min decrease) and men (0.8 mm per 10 b/min decrease; p for difference in trends > 0.29), but at each level of heart rate, the LV chamber dimensions were 0.6 cm larger in men than in women ($p < 0.0001$).

The relation between heart rate and the LV internal diameter was independent of the effect of body size, sex and race (partial $r = -0.23$, $p < 0.0001$).

Relation of heart rate to left ventricular mass. *Children and adolescents*. The heart rate was inversely related to the LV mass ($r = -0.41$, SEE 26 g; $p < 0.0001$), with similar trends in girls (0.70 g increase per b/min decrease) and boys (1.01 g increase per b/min decrease; p for difference in trends > 0.14).

When adjusting for the effect of body size ($height^{2.7}$ and body weight), sex and race, the inverse relation between heart rate and LV mass was completely offset (partial $r = -0.008$).

Adults. The LV mass increased with decreasing heart rate ($r = -0.21$, SEE 36.5 g, $p < 0.0001$) with a trend lower in women (1.1 g per 10 b/min decrease) than in men (5.1 g per 10 b/min decrease; p for difference in

trends = 0.09). This relation was also maintained when the LV mass was normalized for the allometric power of height (i.e. in $m^{2.7}$)[17], but the gender difference was even more pronounced: for a decrease in heart rate of 10 b/min, the LV mass increased by 1.3 g/$m^{2.7}$ in men and only by 30 mg/$m^{2.7}$ in women.

The relation between heart rate and LV mass was only partially influenced by the covariance of body size, sex and race, remaining statistically significant (partial r = -0.16, $p < 0.0001$). The sign and extent of the relation did not change even when age and systolic pressure were considered in the model. Analysis of residuals of the regression of the LV mass index to body size, sex and race demonstrated that the sex difference in the effect of heart rate was attributable to a significantly greater increase in LV mass with age in women (slope of residuals about age 0.23/year) than in men (slope 0.09/year, p for slope difference < 0.0001).

Discussion

This study was designed to determine the relations of heart rate to LV dimensions during body growth, adulthood and maturity in the absence of recognizable pathological conditions that could interfere with normal physiology. The use of a large normal population sample with ages distributed across the entire life span made it possible to implement multivariate procedures and thus to examine the independent effect of heart rate with adjustment for other covariates, allowing a number of physiological inferences.

Heart rate and body size. Similar to other mammals, in our study population of normal-weight, normotensive individuals the heart rate was closely and inversely related to body size during body growth. In adults, the narrow range of body size in our normal-weight population did not allow the detection of significant relations with heart rate. The evidence of the gender difference in heart rate is probably related to the gender-related differences in body size, more than to other biological characteristics associated with sex. This possibility requires further analyses.

In view of the significant association observed between heart rate and body proportions, evaluation of the relations of heart rate to LV dimensions had to consider body size as a covariate. Similar to the preceding analyses, for this evaluation one should also consider that the range of heart rate variability was constant across the age span, whereas the coefficient of variability of LV diameter and mass were markedly higher in children and adolescents (12 and 42%) than in adults (8 and 22%), yielding closer relations in the youngest age stratum.

Heart rate and left ventricular dimensions in children and adolescents. In this age stratum, the heart rate was a negative correlate of the LV chamber diameter. This was an expected result in a population of normal children and adolescents, in which the LV chamber diameter can be assumed to be positively related to the duration of LV filling, and therefore to the magnitude of the stroke volume, confirming previous results in other study populations[18,19]. The relation between heart rate and LV chamber dimensions was largely a function of the strong influence of body growth, being markedly reduced when body size was taken into account.

In contrast, the heart rate was not an independent correlate of the LV mass when body size and gender were also taken into account, suggesting that, during body development, the LV mass is more strongly influenced by the parallel increase in LV wall thickness due to an increasing cardiac workload[11].

Heart rate and left ventricular dimensions in adults. During adulthood and maturity, the heart rate was a negative correlate of the LV chamber dimensions, even after adjusting for body size and gender, and the relation was not influenced by aging. The independence of the heart rate-LV chamber dimension relation found in our study population extends the findings of previous studies including smaller population samples[20-22] to a large-scale study. In contrast with findings in children and adolescents, in adults a low heart rate was also associated with a greater LV mass, and this association was independent of the influences of body size, while it was relatively gender-dependent. This gender effect was especially evident when the LV mass was normalized for body size. The more pronounced inverse association between heart rate and LV mass in men cannot be easily explained in the context of the present analysis, but gender-specific analysis of residuals about age suggests that in women there is an age-related increase in LV mass which is greater than in men. This has already been demonstrated in a number of epidemiological studies[23,24].

The relation between LV mass/height$^{2.7}$ and heart rate remained almost unchanged in multivariate procedures which included blood pressure in the regression model. This indicates a remarkable independence of this association.

Physiological implications. The primary role of heart rate and vascular tone, which are physiologically modulated by a variety of regulatory and adaptive mechanisms, is to supply the amount of oxygen and nutrients required by body tissues, especially muscle and solid organs that comprise the fat-free mass. Thus, pacing-induced increases in heart rate not accompanied by changes in the tissue metabolic demand cause a reciprocal reduction of stroke volume[25], mediated by the decreased end-diastolic LV chamber volume not associated with corresponding changes in the end-systolic volume. Similarly, the increased vagal tone observed in endurance athletes, in the absence of modifications in the resting metabolic demand[26], causes an increase in the LV end-diastolic volume leading to an increased

stroke volume and maintaining a normal cardiac output at rest, despite the reduced heart rate. However, chronic isotonic conditioning also induces eccentric LV hypertrophy[27], thereby providing a cardiac geometric basis for a larger stroke volume. Thus, it is also possible that the increase in LV chamber dimensions, whether due to the effects of the level of physical conditioning or to as yet undefined genetic factors that influence the LV volume[28], may contribute to the determination of the resting heart rate needed to meet tissue metabolic needs, under the assumption of a normal baroceptor control[29]. The absence of an independent association of the LV mass with the heart rate in children supports the hypothesis that the association found in adults might be due to this latter mechanism which is not yet evident during body growth because the variability due to body mass development is overwhelming with respect to any other stimuli. The population under study mostly consisted of individuals who were not under physical training, but precise information is not available and therefore the above possibility could not be further explored.

Study limitations. The study of the relations between heart rate and LV chamber dimensions during body growth is made difficult by the well known inverse relation between heart rate and body size[30] and by the positive relation between LV dimensions and body size[31,32]. This limitation has been at least partly overcome by using multivariate analysis in which measures of body size have been included after mathematical transformation which made them geometrically consistent with the measure of the LV parameter that we were considering (i.e. height and cube root of body weight vs LV dimension, height$^{2.7}$ and body weight vs LV mass).

Results from this study should however be interpreted cautiously because of the intrinsic limitations of cross-sectional surveys when employed for the evaluation of time-related physiological phenomena. Moreover, the results of this analysis were obtained from a normal population and might therefore not be necessarily applicable in pathological conditions or outside the evaluated range of body size.

In conclusion, heart rate has negative association with LV chamber diameter and with LV mass in children-adolescents and in adults. This relation is largely, but not uniquely, mediated by body proportions, especially during body growth.

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