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Heart Size Estimates Indexed Optimally to Body and Chest Size

II. Prognostic Value for Cardiovascular Disease Mortality[1]

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Abstract. The prognostic value of heart size estimates in prediction of cardiovascular disease (CVD) mortality was investigated in 1,807 men (1,609 white, 198 black) and 2,143 women (1,884 white, 259 black) in connection with the NHANES I Epidemiologic Follow-up Study (1982–1984). The sample persons were 35–74 years old at the onset of the study. The average follow-up period was 9.5 years (range 5–12 years). The relative risks were estimated by comparing risks at 90th vs. 10th percentile points of the distributions of each cardiac size index, using Cox regression to adjust for age, cigarette smoking, cholesterol, systolic blood pressure, history of diabetes and history of heart attack. Cardiac enlargement index (CEI; cardiac transverse diameter indexed to body weight, height and chest diameter) was the best independent predictor of CVD mortality (except among white males). The relative risks for CEI ranged from 1.88 (95% confidence interval 1.14–3.10) for white women to 5.33 (1.87–15.20) for black women. Heart volume index (HVI; heart-volume indexed to chest diameter and body weight) had a relative risk of 1.81 (1.28–2.56) for white males. Heart size estimates indexed optimally to body and chest size appear important independent predictors of CVD mortality.

Introduction

A previous report from the First National Health and Nutrition Examination Survey (NHANES I) introduced formulas for using optimal combinations of anthropometric measurements to index radiological heart size to body and chest size [1]. About 40% of the variance of cardiac transverse diameter was explained by chest diameter, body weight and standing height, and about 30% of the variance of cardiac volume by chest diameter and

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body weight alone. Population standards were introduced for heart volume index (HVI) as the ratio of the measured vs. predicted cardiac volume, and for cardiac enlargement index (CEI) as the ratio of the measured vs. predicted cardiac transverse diameter.

The purpose of the present investigation was to determine the risk of cardiovascular disease mortality for these two new cardiac size indexes in connection with the NHANES I Epidemiologic Follow-Up Study (1982–1984) (NHEFS).

Methods

Study Population

The study population of the present investigation is the detailed examination component, a subset of NHANES I. The NHANES I is a health survey conducted in the USA between April 1971 and October 1975. The study population is representative of the US population aged 25–74 years during the study period. Design and operational aspects of NHANES I have been described previously [2–4].

The composition of the study population is summarized in table 1. The main subgroup used in the present investigation included examinees aged 35–77 years who had both a chest X-ray and an ECG of adequate quality for computer analysis and who were traced for vital status in 1982–1984. The study design for NHEFS included an in-depth interview with the surviving participants or with proxies for those who were deceased or incapacitated, taking selected physical measurements, obtaining hospital and nursing home records for admissions occurring during the follow-up period, and obtaining death certificates for the decedents. Ninety-three percent of the original cohort was successfully traced. Interviews were conducted for 93% of traced surviving participants and 84% of the deceased participants. Death certificates are available for > 95% of the decedents. Details of the mortality follow-up have been reported elsewhere [5].

Cardiovascular disease (CVD) death is defined according to the 9th revision of the International Code for Classification of Diseases as an underlying cause of death or rheumatic heart disease (ICD-9 390-398), hypertensive disease (ICD-9 401-405), ischemic heart disease including myocardial infarction and angina pectoris (ICD-9 410-414), and cerebrovascular diseases (ICD-9 430-438).

Radiographic Methods

Posteroanterior roentgenograms were used to measure the transverse thoracic diameter and the transverse cardiac diameter according to the procedure introduced by Danzer [6]. The heart volume was determined from the posteroanterior and lateral roentgenograms using the method of Jonsell [7].

Optimal Indexing of Heart Volume to Body and Chest Size. HVI was devised as follows [1]

White men: $HVI = V/(13.43T^{0.606}W^{0.498})$,
Black men: $HVI = V/(4.13T^{1.237}W^{0.271})$,
White women: $HVI = V/(20.30T^{0.453}W^{0.485})$,
Black women: $HVI = V/(29.42T^{0.435}W^{0.417})$,

where V = measured heart volume (ml), T = thoracic transverse diameter (cm), and W = body weight (kg).

CEI was calculated using the following formulas [1]:

White men: $CEI = C/(45.23T^{0.423}W^{0.401}H^{-0.843})$,
Black men: $CEI = C/(15.44T^{0.428}W^{0.310}H^{-0.560})$,
White women: $CEI = C/(50.54T^{0.296}W^{0.364}H^{-0.765})$,
Black women: $CEI = C/(19.57T^{0.254}H^{0.262}W^{-0.460})$,

where C = measured cardiac diameter (cm), T = thoracic transverse diameter (cm), W = body weight (kg), and H = standing height (cm)

Statistical Methods

The association of each cardiac size index with the risk of CVD mortality was assessed using Cox proportional hazards models taking into consideration the effects of important covariates and the unequal follow-up times contributed by sample persons of the study [8]. All models were constructed separately for each race and sex group.

Estimates of relative risks (hazard ratios) and corresponding two-sided 95% confidence intervals were determined for each Cox regression model comparing values of the 90th and 10th percentile points on the distribution of each cardiac size index in each race/sex subgroup [9]. Similarly, relative risk estimates were determined for other covariates. Ten years was taken as a unit increase for age, 20 mg/dl for serum cholesterol and 20 mm Hg for systolic blood pressure.

Results

Radiological Heart Size and CVD Mortality

HVI was a significant independent predictor of CVD deaths among white men and black women but not among black men and white women (table 2). The relative risk of CVD mortality was 1.81 (1.28 to 2.56, $p < 0.001$) for white men and 3.94 (1.78 to 8.71, $p < 0.001$) for black women. CEI, on the other hand, was significantly associated with excess CVD deaths among white and black women but not among white or black men. The relative risk of CVD mortality for CEI was 1.88 (1.14 to 3.10, $p < 0.05$) for white women and 5.33 (1.87 to 15.20, $p < 0.01$) for black women.

Cox regression of total mortality (not shown) on HVI and the same set of covariates as in table 2 revealed a significant independent association for HVI among white men ($p < 0.001$), white women ($p < 0.05$), and black women ($p < 0.05$). Cox regression of total mortality on CEI showed a significant association among white men ($p < 0.05$), white women ($p < 0.001$) and black women ($p < 0.05$).

The effect on relative risk of a CEI increase by 0.20 is estimated in table 3 in comparison with increases in the values of other CVD risk factors. Although the comparison of the relative effects of various independent variables measured on different scales poses logistic problems, [11] these estimates suggest that CEI ranks high as a predictor of CVD mortality among black men and

black and white women. A 0.20 increase in CEI was associated with a relative risk of CVD mortality of 1.98 (1.77–2.19) in black men, 1.73 (1.38–2.08) in white women and 4.13 (3.96–4.30) in black women. A 0.20 increase in CEI is approximately equivalent to a change from the median value to a value at the 95th percentile point of the CEI distribution among white men and women aged 55 and over [1].

Relative Risks of CVD Mortality Comparing HVI and CEI with Other Indexing Formulas

The relative risks of CVD mortality for the two new cardiac size measurements indexed optimally to body and chest size were evaluated in comparison with the traditional radiological cardiac size indexes, namely the cardiothoracic ratio (cardiac transverse diameter/thoracic transverse diameter, or C/T) and the relative heart

Table 1. Study population extracted from the examinees aged 25–74 years in the detailed component of the NHANES I, who received extensive physical examinations and laboratory tests in 1971–1975.

Category	White men	Black men	White women	Black women
Number examined with chest X-rays and ECG recording at baseline	2,159	278	2,582	359
Number of the above traced for vital status (1982–1984) aged 35 years and older	1,610	198	1,885	259
Number of CVD deaths	137	31	78	22
Number of deaths from all causes	282	60	175	43

* ICD 9th revision codes 390–448.

Table 2. Relative risks (RR)[1] of cardiovascular disease mortality from Cox regression by comparing 90th vs. 10th percentile of X-ray estimates of HVI and CEI by race and sex

Variables	White men		Black men		White women		Black women	
	RR	CI 95%	RR	CI 95%	RR	CI 95%	RR	CI 95%
HVI	1.81	(1.28, 2.56)	1.62	(0.75, 3.51)	1.50	(0.94, 2.41)	3.94	(1.78, 8.71)
CEI	1.24	(0.81, 1.90)	2.60	(0.93, 7.29)	1.88	(1.14, 3.10)	5.33	(1.87, 15.20)

[1] Adjusted for age, cigarette smoking, serum cholesterol, systolic blood pressure, history of diabetes and history of heart attack.

Table 3. Comparative effect of unit increases in independent variables on relative risks of cardiovascular disease mortality from Cox regression[1]

Variables	White men		Black men		White women		Black women	
	RR	CI 95%	RR	CI 95%	RR	CI 95%	RR	CI 95%
Age, years ($\bar{x}$ + 10)	2.42	(1.95, 3.01)	1.59	(1.01, 2.48)	2.74	(1.95, 3.84)	1.51	(0.92, 2.47)
Cigarette smoking (yes = 1, no = 0)	1.98	(1.38, 2.84)	1.93	(0.82, 4.53)	2.45	(1.49, 4.04)	2.67	(1.01, 7.03)
Cholesterol, mg/dl ($\bar{x}$ + 20)	1.02	(0.94, 1.11)	1.16	(0.99, 1.35)	1.11	(1.01, 1.22)	1.06	(0.89, 1.26)
Systolic blood pressure, mm Hg ($\bar{x}$ + 20)	1.26	(1.09, 1.45)	1.23	(0.98, 1.54)	1.52	(1.27, 1.82)	1.11	(0.84, 1.48)
History of diabetes (yes = 1, no = 0)	1.82	(1.05, 3.15)	0.52	(0.07, 4.11)	1.95	(0.95, 3.98)	1.52	(0.52, 4.48)
History of heart attack (yes = 1, no = 0)	3.30	(2.21, 4.93)	2.69	(0.83, 8.71)	1.31	(0.69, 2.47)	2.35	(0.64, 8.62)
CEI ($\bar{x}$ + 0.20)	1.20	(0.84, 1.72)	1.98	(1.95, 4.15)	1.73	(1.12, 2.68)	4.13	(1.70, 10.04)

[1] Unit increase for RR estimates for age is 10 years, 20 mg/dl for cholesterol, 20 mm Hg for systolic blood pressure and 0.20 for CEI.
[2] CI = 95% confidence interval.

Table 4. Relative risks relating various cardiac size indexes to cardiovascular disease mortality among men aged 35–74 years

Cardiac size index	Point estimate for percentile distribution		Beta[1]	SE	RR[2]	CI 95%
	10th, %	90th, %				
White men						
V/H	4.34	7.44	0.1635	0.0567	1.66	(1.18, 2.34)
V/BSA	402.2	648.5	0.0023	0.0007	1.76	(1.26, 2.47)
HVI	0.816	1.29	1.1731	0.3517	1.74	(1.26, 2.42)
C/H	0.072	0.099	5.1669	8.0800	1.15	(0.75, 1.76)
C/T	0.402	0.525	−0.0139	1.7509	1.00	(0.65, 1.52)
CEI	0.907	1.14	0.7856	0.8836	1.20	(0.86, 1.80)
Black men						
V/H	4.13	7.24	0.1872	0.1159	1.79	(0.88, 3.63)
V/BSA	384.7	635.2	0.0030	0.0015	2.12	(1.02, 4.43)
HVI	0.797	1.302	1.4363	0.7413	2.06	(0.99, 4.30)
C/H	0.069	0.098	31.689	16.425	2.51	(0.99, 6.38)
C/T	0.401	0.546	7.073	3.385	2.79	(1.07, 7.30)
CEI	0.870	1.149	4.483	1.647	3.49	(1.85, 6.60)

BSA = Body surface area (m^2); C = cardiac transverse diameter (cm); CEI = cardiac enlargement index; CVI = cardiac volume index; H = body height (cm); T = thoracic transverse diameter (cm); V = cardiac volume by X-ray (ml).

[1] Coefficient estimates (beta) and standard errors (SE) from Cox regression used to adjust for age, systolic blood pressure, history of heart attack, and body height.

[2] Relative risks (RR) with 95% confidence intervals (CI) comparing 90th vs. 10th percentile point of the distribution of each cardiac size index.

volume (heart volume indexed to body surface area, or V/BSA) (tables 4, 5). In addition, relative risks were calculated for cardiac volume and cardiac transverse diameter indexed linearly to body height (V/H and C/H, respectively). These latter cardiac size indexes were included because it has been recently suggested that indexing of the echocardiographic left ventricular mass to standing height rather than to other measures of body size may be an effective way of detecting left ventricular hypertrophy [12]. Such assertions seemed plausible since it is conceivable that indexing cardiac size to body weight or body surface area will diminish the apparent cardiac size increase otherwise observed in obesity.

In these comparative evaluations, Cox regression was used to adjust for age, systolic blood pressure, history of heart attack and body height. Body height was included as a covariate because it was used in most of these cardiac size indexes and because of the possibility that it may itself be an independent predictor of CVD mortality.

The relative risks of CVD mortality for cardiac volume indexed by these different ways were all of the same order of magnitude (tables 4, 5). Cardiac transverse diameter indexed by these different methods also yielded relative risks of comparable magnitude.

Discussion

The results from the present study indicate a considerable diversity in the prognostic information content of cardiac size indexes derived from chest X-ray measurements. HVI and CEI were both significant independent predictors of CVD mortality among black women, HVI among white men, and CEI among white women when adjustments were made for standard CVD risk factors by incorporating them into the Cox regression model. Although not significant, the relative risks for both cardiac size variables among black men were of the same order of magnitude as among white men. The lack of significance probably reflects the small sample size and relatively small number of CVD events.

When comparing relative risks of CVD mortality at the 90th vs. the 10th percentile point of each cardiac size variable, the relative risks for HVI ranged from 1.81 among white men to 3.94 among black women, after adjustment for age, cigarette smoking, serum cholesterol, systolic blood pressure, history of heart attack and history of diabetes. Similarly, relative risk as high as 5.33 (1.87–15.20) was found for CEI among black women.

Table 5. Relative risks relating various cardiac size indexes to cardiovascular disease mortality among women aged 35–74 years

Cardiac size index	Point estimate for percentile distribution		Beta[1]	SE	RR[2]	CI 95%
	10th, %	90th, %				
White women						
V/H	3.42	5.80	0.2905	0.1056	2.00	(1.22, 3.27)
V/BSA	338.5	530.3	0.0036	0.0012	2.02	(1.27, 3.13)
HVI	0.827	1.291	1.4725	0.4676	1.98	(1.29, 3.03)
C/H	0.067	0.094	42.4801	12.1292	3.15	(1.66, 5.98)
C/T	0.403	0.539	8.3072	2.0830	3.10	(1.78, 5.39)
CEI	0.902	1.131	4.108	0.9884	2.56	(1.31, 5.02)
Black women						
V/H	3.48	6.15	0.5742	0.1804	4.63	(1.80, 11.91)
V/BSA	336.6	542.4	0.0075	0.0019	4.68	(2.17, 10.07)
HVI	0.816	1.29	3.0135	0.7497	4.17	(2.08, 8.37)
C/H	0.072	0.097	56.6504	25.4249	4.12	(1.19, 14.32)
C/T	0.444	0.575	11.9213	3.9647	4.77	(1.72, 13.19)
CEI	0.910	1.145	7.4312	2.1679	5.73	(2.11, 15.56)

Footnotes as in table 4.

The results from the present study also confirm previous reports on the prognostic value of cardiac size as expressed by the traditional ways of indexing, namely cardiac transverse diameter indexed linearly to chest diameter (cardiothoracic ratio) and heart volume indexed to body surface area (relative heart volume) [10, 13–15]. The method of indexing itself did not seem to make much difference regarding the prognostic value of cardiac size, and the choice between alternative ways of indexing has been made by other considerations than the relative risks associated with them. HVI and CEI are independent of normal body and chest size variations which simplifies their use in multivariate analyses by reducing the number of covariates which otherwise may have significant interactions with heart size and among themselves.

Our previous report from NHANES I indicated that about 40% of the variance of the cardiac transverse diameter was explained by chest diameter, body weight and standing height [1]. Chest diameter and body weight together explained about 30% of the variance of cardiac volume. The use of cardiothoracic ratio and cardiac volume indexed to body surface area for estimating the prevalence of cardiomegaly has been justifiably criticised because of their dependence on body and chest size and anthropometric differences in chest and heart size relationships between blacks and whites [16–19]. Optimal indexing to chest and body size separately for each race and sex group as was done for HVI and CEI in the NHANES I study population will alleviate such problems in future studies.

Possible Mechanisms of Excess Risk with Increased Heart Size

Increased level of ventricular ectopic activity has been observed among hypertensive subjects with LVH [20]. Perhaps more significant in this context are recent reports which have demonstrated the association of LVH with an increased prevalence of complex ventricular arrhythmias [21, 22]. In the study of McLenachan et al. [21] nonsustained ventricular tachycardia occurred in 14 of their 50 hypertensive patients with ECG-LVH by voltage criteria alone, and in only 4 of the 50 hypertensive patients without ECG-LVH, both contrasting to the prevalence of 1 of 50 normotensive controls. There was no association of ventricular tachycardias with diuretic therapy or hypokalemia. Of 18 patients who had ventricular tachycardias, 17 had left ventricular mass index by echocardiogram exceeding 140 g/m^2. The report by Levy et al. [22] from the Framingham Study revealed a significant association of LVH by echocardiogram with each of the 6 ventricular arrhythmia severity grades in men and with 4 of 6 grades in women. There was a significant association between ECG-LVH by voltage criteria and 4 of the 6 severity grades of ventricular arrhythmias among men but not among women, at least partly due to low prevalence of

ECG-LVH according to the criteria used. These observations suggest that an increased left ventricular mass, alone or in combination with ischemic myocardial damage, may predispose at least some high-risk subgroups to ventricular arrhythmias and possibly to sudden death.

Implications of the Results

The availability of race/sex-specific standards for radiological cardiac size measurements can be anticipated to facilitate population comparisons in epidemiological studies. They will also facilitate the choice of comparable upper normal limits for criteria for cardiomegaly. Equally important is the availability of X-ray estimates of heart volume and cardiac enlargement index on a continuous scale standardized to normal variations in body and chest size. This is likely to be particularly useful in monitoring differential trends in progression and regression of left ventricular hypertrophy between treatment groups in clinical trials designed to test the effectiveness of various intervention modalities. Also important are the prospects for enhanced detection of secular trends in cardiac size in relation to changes in the prevalence of hypertension and other CVD risk factors assessed in periodic health examinations such as NHANES I and the subsequent national health surveys in the US.

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