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Association between left ventricular hypertrophy and erythrocyte sodium-lithium exchange in normotensive subjects with and without NIDDM

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Summary The determinants of left ventricular mass in normal control subjects and subjects with non-insulin-dependent diabetes (NIDDM) are ill-defined. We therefore recorded M-mode and pulsed Doppler echocardiograms and 24-h ambulatory blood pressure in 57 normotensive subjects, 34 with NIDDM and 23 matched non-diabetic control subjects. Measurements of erythrocyte sodium-lithium countertransport, plasma angiotensin II, plasma and platelet catecholamines and fasting plasma insulin were also made. Six control subjects (26 %) and 15 diabetic subjects (44 %) had some degree of left ventricular hypertrophy. Subjects with left ventricular hypertrophy ($n = 21$) had an elevated mean rate of sodium-lithium countertransport (0.40 ± 0.13 vs 0.31 ± 0.09 mmol $\cdot$ l^{-1} $\cdot$ h^{-1}; $p < 0.01$), parallel differences being observed in both the diabetic and control groups. Twelve of the subjects with left ventricular hypertrophy (57 %) had elevated rates of sodium-lithium countertransport compared to only seven (19 %) of those without ($p < 0.05$). There was no consistent difference between those with and without left ventricular hypertrophy in any other clinical or biochemical variable. Multivariate analysis, with the presence or absence of left ventricular hypertrophy as the dependent variable, demonstrated that the maximal rate of sodium-lithium countertransport was the only variable that independently contributed to left ventricular hypertrophy (partial $r = 0.35$; $F_{1,55} = 7.74$; $p = 0.007$). This study demonstrates for the first time an association between left ventricular hypertrophy and erythrocyte membrane cation transport that is independent of hypertension, is present in both diabetic and non-diabetic groups, and may represent a link between elevated rates of membrane sodium transport and cardiovascular risk. [Diabetologia (1995) 37: 454–460]

Key words Left ventricular hypertrophy, diabetes mellitus, sodium-lithium countertransport.

Left ventricular hypertrophy, when derived from standard M-mode echocardiograms, is a remarkably powerful predictor of future cardiovascular events [1, 2]. This predictive power has been demonstrated in both normotensive and hypertensive populations [1, 3], and in both men and women [4]. Subjects with non-insulin-dependent diabetes (NIDDM) suffer from cardiovascular disease at a rate in excess of that predicted by known cardiovascular risk factors [5], and there is some limited evidence that NIDDM is independently associated with an increased left ventricular mass [6].

Age, body mass index and blood pressure all contribute to population variability in left ventricular mass [7], but the potential contributions of the renin-angiotensin system [8], plasma catecholamines [9], insulin and insulin resistance [10] and membrane cation transport [11] are well recognised, at least in hypertensive populations. NIDDM patients and non-diabetic subjects differ in many of these variables, but whether this contri-

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Abbreviations: Na-Li CT, Sodium-lithium countertransport; LVH, left ventricular hypertrophy; AER, urinary albumin excretion rate.

butes to differences in left ventricular mass is unknown.

The aims of this cross-sectional echocardiographic study were to compare the left ventricular mass of normotensive NIDDM subjects with matched non-diabetic control subjects and to examine the separate potential determinants of left ventricular mass in these two groups.

Patients and methods

Hospital Ethical Committee approval and informed consent were obtained before we studied 34 subjects who fulfilled the World Health Organisation diagnostic criteria for NIDDM [12]. These subjects were recruited from an outpatient population (without regard to gender or ethnic origin), if they were 35 to 65 years old with a body mass index of less than 32 kg/m^2 and a blood pressure below 160/90 mm Hg. This initial blood pressure reading was taken by a single observer with a Hawksley random zero sphygmomanometer (Hawksley and Sons, Lancing, Sussex, UK). Three readings were taken on the right arm after 10-min supine rest, by a single observer, and a mean value calculated. In addition, all subjects had a normal 12-lead electrocardiogram and were negative for macroproteinuria on urinalysis (Albustix, Ames, London UK). No subject had a history of treated hypertension or cardiac disease, and none had ever received insulin or any antihypertensive medication. In 13 subjects (38 %), adequate glycaemic control was maintained by dietary measures, while the remaining subjects received oral hypoglycaemic agents.

Twenty-three non-diabetic control subjects were recruited using the same criteria, except that all had a normal fasting blood glucose and a normal glycated haemoglobin. Control subjects were selected to ensure that the groups were comparable for gender, ethnic origin and body mass index.

Methods. All subjects underwent standard M-mode and pulsed Doppler echocardiography, 24-h ambulatory blood pressure monitoring and fasting venesection. All blood pressure and echocardiographic measurements were made by single observers who were unaware of the subjects' clinical state.

A more accurate measure of the pressure load on the left ventricle is given by 24-h ambulatory blood pressure recording and "white-coat" hypertension is avoided [13]. All subjects underwent blood pressure monitoring with a Takeda TM 2420 system with measurements every 15 min during the day (08.00–22.00 hours) and every 30 min during the night (22.00–08.00). Mean systolic and diastolic blood pressures were calculated for the day, night and entire 24 h.

Conventional M-mode echocardiograms were recorded using a mechanical scanner system (ATL-UMA) with a 3 MHz duplex probe. Left ventricular measurements and left ventricular mass index (LVMI; g/m^2 body surface area) were calculated according to the Penn convention [14] and the upper limit of normal was taken as 131 g/m^2 and 100 g/m^2 (women). These widely accepted figures are based on the large population-based data of Levy et al. [15].

Pulsed Doppler echocardiograms were recorded simultaneously. This method measures peak left ventricular filling velocities during the early (E) and later atrial phase (A) of diastolic filling. An E : A ratio of less than 1.0 allows the separation of normal from abnormal angiographic diastolic filling in 93 % of cases [16], and may suggest a less compliant left ventricle.

On fasting blood samples, plasma glucose concentrations was measured by a glucose oxidase method, glycated haemoglobin (HbA_1) by the Corning method (Corning 701 system, Ciba, Sussex, UK, normal range 6.5–8.5 %) total cholesterol and triglycerides by standard enzymatic methods (Technicon RA 1000 analyser, Technicon Instruments, Basingstoke, Hants, UK), HDL-cholesterol by a heparin-manganese precipitation technique, LDL-cholesterol by calculation from the Friedewald formula [17], plasma insulin using a specific two-site immunoradiometric method that does not react with proinsulin or its conversion intermediates [18] and plasma angiotensin II by radioimmunoassay [19]. Plasma noradrenaline and adrenaline and platelet noradrenaline were measured using a technique described previously [20]. Platelet catecholamines may give a more integrated measurement of circulating noradrenaline, avoiding rapid fluctuations seen in plasma levels [24]. Finally, the maximal rate of erythrocyte sodium-lithium countertransport (Na-Li CT) was measured in all subjects using a method modified from that described by Canessa et al. [22]. The upper limit of normal was taken to be 0.40 $mmol \cdot l^{-1} \cdot h^{-1}$ using this technique [22]. A single times overnight urine collection was obtained from the diabetic subjects to allow calculation of urinary albumin excretion rate (AER) using an in-house ELISA method [23].

Statistical analysis

All data are shown as a mean (SD) or as a median and range for non-normally distributed variables (plasma insulin and AER). Differences between the two groups or subgroups were analysed using unpaired Student's *t*-tests or Mann-Whitney U tests where appropriate. Differences in distributions between groups were analysed using chi-squared analysis. Simple linear and stepwise multiple regression analyses were carried out with E : A ratio as a dependent variable. Because of the potential influences of gender and ethnicity on the raw data for left ventricular mass index, the presence or absence of left ventricular hypertrophy was used as the dependent variable in multivariate analyses. Diabetes and race were entered as dummy independent variables. The other independent variables included were age, body mass index, mean daytime, nighttime and 24-h blood pressures, insulin, glucose, angiotensin II, plasma noradrenaline and adrenaline, AER and sodium-lithium countertransport. Insulin concentrations and urinary AER were log transformed before inclusion in univariate and parametric multivariate analyses.

Results

Clinical features (Table 1). The clinical features of the diabetic and control groups are shown in Table 1.

Blood pressure (Table 2). Mean 24-h systolic and diastolic blood pressures did not differ significantly between groups. Night and daytime mean blood pressures also did not differ between groups (data not shown).

Biochemical data (Table 2). There was by definition a significant difference in mean blood glucose concentrations and HbA_1 between groups. Three of the

Table 1. Basic clinical data in control and diabetic groups

	Control subjects	Diabetic subjects
Number	23	34
Age (years)	47.4 (7.0)	52.7 (8.5)[a]
Sex (male : female)	20 : 3	32 : 2
Race (C : A : AC)	20 : 1 : 2	23 : 8 : 3
Body mass index (kg/m^2)	24.2 (2.2)	25.7 (2.7)
Current or ex-smoker *(n)*	6 (26 %)	15 (41 %)
Known parental hypertension *(n)*	4 (17 %)	4 (11 %)
Diabetes duration (years)	–	6.8 (6)

All data as mean and one SD. [a] $p < 0.05$.
C, Caucasian; A, Asian; AC, Afro-Caribbean

34 diabetic subjects (8.8 %) had a urinary AER above 20 μg/min.

There was no significant difference between groups for any biochemical measurement other than a lower plasma noradrenaline ($p < 0.05$) and a higher LDL-cholesterol ($p < 0.05$) in the diabetic group.

There was no significant difference between groups in mean rates of Na-Li CT, but there was a significant difference in the distribution of individual values. Of the 23 control subjects, only 4 (17 %) had elevated rates of Na-Li CT, compared to 15 of the 34 diabetic subjects (44 %; $p < 0.05$).

Echocardiographic data (Table 2). There was no difference in mean left ventricular mass index between groups (Table 2). Of the control group, 6 subjects (25 %) had some degree of left ventricular hypertrophy, compared to 15 (44 %) of the diabetic group. This difference was not significant ($p = 0.09$). The mean E : A ratio was significantly lower in the diabetic group ($p < 0.0001$) and the heart rate significantly higher ($p < 0.001$).

Left ventricular hypertrophy (Tables 3 to 5). Table 3 shows the clinical, biochemical and echocardiographic data for the 21 subjects from both groups with left ventricular hypertrophy (LVH) and the remaining 36 patients without LVH. These groups did not differ regarding age, BMI, gender, ethnic origin mean 24-h systolic and diastolic blood pressures, E : A ratios or in any measured biochemical variable. The most striking difference between groups was in the mean rate of Na-Li CT, which was significantly higher in the group with LVH (0.4 ± 0.13 ϖσ 0.31 ± 0.09 $mmol \cdot l^{-1} \cdot h^{-1}$; $p < 0.005$). In addition, more than half of the group with LVH had elevated rates of Na-Li CT (12 of 21; 57 %) compared to only 19 % of those without LVH (7 of 36; $p < 0.05$). These differences are summarised in Figure 1.

Table 2. Echocardiographic and biochemical characteristics of the control and diabetic subjects

	Control subjects	Diabetic subjects
Number	23	34
E : A ratio	1.47 (0.46)	1.0 (0.29)[c]
Left ventricular mass index (g/m^2)	111.5 (25)	118.5 (25)
Left ventricular hypertrophy *(n)*	6 (26 %)	15 (44 %)
Heart rate (beats per min)	66 (11)	74 (8)[b]
Na-Li CT ($mmol \cdot l^{-1} \cdot h^{-1}$)	0.32 (0.11)	0.37 (0.11)
Raised Na-Li CT *(n)*	4 (17 %)	15 (44 %)[a]
24-h systolic blood pressure (mm Hg)	120.2 (12.9)	125.8 (12)
24-h diastolic blood pressure (mm Hg)	75.3 (6.2)	77.4 (8)
Plasma insulin (pmol/l)	31.3 (6.6–183)	57.5 (2.9–183)
Plasma angiotensin II (pmol/l)	12.4 (3.3)	11.9 (3.4)
Plasma noradrenaline (pmol/ml)	1.9 (0.6)	1.5 (0.7)[a]
Plasma adrenaline (pmol/ml)	0.2 (0.1)	0.3 (0.2)
Platelet noradrenaline (pmol/mg)	1.26 (0.53)	1.71 (0.91)
HbA_1 (%)	6.9 (0.8)	10.2 (2.0)
Fasting plasma glucose (mmol/l)	5.1 (0.9)	10.3 (3.9)
Total cholesterol (mmol/l)	5.4 (0.8)	5.6 (1.2)
HDL-cholesterol (mmol/l)	1.3 (0.6)	1.1 (0.2)
LDL-cholesterol (mmol/l)	3.0 (1.2)	3.6 (1.0)[a]
Triglycerides (mmol/l)	1.6 (0.8)	1.4 (0.8)

All data as mean and one SD except for insulin levels (median and range). [a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.0001$

The association between LVH and elevated mean rates of Na-Li CT was also evident in the diabetic group (Table 4). In the control group, the difference in mean Na-LI CT between those with and without LVH was less striking (0.38 ± 0.16 vs 0.29 ± 0.06; $p = 0.09$, Table 5). It is important to note that the subgroups with LVH did not differ consistently from those without regarding age, BMI, gender, ethnic origin, blood pressures, E : A ratio, glycaemic control, plasma insulin, catecholamines or plasma angiotensin II (Tables 4 and 5). Nor was there any significant difference in any lipid measurement between these groups.

Table 3. Clinical and biochemical data for subjects with and without left ventricular hypertrophy

	Left ventricular hypertrophy	
	Present	Absent
Number *(n)*	21	36
Left ventricular mass index (g/m^2)	136.5 (23.0)	102.0 (15.6)[c]
Age (years)	51.7 (8.9)	49.8 (7.9)
BMI (kg/m^2)	24.8 (2.6)	25.3 (2.5)
Sex (male : female)	17 : 4	34 : 2
Diabetes	15	19
Ethnic origin (C : A : AC)	17 : 2 : 2	26 : 7 : 2
E : A ratio	1.07 (0.34)	1.25 (0.46)
24-h systolic blood pressure (mm Hg)	126.2 (13.9)	122.0 (12.1)
24-h diastolic blood pressure (mm Hg)	76.9 (8.6)	76.7 (6.5)
Plasma insulin (nmol/l)	59.4 (29.5)	53.3 (43.7)
Angiotensin II (pmol/l)	11.4 (3.4)	12.6 (3.3)
Platelet noradrenaline (pmol/mg)	1.27 (0.78)	1.68 (0.85)
Plasma noradrenaline (pmol/ml)	1.66 (0.75)	1.67 (0.61)
Plasma adrenaline (pmol/ml)	0.27 (0.25)	0.23 (0.13)
Na-Li CT ($mmol \cdot l^{-1} \cdot h^{-1}$)	0.40 (0.13)	0.31 (0.09)[b]
Raised Na-Li CT *(n)*	12 (57 %)	7 (19 %)[a]

All data as mean and one SD. [a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.0001$

Relationships between variables

E : A ratio. Univariate analysis of the total study population ($n = 57$) demonstrated relationships between E : A ratio and age ($r = -0.48$; $p < 0.00001$), systolic blood pressure ($r = -0.56$; $p < 0.000001$), heart rate ($r = -0.46$; $p < 0.00001$), presence of diabetes ($r = -0.53$; $p < 0.00001$), platelet noradrenaline ($r = 0.35$; $p < 0.01$), plasma insulin ($r = -0.29$; $p < 0.05$) and BMI ($r = 0.23$; $p = 0.08$). Left ventricular mass index was not significantly related to the E : A ratio. Multiple regression demonstrated that only systolic blood pressure, heart rate, diabetes and BMI were significant independent contributors to variability in E : A ratio (Combined $r = 0.78$, adjusted $R^2 = 58\,\%$, $F = 18.3$; $p < 0.0001$). Diabetes independently accounted for 8 % of the total variability explained, and systolic blood pressure 18 %.

Erythrocyte Na-Li CT did not contribute to the presence or absence of diabetes on multivariate analysis.

Left ventricular hypertrophy. Multivariate analysis of the total population ($n = 57$), with the presence or absence of LVH as the dependent variable, demonstrated that Na-Li CT was the only variable that was significantly related to the presence of LVH ($r = 0.35$; adjusted $R^2 = 10.75\,\%$; $F_{1,55} = 7.74$; $p = 0.007$). No other variable contributed to the presence of LVH.

Table 4. Clinical and biochemical data for the diabetic subjects with and without left ventricular hypertrophy

	Left ventricular hypertrophy	Normal left ventricular mass index
Number *(n)*	15	19
Left ventricular mass index (g/m^2)	139.1 (20)	101.0 (16)[c]
Age (years)	53.1 (5)	52.4 (9)
BMI (kg/m^2)	25.6 (2)	26.1 (3)
Sex (male : female)	12 : 3	18 : 2
Ethnic origin (C : A : AC)	11 : 2 : 2	12 : 6 : 1
Diabetes duration (years)	6.7 (5.5)	6.9 (5.4)
E : A ratio	0.97 (0.31)	0.99 (0.25)
24-h systolic blood pressure (mm Hg)	126.0 (14)	125.7 (12)
24-h diastolic blood pressure (mm Hg)	78.3 (10)	76.6 (7)
HbA_1 (%)	10.5 (2.2)	10.0 (1.8)
Albumin excretion rate (μg/min)	5.2 (0.2–130.2)	4.8 (0.8–39.6)
Plasma insulin (nmol/l)	44.1 (12.6–177)	62.3 (4.9–183.3)
Angiotensin II	10.9 (3.3)	13.4 (3.2)
Plasma noradrenaline (pmol/ml)	1.4 (0.7)	1.6 (0.7)
Plasma adrenaline (pmol/ml)	0.2 (0.1)	0.2 (0.1)
Platelet noradrenaline	1.35 (0.86)	2.0 (0.98)[a]
Na-Li CT ($mmol \cdot l^{-1} \cdot h^{-1}$)	0.41 (0.12)	0.32 (0.09)[a]
Raised Na-Li CT *(n)*	10 (66 %)	6 (31 %)[a]

All data as mean and one SD except for insulin and albumin excretion rate (median and range). [a] $p < 0.05$; [c] $p < 0.0001$

Discussion

It is well recognised that a minority of normotensive middle-aged subjects will demonstrate mild to moderate degrees of LVH [24]. What is novel about the present findings is that this subgroup with an increased left ventricular mass, who are potentially at an increased risk of future cardiovascular events [1–3], are characterised by elevated mean rates of Na-Li CT and an increased frequency of elevated rates of Na-Li CT. This finding was evident in the total study population and in the diabetic group (Tables 3–5).

In the present study 26 % of normotensive middle-aged control subjects demonstrated mild degrees of

Table 5. Clinical and biochemical data for the control subjects with and without left ventricular hypertrophy

	Left ventricular hypertrophy	Normal left ventricular mass index
Number *(n)*	6	17
Left ventricular mass index (g/m^2)	140.4 (18)	101.0 (18)[c]
Age (years)	46.9 (6)	
BMI (kg/m^2)	24.6 (1.8)	23.0 (2.7)
Sex (male : female)	4 : 2	16 : 1
Ethnic origin (C : A : AC)	6 : 0	14 : 2 : 1
E : A ratio	1.33 (0.4)	1.52 (0.5)
24-h systolic blood pressure (mm Hg)	122.5 (19.5)	119.3 (10.2)
24-h diastolic blood pressure (mm Hg)	72.7 (3.4)	75.8 (6.9)
Plasma insulin (nmol/l)	61.8 (27–109)	28.6 (7–184)
Angiotensin II (pmol/l)	12.3 (3.9)	11.8 (3.3)
Plasma noradrenaline (pmol/ml)	2.2 (0.4)	1.7 (0.52)[a]
Plasma adrenaline (pmol/ml)	0.40 (0.3)	0.24 (0.1)
Platelet noradrenaline (pmol/mg)	1.13 (0.6)	1.3 (0.49)
Na-Li CT ($mmol \cdot l^{-1} \cdot hr^{-1}$)	0.38 (0.16)	0.29 (0.06)
Raised Na-Li CT *(n)*	2 (33 %)	2 (12 %)

All data as mean and one SD except for insulin (median and range). [a] $p < 0.05$; [c] $p < 0.0001$

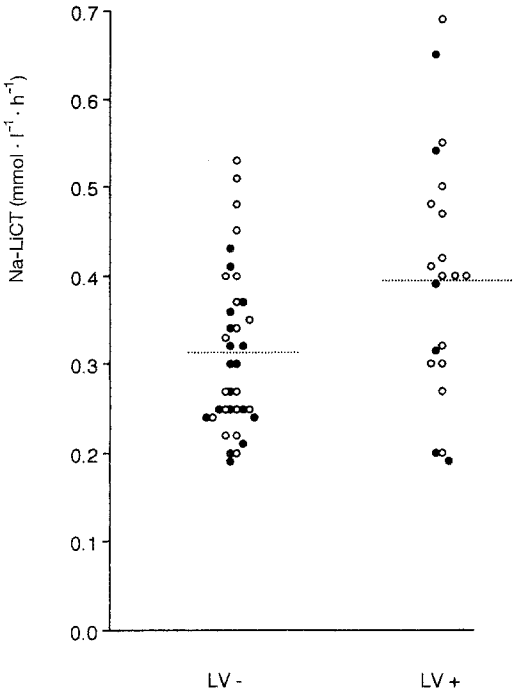

Fig. 1. Individual values for Na-Li CT in those with (LV +) and without (LV –) left ventricular hypertrophy. Subjects with NIDDM are shown as ○, and control subjects as ●. Difference between group means significant at $p = 0.003$

LVH. The age-specific prevalence of LVH in the Framingham population, for subjects between 50 and 59 years old was 18 % for men with systolic blood pressures between 130 and 139 mm Hg, and was 16–19 % in the study population overall, using various diagnostic criteria for LVH [24]. In our population there was a trend towards a greater frequency of LVH in the diabetic subjects, of whom 44 % were affected. Galderisi et al. [6] demonstrated that 42 women from the Framingham cohort, with predominantly NIDDM, had a significantly greater left ventricular mass index than 2349 women without, and that the presence of diabetes was an independent contributor to left ventricular mass. However, no data on group blood pressures were provided, although the presence of hypertension was controlled for in multivariate analysis. A trend towards an excess of LVH in normotensive diabetic subjects could reflect higher maintained nocturnal blood pressures in a group with autonomic dysfunction [25], and the diabetic patients in the present study did have higher mean heart rates which could indicate autonomic dysfunction. However, there was no difference in mean nighttime blood pressures between the diabetic and control group, or between those with and without LVH in this study.

The most striking finding in the present study was that subgroups with LVH differed from those without in having elevated rates of mean Na-Li CT, but not in any other measured clinical or biochemical variable. To the best of our knowledge, this is the first time that this has been clearly demonstrated in normotensive populations, although there are several reports of similar associations in various hypertensive groups [11, 26, 27]. This reported link between cardiac hypertrophy and more elevated rates of Na-Li CT in hypertensive groups does not necessarily indicate a *direct* association, and there are more physiologically plausible explanations. Hypertensive subjects with elevated rates of Na-Li CT could be a subgroup with slight elevations in blood pressure with the normal range before "true" hypertension developed [28, 29], or with a greater duration of hypertension [26] or with exaggerated pressor responses to exercise [27], all of which would account for an exaggerated hypertrophic response in this group.

The same finding in the present study, in unequivocally normotensive subjects, clarifies this relationship, and does suggest a direct link between LVH and membrane cation transport that is *independent* of hypertension.

The measurement of rates of erythrocyte Na-Li CT may reflect some function of membrane sodium-proton (Na^+-H^+) exchange, although this relationship remains to be clarified [30]. Elevated rates of membrane Na^+-H^+ exchange may maintain a more

alkaline intracellular pH [31] and promote protein synthesis [32], the intracellular mobilization of Ca^{++} in fibroblasts and smooth muscle cells may be pH dependent [33], and activity of protein kinase C may theoretically be enhanced by elevated rates of membrane Na-H exchange [34]. These roles in cell proliferation and stimulus-response coupling suggest that groups with elevated rates of Na-H or Na-Li CT represent a phenotype more likely to respond to any given stimulus with a growth response.

Two other studies have examined the association between membrane cation transport and left ventricular mass in normotensive populations. Semplicini et al. [35] found no difference in left ventricular mass index between normotensive insulin-dependent diabetic patients with and without elevated rates of Na-Li CT, although the group with elevated rates of Na-Li CT, did have a marginally greater interventricular septal width. The Tecumseh blood pressure study [28], examined 705 young subjects (mean age 31 years). The subgroup ($n = 91$) with elevated rates of Na-Li CT had a slightly but significantly lower left ventricular mass index, than those with normal rates, despite having higher blood pressures. The high transport group did however show evidence of ventricular remodelling, and as the authors point out, the pattern of hypertrophy could change as these subjects age. The subjects in the present study were on average about 20 years older than those in the Tecumseh study.

In normotensive subjects LVH has repeatedly been shown to predict the later development of hypertension [36, 37], and the children of hypertensive adults have a greater left ventricular mass than the children of normotensive adults [38], suggesting an inherited component to variability in left ventricular mass. Much of the variability in Na-Li CT is also inherited [39], and the present study makes it tempting to speculate that elevated rates of Na-Li CT are the bridge between LVH in normotensive subjects and the later development of hypertension. However, this can be answered only by long-term prospective studies.

Although there has been great interest in the role of catecholamines, angiotensin II and insulin as potential determinants of left ventricular mass, much of the support for such relationships has been derived indirectly [8] or from in vitro studies [40, 41]. In vivo studies in man, with or without hypertension, have been less impressive [28, 42]. In the present study there was no consistent difference in angiotensin II, catecholamines or plasma insulin between groups with and without LVH.

Gender differences in left ventricular mass and racial differences in Na-Li CT [43] do not invalidate the cross-sectional comparisons of matched groups in the present study.

A peripheral finding in this study was the independent contribution of diabetes to impaired diastolic filling. Similar findings have been published for normotensive subjects with insulin-dependent diabetes [44], and could reflect the increased myocardial interstitial fibrosis described even in some normotensive diabetic subjects without coronary artery disease [45, 46]. Whether this impaired diastolic dysfunction related to the diabetic state per se could contribute to their excess mortality after myocardial infarction [47] warrants further study.

In conclusion, this study has demonstrated that a subgroup of both normotensive control subjects and subjects with NIDDM have mild degrees of LVH. This subgroup is characterised by elevated mean rates of Na-Li CT compared to those without, and does not otherwise differ in any clinical, biochemical or echocardiographic parameter. This suggests for the first time an independent association between LVH, cardiovascular risk and elevated rates of Na-Li CT in normotensive subjects with and without NIDDM.

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