DETERMINANTS OF LEFT VENTRICULAR GEOMETRIC ALTERATIONS AND RELATED CLINICAL AND METABOLIC FACTORS IN A GENERAL POPULATION

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SUMMARY

Background: Left ventricular (LV) remodeling has been shown to impart prognostic significance in previous studies. However, the underlying exact mechanisms involved and interactions between LV geometry alterations and age with other clinical and biochemical variables in general population have not been well established.

Methods: A total of 406 consecutive subjects were enrolled in a health evaluation center-based population study (mean age, 51.5±10.9 years; 42% women). Data including baseline characteristics, echocardiography, biochemistry and biomarkers were all collected and evaluated. Univariate and multivariate regression analysis was performed to test the relationship between relative wall thickness (RWT) and other variables. We also divided the subjects into older and younger groups, compared RWT between the two groups, and analyzed the distribution of LV geometry in these groups.

Results: The prevalence of diabetes and hypertension in our study population was relatively small (11.6% and 16.5%, respectively). The most common type of LV geometry in our study was normal (67.5%) and concentric remodeling (30.3%) compared with a relatively small proportion of concentric LV hypertrophy (1.5%) and eccentric hypertrophy (<1%). Of all 406 subjects evaluated, age, uric acid, height, systolic blood pressure and serum insulin level were all independent factors associated with RWT in a multivariate regression model.

Conclusion: In our study, we revealed that aging, together with baseline blood pressure and serum biochemistries, were associated with LV geometric alterations. These data suggest that the LV remodeling process actually involves dynamic and complex interactions with multiple metabolic factors in an unselected general population in Taiwan. [International Journal of Gerontology 2009; 3(1): 66–74]

Key Words: aging, biomarkers, geometry, relative wall thickness, remodeling

Introduction

Left ventricular (LV) geometric remodeling, like concentric ventricular hypertrophy, has been shown to be associated with elevated cardiovascular morbidity and mortality¹⁰⁻¹². Hypertension as a primary cause of LV remodeling, together with other metabolic abnormalities⁶⁻⁷, characterizes cardiac structural and functional abnormalities. Both experimental and clinical data have already demonstrated the association between phenotypic ventricular remodeling with aging and serologic evidence of myocardial fibrosis linking to ventricular stiffness⁸, diastolic dysfunction⁹ and, eventually, heart failure development¹⁰⁻¹². LV remodeling, a marker of cardiac target organ damage, may thus...
serve as an easy and clinically feasible surrogate for cardiac functional abnormality in daily practice.

LV geometry can actually be categorized according to relative wall thickness (RWT) and LV mass index\textsuperscript{13,14}, including normal geometry, concentric remodeling (increased RWT but normal LV mass), concentric hypertrophy (increased RWT and LV mass) and eccentric hypertrophy (normal RWT but increased LV mass). Concentric remodeling, as a trivial form of remodeling, may occur before hypertrophy. Although it has been shown that concentric remodeling may be related to various cardiovascular risk factors and comorbidities so far, a debate remains regarding the minor phenotype of concentric remodeling and cardiovascular prognosis\textsuperscript{3-5,15}. Furthermore, the association or relationship between LV concentric geometry and other parameters including age, clinical variables and biochemistries in an Asian population has not been well established. Thus, we sought to investigate the determinants and the association between these LV geometric alterations and clinical or metabolic factors from biochemical assays in a general population.

Materials and Methods

Study setting and subject enrollment

The design of this study was approved by the local ethics committee in accordance with the Declaration of Helsinki. We consecutively enrolled participants from the health evaluation center of Mackay Memorial Hospital, a medical center in Taipei, Taiwan, during the period from January 2003 to December 2006. A thorough review of medical history, physical examination, 12-lead electrocardiogram and chest X-ray were all performed. All baseline characteristics including age, height, weight, body mass index and routine laboratory data regarding routine biochemistries (including liver, renal profiles), complete blood cell counts and biomarkers were taken. Cuff blood pressures at rest were taken by medical staff blinded to the other test results. Patients with decompensated heart failure, poorly controlled diabetes (hemoglobin A1c [HbA\textsubscript{1c}] > 9.0%) or renal insufficiency (creatinine, > 2.5 mg/dL) were excluded in our study. Patients with at least a moderate degree of valvular heart disease, pulmonary hypertension (systolic pulmonary arterial pressure, > 50 mmHg), previous cardiac surgery, existence of congenital heart disease or LV ventricular ejection fraction < 50% were excluded in this study.

Biochemistry and biomarkers

Fasting plasma glucose and other laboratory data including lipid and renal profiles were obtained by a Hitachi 7170 automatic analyzer (Hitachi Corp. Hitachinaka, Ibaraki, Japan), and immunoreactive insulin was measured by radioimmunoassay (PerkinElmer Automatic Gamma Counter 1470; PerkinElmer, Waltham, MA, USA). HbA\textsubscript{1c} level was assessed by high-performance liquid chromatography (Bio-Rad Variant II; Bio-Rad Laboratories, Hercules, CA, USA). Insulin resistance was calculated using the homeostasis model assessment–insulin resistance (HOMA-IR) method: HOMA-IR = fasting glucose (mmol/L) × fasting insulin (μU/mL)/22.5. Complete blood counts were assessed by Coulter Gen-S (Beckman Coulter, Miami, FL, USA). Biomarkers including high-sensitivity C-reactive protein (hs-CRP; Immulite assay; Siemens Healthcare Diagnostics GmbH, Eschborn, Germany) and pro-B-type natriuretic peptide (pro-BNP)
level by electrochemiluminescence immunoassay (Roche E170; Roche Diagnostics GmbH, Mannheim, Germany) were collected.

Statistics
Continuous data were presented as mean ± standard deviation and were compared with an unpaired t test or Mann-Whitney U test as appropriate. Categorical or proportional incidence data were expressed as ratios and compared by the Chi-squared or Fisher’s exact test. Backward stepwise multivariate regression analysis was used to select the most powerful models for the independent variables associated with RWT in our study. Significance and relationships associated with RWT were chosen by univariate regression. A p value < 0.1 was used for the multivariate model. Potential colinearity of different variables entered into the multivariate model was tested by variance inflation factor (VIF) to ensure that these variables were not entered simultaneously. All VIFs < 5 were assumed to be efficient in the selection of such variables without significant colinearity. The data were analyzed with the software package STATA 8.0 (StataCorp, College Station, TX, USA).

RWT and other variables were compared in different age groups (≥ 60 and < 60 years). Parameters were also compared between the groups with concentric geometry or without concentric geometry in the two age groups. The p value was set for a two-tailed probability, and a p value < 0.05 was considered statistically significant.

Results
Baseline characteristics
A total of 942 subjects were initially screened and reviewed, and finally 406 (mean age, 51.5 ± 10.9 years; 42% women) participants were enrolled in our study after exclusion for inadequate criteria or missing data. The baseline demographic data and echocardiographic variables are displayed in Tables 1 and 2, respectively. There were a total of 274 patients (67.5%) with normal LV geometry, 123 (30.3%) had concentric remodeling pattern, six (1.5%) had concentric hypertrophy and three (< 1%) had eccentric hypertrophy according to our study definition. The final population of the present study consisted of 47 cases (11.6%) of diabetes and 67 cases (16.5%) of hypertension with 15 participants (3.7%) on regular medication for hyperlipidemia (either fibric acid or statin therapy), 66 participants (16.3%) on anti-hypertension therapy and 24 participants (5.9%) on hypoglycemic agents.

The whole study population was divided into two groups, including the older group (n = 76) and the younger group (n = 330). Baseline characteristics, laboratory tests, including biochemistries, biomarkers and complete blood counts, and echocardiographic findings were compared (Tables 1 and 2). The average age of the older and younger groups was 67.8 ± 6.3 years and 47.6 ± 7.8 years, respectively (p < 0.001). Compared with the younger group, the older group had shorter height, greater waist and higher systolic blood pressure (p < 0.05). The mean systolic blood pressures of the older and younger group were 130.4 ± 18.5 mmHg and 118.0 ± 15 mmHg, respectively (p < 0.001). A borderline higher uric acid level was observed in the older group when compared with the younger one (p = 0.05). Moreover, higher blood urea nitrogen, glucose, HbA1c, hs-CRP and pro-BNP, and lower serum hemoglobin, platelet counts and albumin level were all found in the older group (p < 0.05).

Echocardiography and LV geometry
Table 2 shows that LV wall thickness were thicker in the older when compared with the younger group, including end-diastolic interventricular septum (11.3 ± 1.8 mm vs. 10.2 ± 1.7 mm; p < 0.001) and end-diastolic posterior wall (11 ± 1.3 mm vs. 10.1 ± 1.4 mm; p < 0.001). There was a trend toward higher ascending aortic diameter in the younger group that did not reach statistical significance (p = 0.13), while the aortic root diameter seemed to be larger in the younger group (p = 0.04). There was no significant difference in left atrial diameter between these two groups assessed by the traditional M-mode method (p = 0.18). The global ventricular ejection fraction was within normal limits (66.4% ± 5.9%), suggesting a fair cardiac performance in our population. In the older group, the LV mass (183.4 ± 41.1 g vs. 156.7 ± 38.7 g; p < 0.001) and LV mass index (72.5 ± 17.2 g/m² vs. 58.1 ± 13.7 g/m²; p < 0.001) were significantly larger, and that RWT was also larger in the older than the younger group (42.7% ± 6.6% vs. 39.3% ± 6.7%; p < 0.001). The proportion of normal geometry, concentric remodeling, concentric hypertrophy and eccentric hypertrophy was 51.3%, 38.2%, 6.6% and 4.0%, respectively, in the older group, and 71.2%, 28.5%, 0.3% and 0%, respectively, in the younger group.

We also tested the independence of RWT and age by 2 × 2 categories using the Chi-squared test with a
partition value of 0.42 and age of 60 years. This comparison showed that the distribution in the two categories was not randomly aligned but was really arranged in a different distribution ($\chi^2 = 7.25; p = 0.0071$).

**Independent factors and associated determinants of LV geometric alterations**

Univariate regression model revealed that increasing age, lower body height, higher body weight, larger waist circumference, higher systolic blood pressure, higher biochemistry levels including serum blood urea nitrogen, creatinine, HbA1c, uric acid, insulin, homocysteine were all significantly associated with higher RWT ($p < 0.10$).

These parameters were then enrolled into stepwise multivariate regression model and only increasing age, higher uric acid, lower body height, higher systolic blood pressure, higher insulin and a trend toward higher creatinine level remained as significant independent variables associated with higher RWT (Table 3). All variables had a VIF of $< 5$, which safely precluded the possibility of potential colinearity. The linear regression, presented as a scatter plot between RWT and age, is shown in Figure 1.

The associations between RWT and age relating to other metabolic factors are displayed in Figure 2 by a bar plot showing quartiles of each variable, which helps illustrate the complex interaction of aging and other variable factors on the degree of LV geometric alterations. Similar to our other observations, increasing age and higher serum metabolic factors were associated with higher RWT, with a trend toward higher RWT with increasing age and decreased renal function defined by serum creatinine level.

### Table 1. Baseline characteristics and biochemistries in different age groups*

<table>
<thead>
<tr>
<th></th>
<th>Age ≥ 60 (n = 76)</th>
<th>Age &lt; 60 (n = 330)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female ratio</td>
<td>1.17:1</td>
<td>1.43:1</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>67.8 ± 6.3</td>
<td>47.6 ± 7.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159.4 ± 8.5</td>
<td>164.1 ± 8.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.4 ± 10.3</td>
<td>65.7 ± 12</td>
<td>0.077</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>24.9 ± 3.6</td>
<td>24.3 ± 3.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Buttock (cm)</td>
<td>92.9 ± 6.5</td>
<td>93.5 ± 7.1</td>
<td>0.53</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>84.8 ± 9.7</td>
<td>81.9 ± 10.2</td>
<td>0.027</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>130.4 ± 18.5</td>
<td>118.0 ± 15</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>74.2 ± 8.2</td>
<td>73.9 ± 9.6</td>
<td>0.93</td>
</tr>
<tr>
<td>Heart rate (/min)</td>
<td>72.9 ± 10</td>
<td>73.8 ± 10.7</td>
<td>0.52</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.7 ± 1.3</td>
<td>14.5 ± 1.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Platelets ($\times 10^7/\mu$L)</td>
<td>247.4 ± 62.5</td>
<td>267.4 ± 54.7</td>
<td>0.011</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.3 ± 0.3</td>
<td>4.4 ± 0.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Alk-P (IU/L)</td>
<td>75.0 ± 23.4</td>
<td>68.1 ± 17.7</td>
<td>0.015</td>
</tr>
<tr>
<td>sGPT (IU/L)</td>
<td>26.4 ± 15.1</td>
<td>32.4 ± 27.8</td>
<td>0.012</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>13.1 ± 3.98</td>
<td>11.4 ± 3.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Glucose AC (mg/dL)</td>
<td>106.7 ± 28.6</td>
<td>98.5 ± 20.9</td>
<td>0.016</td>
</tr>
<tr>
<td>Glucose PC (mg/dL)</td>
<td>141.3 ± 60</td>
<td>111.4 ± 39.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>5.8 ± 0.9</td>
<td>5.5 ± 0.8</td>
<td>0.0077</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>6.2 ± 1.4</td>
<td>5.9 ± 1.3</td>
<td>0.05</td>
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<tr>
<td>hs-CRP</td>
<td>0.29 ± 0.5</td>
<td>0.19 ± 0.4</td>
<td>0.003</td>
</tr>
<tr>
<td>Pro-BNP (pg/mL)</td>
<td>84.9 ± 115.1</td>
<td>32.3 ± 91.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>13 (17.1)</td>
<td>77 (23.3)</td>
<td>0.18</td>
</tr>
<tr>
<td>Anti-lipid agents</td>
<td>29 (38.2)</td>
<td>96 (29.1)</td>
<td>0.17</td>
</tr>
<tr>
<td>Medication for hypertension</td>
<td>29 (38.2)</td>
<td>37 (11.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Medication for diabetes</td>
<td>10 (13.2)</td>
<td>14 (4.2)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± standard deviation or n (%). SBP = systolic blood pressure; DBP = diastolic blood pressure; Alk-P = alkaline phosphatase; sGPT = serum glutamate pyruvate transaminase; BUN = blood urea nitrogen; AC = ante cibum; PC = post cibum; hs-CRP = highsensitivity C-reactive protein; pro-BNP = pro-B-type natriuretic peptide.*
Discussion

Our current data support that even in a population with a low prevalence of diabetes, hypertension and relatively preserved global ventricular systolic function, a relationship between LV structural alterations and increasing age, systolic blood pressure or other metabolic abnormalities remained in a Taiwanese population.

With increased age, systolic blood pressure tends to elevate in conjunction with the progressive widening of pulse pressure and vascular stiffness, leading to higher incidence of cardiovascular diseases and stroke. While the vascular stiffness increases, the myocardium...
is implicated by diastolic dysfunction and structural remodeling with aging. De Simone et al. reported the association between LV concentric geometric changes and impaired relaxation in patients with hypertension. Other comorbidities such as diabetes or renal dysfunction further accelerate ventricular structural and geometric changes. The alterations of ventricular geometry actually include concentric remodeling, concentric hypertrophy and eccentric hypertrophy. The importance of significant LV remodeling like ventricular hypertrophy in predicting cardiovascular risk is well established, but the data is inconsistent in the minor form of concentric remodeling. Clinical factors including race, gender, body size and age have been reported to relate to LV hypertrophy. In addition, the relationship of LV concentric remodeling rather than hypertrophy with several components of insulin resistance syndrome was also found in elderly men. In the present study, we did observe that after multivariate adjustment, age, systolic blood pressure and serum insulin level were highly associated with the LV geometric alterations in terms of concentric remodeling. A mild relationship between renal function in terms of serum creatinine level and

Figure 1. Scatter plot and linear regression between relative wall thickness (RWT) and age. With aging, the RWT tends to increase in a linear fashion.

Figure 2. Relationship between relative wall thickness (RWT) and age and other variables. Numbers 1–4 in the scales of age and other variables represent four quartiles of each variable. Higher systolic blood pressure (upper left panel), higher serum insulin level (upper right panel) and higher uric acid level seemed to be associated with aging, as well as higher RWT. Although there is a trend indicating poorer renal function relating to higher RWT and aging, this finding is statistically non-significant. Cre = creatinine; SBP = systolic blood pressure.
RWT, although insignificant after multivariate adjustment, was observed in the current data. One possible reason could be the relatively preserved renal function (creatinine range, 0.5–1.3 mg/dL) in our study population that made this impact trivial or this clinical effect less obvious. Biomarkers representing several distinct biologic pathways associated with the ventricular remodeling process have recently been reported in a large study, supporting the same observation that higher biomarker levels (hs-CRP and pro-BNP) are associated with aging and increased RWT as in our current study. Recently, decreased regional systolic function in LV concentric remodeling was found in a magnetic resonance imaging study. Associated work regarding early changes of LV systolic function when evaluated by tissue Doppler imaging showed that increasing RWT was related with lower LV strain and strain rate representing subclinical ventricular dysfunction.

In this study, a positive linear correlation between RWT and age was observed. In line with previous literature reviews, this relationship remained independent after multivariate adjustment for other potential factors. The higher the systolic blood pressure, the greater was the RWT. This relationship is compatible with the traditional thought that the initial process and pathogenesis of LV remodeling comes from ventricle overload. Moreover, insulin level was also associated with RWT in our study. The relationship between LV remodeling and insulin resistance have been discussed by other authors. Sundström et al. reported that LV concentric remodeling is related to insulin resistance syndrome in elderly men. In patients with hypertension, insulin growth factor-1 as a trophic factor of ventricular extracellular matrix turnover is an important and independent determinant of RWT. Moreover, uric acid level also seemed to play an independent role in the LV remodeling process from our current data, with a higher uric acid level associated with higher RWT. In animal models, interstitial purine metabolites were increased in hearts with evidence of LV remodeling. Although the exact role of uric acid level in cardiovascular disease has remained obscure so far, a close link with metabolic abnormalities, including serum HbA1c, glucose level and insulin resistance, have also been reported recently in a clinical study. In an Asian population, uric acid was found to be related to LV hypertrophy and remodeling in Japanese men. In that study, a higher uric acid level was predominantly associated with ventricular hypertrophy in males alone, but not actual remodeling. The real impact of serum uric acid level on early LV structural alterations like remodeling in the Asian population may need a future survey with a larger sample size. Similar to previous studies, the relationship between concentric geometry and serum uric acid was confirmed in this study. LV hypertrophy was also related to chronic renal failure. In our study, however, the relationship between serum creatinine and RWT was not significant.

To evaluate the impact of age on LV geometry, we further analyzed the data in two different age groups (≥60 years and <60 years). The mean age difference between the two groups was nearly 20 years, so they may represent totally different age populations. Irrespective of age, the mean blood pressure and glucose profiles were mostly within normal ranges, and only a very small number of participants had hypertension, diabetes or received medications for hyperlipidemia. In both groups, the majority of LV geometry was normal geometry with a second-order prevalence to LV concentric remodeling. In the current study, the proportion of concentric and eccentric hypertrophy was relatively small when compared with normal or concentric remodeling geometry. Most of the cases with concentric geometry (RWT > 0.42) were concentric remodeling without hypertrophy. The distribution of LV geography was different from previous different cohorts. The small percentage of hypertrophy in our study could be explained by normal mean blood pressure with relatively healthy baseline demographics, and may imply that the significant difference of all variables may come from the effect of aging. Moreover, average RWT in the older group was greater than that of the younger one. This difference may translate into finding a higher prevalence of concentric remodeling in the older group. Nevertheless, whether the existence of higher systolic blood pressure in older people contributed to the increased prevalence of concentric remodeling is unknown, since the average blood pressure in both groups was relatively low.

Limitations

Several limitations should be considered in this study. First, this is a retrospective cross-sectional study, and the sample size of the total and the elderly population was relatively small compared with other studies. In addition, the representative data of this study came...
Determinants of LV Geometric Alterations

from the participants of the health evaluation center, and a wider clinical application and the relevance to a broader population may thus be limited. Although our data may not completely hold true as being the standard for a general Asian population, the smaller percentage of comorbidities in our study, however, may reflect a real-world situation rather than a specific diseased population.

Furthermore, heart failure development with preserved ventricular ejection fraction resulting from LV damage from coexisting hypertension, diabetes or other metabolic abnormalities is becoming more and more popular in clinical settings. However, the prevalence of such diseases in our subjects was small and, thus, beyond the scope of our study. Finally, other echocardiographic parameters that might help in detecting and stratifying ventricular diastolic dysfunction, such as the Doppler of mitral inflow or tissue Doppler imaging, were not available in our database. A detailed coverage of such parameters associated with aging or metabolic abnormalities may be helpful, although such Doppler evaluation might theoretically be more load-dependent and less reproducible in clinical settings37.

Conclusion

Although the clinical significance of concentric remodeling was inconsistent from previous studies, we did observe a close relationship between a minor phenotype of geometric alterations with aging and other early metabolic abnormalities. The normal aging process, together with higher baseline systolic blood pressure or some serum metabolic abnormalities, were all associated with LV geometric alterations in terms of concentric remodeling. These data suggest that LV remodeling actually involves dynamic and complex interactions with multiple clinical and metabolic factors in an unselected general population living in Taiwan, and may possibly impact future cardiovascular morbidities.

References

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