Decreased intralymphocytic magnesium content is associated with diastolic heart dysfunction in patients with essential hypertension

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Diastolic heart failure (DHF) is a clinical syndrome characterized by the symptoms and signs of heart failure, preserved ejection fraction (EF) and abnormal diastolic function [1]. Hypertension is the most common risk factor and the principal precursor for DHF [2]. Hypertension-induced left ventricular (LV) hypertrophy that includes myocardial hypertrophy and abnormal accumulation of fibrillar collagen causes a decreased compliance and LV diastolic dysfunction. It is estimated that 20–60% of patients with heart failure have preserved EF [3,4]. Unfortunately, in contrast to the situation of heart failure with low EF, the mortality and morbidity of DHF have not been significantly decreased in the past decades [5,6].

Magnesium is the second most abundant intracellular cation. As a cofactor for many enzymes, magnesium plays a role in various biological functions including energy metabolism and muscle contraction [7]. It is known that activation of the rennin–angiotensin–aldosterone system and the use of diuretics in patients with essential hypertension or cardiac failure may deplete serum potassium and affect intracellular magnesium homeostasis [8,9]. We have shown the importance of maintaining magnesium homeostasis in reducing arrhythmia and myocardial hypertrophy in patients with heart failure or hypertension [10,11]. However, the role of magnesium homeostasis in diastolic heart dysfunction is not known yet. Thus, we designed this study to address this issue. Since myocardium of patients is usually not easily accessible, we measured intralymphocytic magnesium content to reflect the magnesium content in myocardial cells.

This was a single center prospective study that conformed to the ethical principles outlined in the Declaration of Helsinki. The study protocol was approved by the ethics committee of the First Affiliated Hospital of the Sun Yat-Sen University (Guangzhou, China). Consecutive 206 essential hypertension patients with diastolic heart dysfunction documented by Doppler echocardiography from November 2007 to October 2009 were enrolled. Patients with diastolic heart dysfunction and clinical signs and symptoms of heart failure as described in the European Society of Cardiology Guidelines published in 2008 [12] were attributed to DHF group (group A). Those free of signs and symptoms of heart failure were in group B. Fifty essential hypertension patients with neither diastolic heart dysfunction nor signs and symptoms of heart failure were in group C. All patients met the criteria for diagnosis of essential hypertension as set forth by the European Society of Hypertension and European Society of Cardiology in 2007 [13]. Patients enrolled in this study received conventional treatments that included angiotensin converting enzyme inhibitors or angiotensin II type 1 receptor antagonist, thiazide diuretics, calcium channel blockers, β-adrenergic receptor blocking agents, and spironolactone as shown in Table 1. Patients were excluded from the study if they had: (1) severe

Table 1
General condition, basic laboratory results and medications among patients in various groups.

	Diastolic dysfunction with heart failure symptoms or signs (group A, $n=106$)	Diastolic dysfunction without heart failure (group B, $n=100$)	Essential hypertension patients without diastolic dysfunction (group C, $n=50$)
Male/female (case)	51/55	44/56	27/23
Age (years)	61.2 ± 10.8	60.1 ± 11.8	61.7 ± 11.7
Body height (cm)	164.8 ± 6.4	164.54 ± 6.4	165.4 ± 6.1
Body weight (kg)	68.7 ± 8.3*	66.0 ± 8.4	64.9 ± 6.3
Systolic BP (mm Hg)	154 ± 7	155 ± 8	154 ± 7
Diastolic BP (mm Hg)	82 ± 8	84 ± 9	84 ± 8
Heart rate (beat/min)	90.7 ± 6.0*^	79.3 ± 6.3*	61.6 ± 6.2
Fasting glucose (mmol/L)	6.4 ± 0.9	6.2 ± 0.9	6.2 ± 0.8
PG (mmol/L)	9.44 ± 2.1	8.7 ± 1.8	8.9 ± 1.9
Serum Cr (μmol/L)	105 ± 12	103 ± 11	105 ± 12
Potassium (mmol/L)	4.2 ± 0.4	4.1 ± 0.4	4.1 ± 0.3
Sodium (mmol/L)	139 ± 6	139 ± 5	139 ± 6
Chloride (mmol/L)	101 ± 6	101 ± 4	101 ± 4
Medication			
Thiazide diuretics (%)	43	40	41
Spironolactone (%)	19	17	18
β-Block (%)	31	30	29
ACEI (%)	47	49	46
ARB (%)	45	43	44
CCB (%)	43	44	43
Statins (%)	87	85	89
Aspirin (%)	92	95	93

*$P<0.05$ compared with group C. ^$P<0.05$ compared with group B. The doses for hydrochlorothiazide and spironolactone are 25 mg/day and 20 mg/day, respectively.
ACEI: angiotensin II converting enzyme inhibitor; ARB: angiotensin II type 1 receptor antagonist; BP: blood pressure; CCB: calcium channel blocker; Cr: creatinine; PG: 2 h post-meal glucose.

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Table 2
Comparison of conventional Doppler echocardiography and magnesium concentrations among patients in various groups.

	Diastolic dysfunction with heart failure signs or symptoms (group A, $n=106$)	Diastolic dysfunction without heart failure (group B, $n=100$)	Essential hypertension patients without diastolic dysfunction (group C, $n=50$)
IVS (mm)	13.1 ± 1.1*^	12.3 ± 0.5*	11.1 ± 1.2
LVPW (mm)	10.5 ± 1.2*^	9.8 ± 1.1	9.5 ± 0.9
LVM (g)	217 ± 48*^	181 ± 40*	160 ± 28
LVMI (g/m^2)	125 ± 26*^	106 ± 21*	95 ± 17
E/A wave ratio	0.82 ± 0.22*	0.76 ± 0.19*	1.35 ± 0.17
IVRT (ms)	115 ± 3*^	108 ± 3	108 ± 2
DT (ms)	240 ± 36*^	183 ± 20*	156 ± 11
AR cm/s	35.8 ± 1.8*^	31.9 ± 1.9*	28.1 ± 2.5
EF (%)	70.1 ± 8.5*	72.2 ± 4.7	73.4 ± 3.8
FS (%)	36.9 ± 6.0*^	41.6 ± 3.8*	44.6 ± 3.6
SMg (mmol/L)	1.10 ± 0.22	1.11 ± 0.14	1.08 ± 1.00
LCMg (10^{-7} μg/cell)	1.82 ± 0.33*^	2.31 ± 0.35*	2.64 ± 0.43

*$P<0.05$ compared with group C. ^$P<0.05$ compared with group B.
AR: pulmonary vein flow from atrial reversal; DT: deceleration time; EF: ejection fraction; FS: fractional shortening; IVRT: isovolumic relaxation time; IVS: interventricular septal; LCMg: lymphocytic ionized magnesium content; LVM: left ventricular mass; LVMI: left ventricular mass index; LVPW: left ventricular wall; SMg: serum magnesium.

liver and renal dysfunction with a serum creatinine level ≥221 mmol/L or a serum potassium level ≥5.5 mmol/L; (2) unstable angina or acute myocardial infarction; (3) secondary hypertension; (4) therapy of non-steroid anti-inflammatory drug or steroids; or (5) atrial fibrillation.

Conventional Doppler echocardiography examination was performed using a Vivid 7 dimension (General Electric Corporation, Fairfield, CT, USA) by two independent cardiologists who were blinded to the study protocol. Patients were under baseline condition during the examination. Left ventricular systolic dysfunction was defined as having an EF below 50% or a fractional shortening (FS) below 25%. To evaluate diastolic function, the characteristics of mitral inflow [mitral E and A waves, E wave deceleration time (DT) and isovolumic relaxation time (IVRT)] and pulmonary vein flow [systolic waves (S), diastolic waves (D) and atrial reversal (AR)] were studied. Abnormal diastolic function was defined as having: 1) a mitral E/A wave ratio below 1 or a mitral E wave DT ≥220 ms; and 2) an IVRT ≥100 ms or pulmonary vein AR ≥35 cm/s.

Patients were fasted overnight and then 15 mL blood was collected in the morning for measuring intralymphocytic magnesium content, liver function, and plasma creatinine and electrolyte concentrations. Lymphocytes were separated from other blood components by dextran sedimentation and centrifugation on Ficoll–Hypaque density gradient as described previously [14].

To measure intracellular magnesium content, lymphocytes were loaded with 10 μM furaptra-AM (furaptra acetoxymethyl ester; Second Chemical Agent Factory of Shanghai, Shanghai, China) in tissue culture medium 199 for 0.5 h at 37 °C. Intracellular ionized magnesium content was determined as described before [15].

Quantitative data were expressed as means ± S.D. One way analysis of variance or one way analysis of variance on ranks followed by Tukey test or Dunn's method was used for continuous parametric data. *Z*-test was used for proportion data and chi-square test was used for analyzing dichotomous parametric data. Pearson product moment correlation was performed to test the strength of the correlation between pairs of variables.

Body weight and heart rate (HR) of patients in group A were higher than that in group C. HR of patients in group A was also higher than that in group B. All other general parameters including blood fasting glucose, electrolytes and drug therapies were not significantly different among the three groups (Table 1).

There were no differences in serum magnesium among the groups. Left ventricular EF of group A was slightly lower than that of group C. The ranking order for intralymphocytic ionized magnesium content and left ventricular fraction shortening was: group C > group B > group A. The E/A ratio of patients in group A and group B was significantly lower than that of patients in group C. The ranking order for interventricular septal

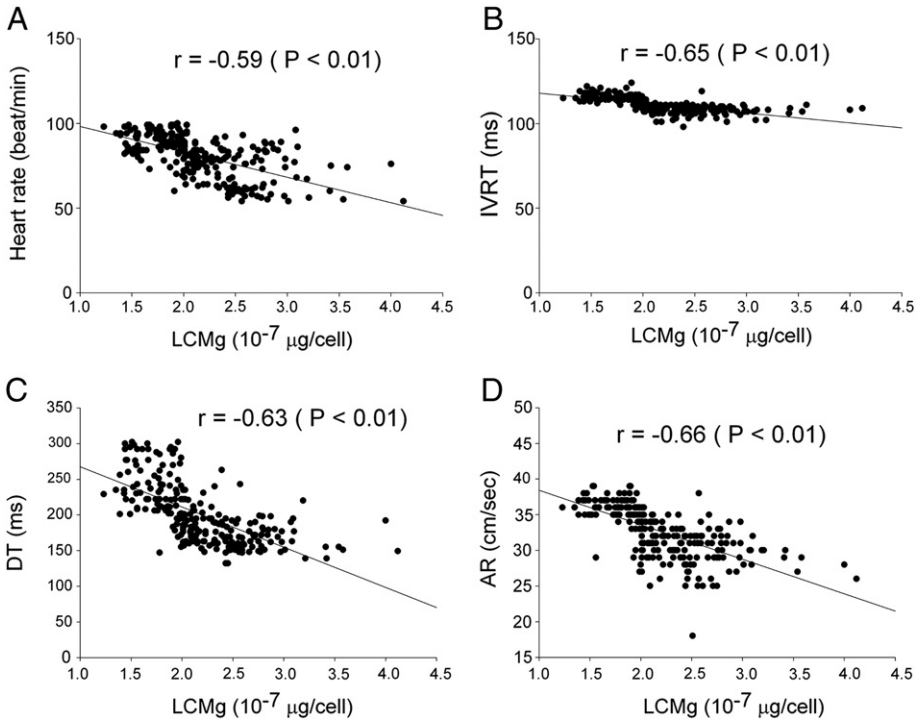

Fig. 1. Correlation of intralymphocytic ionized magnesium content (LCMg) with heart rate (panel A), isovolumic relaxation time (IVRT) (panel B), E wave deceleration time (DT) (panel C) and pulmonary vein flow from atrial reversal (AR) (panel D) ($n=256$).