Impact of dietary sodium intake on left ventricular diastolic filling in early essential hypertension

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Aims Dietary sodium intake modulates left ventricular hypertrophy in established essential hypertension independent of blood pressure level. We conducted this study to elucidate the relationship between sodium intake and left ventricular structural or functional changes in early essential hypertension.

Methods Forty-four young male patients (age 25.9 ± 2.6 years) with mild essential hypertension that had never been treated and 45 normotensive male control subjects of similar age were examined. Dietary sodium intake was measured from 24 h urinary sodium excretion, blood pressure from 24 h ambulatory monitoring (SpaceLabs 90207), left ventricular structure from 2-D guided M-mode echocardiography, and diastolic filling of the left ventricle (as the main compound of diastolic function in a young population) by pulse-wave Doppler sonography.

Results In hypertensive patients, daily sodium excretion correlated with the ratio of late (A) to early (E) maximum velocity (Vmax A/E; r = +0.27, P = 0.07), velocity time integrals (A/E; r = +0.54, P < 0.001) as well as atrial contribution, as a percent of left ventricular filling (VH ATCO; r = +0.52, P < 0.001) independent of heart rate, whereas the opposite correlations were observed in normotensives (all P < 0.001). Stepwise multiple regression analysis confirmed these results. Sodium excretion emerged as the strongest independent determinant of impaired diastolic filling in hypertensive patients (velocity time integrals A/E: R² = 0.49, β = +0.57, P = 0.0001; VH ATCO: R² = 0.48, β = +0.56, P < 0.0001; Vmax A/E: ns). In normotensive subjects, sodium excretion was a similar strong, but inverse determinant of diastolic filling (velocity time integrals A/E: R² = 0.40, β = −0.43, P = 0.0028). Heart rate was a strong determinant of diastolic filling in hypertensive patients (β = +0.55, P = 0.0002) and in normotensive subjects (β = +0.34, P = 0.011). Left ventricular mass and end-diastolic volume index were not related to diastolic filling in either group.

Conclusion In early essential hypertension, sodium excretion is correlated with impaired left ventricular diastolic filling independent of left ventricular mass. The renin-angiotensin-aldosterone system might be a mediator of the observed correlation.

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Key Words: Essential hypertension, sodium, diastolic filling.

Introduction

Dietary salt intake is known to profoundly influence the structure of the left ventricle in hypertensive heart disease. Previous clinical and intervention studies examining patients with established essential hypertension have identified dietary sodium intake as a determinant of left ventricular hypertrophy independent of the level of hypertensive blood pressure[1–4]. Although the impact of salt intake on left ventricular hypertrophy was confirmed in established essential hypertension, little is known about the relationship between sodium intake and left ventricular structure at the onset of hypertensive heart disease.

Diastolic dysfunction of the left ventricle is found in the absence[5] or the presence[6] of left ventricular hypertrophy in patients with essential hypertension. It has been reported that a substantial proportion of patients with essential hypertension have evidence of impaired diastolic function without signs of left ventricular hypertrophy[7]. Other studies showed that the diastolic function of the left ventricle declines, from normotensive subjects to patients with essential hypertension without left ventricular hypertrophy to those with left ventricular hypertrophy[8,9]. These findings might indicate that the pathogenetic changes in the
myocardium in hypertensive heart disease lead to diastolic dysfunction of the left ventricle prior to the development of myocardial hypertrophy.

In the current study, we examined previously untreated young patients with mild essential hypertension to determine whether urinary sodium excretion is related to left ventricular structural or functional changes, namely left ventricular hypertrophy and diastolic filling, at the early stages of essential hypertension. Our data indicate that in contrast to the normotensive control group, diastolic filling of the left ventricle is adversely influenced by urinary sodium excretion in essential hypertension independent of other confounding factors.

### Methods

#### Study population

Forty-four male patients with mild essential hypertension, World Health Organisation (WHO) stage I-II, that had never been treated (age 25.9 ± 2.6 years) and 45 age-matched male normotensive subjects (age 26.2 ± 2.7 years) were examined (Table 1). Borderline arterial hypertension was considered established when at least three out of four casual blood pressure readings on two different occasions (at least 2 weeks apart) assessed after 5 min with the patient resting in a sitting position were ≥140 mmHg systolic or ≥90 mmHg diastolic. Normotension was said to be confirmed when all four casual blood pressure measurements taken in a similar way as above were less than 140/90 mmHg. All casual blood pressure measurements were taken in a sitting position after 5 min of rest with a standard sphygmomanometer. Cuff size was adjusted according to the individual’s arm circumference. A ‘normal’ cuff size was: 14 cm wide, with a circumference of 24 to 32 cm; a ‘large’ cuff size was: 16 cm wide, with a circumference of 32 to 42 cm.

Hypertensive patients were recruited from a screening of students for high blood pressure at the University campus. The WHO criteria were used to diagnose borderline arterial hypertension. At least three out of four casual blood pressure readings were assessed, after the patient had sat resting for 5 min. The readings (≥140 mmHg systolic or ≥90 mmHg diastolic) were taken with a standard sphygmomanometer on two different occasions (at least 2 weeks apart). Cuff size was adjusted according to the patient’s arm circumference. None of the patients had been diagnosed to have arterial hypertension prior to the study, and no patient had ever received any cardiovascular mediation in the past. None of the participants had followed any specific dietary guidelines before the haemodynamic evaluation. Normotensive subjects participated as volunteers and underwent a complete routine clinical work-up to ensure that their cardiovascular system was normal.

Clinical and extensive laboratory investigations showed completely normal results in the normotensive subjects. Patients with essential hypertension were enrolled only if secondary hypertension as well as WHO stage III of hypertensive disease had been ruled out. Therefore, exclusion criteria were: advanced hypertensive fundoscopy changes, myocardial infarction, or other evidence of coronary artery disease, congestive heart failure, and hepatic or renal insufficiency. Exercise stress testing or detailed evaluation of renal arteries (intra-arterial digital substraction angiography), analysis

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**Table 1 Characteristics of hypertensive and normotensive individuals**

<table>
<thead>
<tr>
<th></th>
<th>Hypertensive patients (n=44)</th>
<th>Normotensive subjects (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.9 ± 2.6</td>
<td>26.2 ± 2.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.5 ± 8.9**</td>
<td>75.1 ± 8.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>182.2 ± 7.5</td>
<td>181.7 ± 7.2</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>2.04 ± 0.13*</td>
<td>1.96 ± 0.13</td>
</tr>
<tr>
<td>Body mass index (kg. m⁻²)</td>
<td>24.9 ± 2.8**</td>
<td>22.7 ± 2.0</td>
</tr>
<tr>
<td>Casual blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>144 ± 12**</td>
<td>122 ± 8</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>89 ± 10**</td>
<td>75 ± 8</td>
</tr>
<tr>
<td>24-h blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>131 ± 7**</td>
<td>121 ± 6</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>79 ± 15**</td>
<td>71 ± 5</td>
</tr>
<tr>
<td>Left ventricular mass (g)</td>
<td>260 ± 44**</td>
<td>214 ± 38</td>
</tr>
<tr>
<td>Left ventricular mass/body surface area (g. m⁻²)</td>
<td>127 ± 22**</td>
<td>109 ± 16</td>
</tr>
<tr>
<td>Ratio of velocity time integral A/E (VTI A/E)</td>
<td>0.36 ± 0.10**</td>
<td>0.27 ± 0.09</td>
</tr>
<tr>
<td>Ratio of diastolic peak late to early velocity (VMAX A/E)</td>
<td>0.69 ± 0.12**</td>
<td>0.58 ± 0.16</td>
</tr>
<tr>
<td>Atrial contribution to left ventricular filling (%) (VH ATCO)</td>
<td>26.2 ± 5.1**</td>
<td>20.8 ± 5.0</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>66.0 ± 6.3</td>
<td>65.7 ± 5.5</td>
</tr>
<tr>
<td>Midwall fractional fibre shortening (%)</td>
<td>16.9 ± 2.0*</td>
<td>18.3 ± 1.9</td>
</tr>
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*P<0.005 **P<0.001 hypertensive vs normotensive subjects.
of hormones and endocrine metabolites were conducted only if indicated. Informed written consent was obtained from each individual. The protocol was approved by the University Clinical Investigation and Ethics Committee of the University of Erlangen/Nuremberg.

**Measurements**

Dietary salt intake was assessed, while patients were on an ad libitum diet, by measuring sodium excretion in urine collected over 24 h, which represents a rough but valuable estimate of daily sodium intake\(^\text{[10]}\). To ensure complete collection of urine, all samples with a volume of less than 600 ml. 24 h\(^{-1}\) (n = 2) and those containing less than the expected creatinine/kg body weight, i.e. less than 15 mg. kg\(^{-1}\) body weight. 24 h\(^{-1}\) (n = 3) were excluded\(^\text{[11, 12]}\). Twenty-four hour blood pressure monitoring took place in parallel with the 24 h urine collection. The measurements were taken with an automatic portable device (Spacelab 90207, Redmont, U.S.A.). Awake and sleeping blood pressure was individually adapted for each patient\(^\text{[13]}\).

Two-dimensional guided M-mode echocardiography and continuous wave/pulse wave Doppler sonography were performed at the same time of day in every subject using an ultrasonoscope (Picker-Hitachi CS 192, Tokyo, Japan) with a 2·5 MHz probe. Echocardiograms were recorded at rest in the third or fourth intercostal space lateral to the left sternal border in the end-expiratory phase, with the patient recumbent in the supine or half left-sided position. An average of five beats of each tracing was read independently by two physicians\(^\text{[14]}\). Raw parameters to evaluate left ventricular structure were the end-diastolic septal wall thickness the end-diastolic posterior wall thickness, and the end-systolic as well as the end-diastolic diameter of the left ventricle. An ECG was recorded simultaneously with the echocardiographic examination, in order to define end-diastole at the onset of the QRS complex and to measure heart rate.

According to the American Society of Echocardiography (ASE), left ventricular mass (ASE cube left ventricular mass) was calculated according to the standard formula of Troy et al.\(^\text{[15]}\), which takes both septal and posterior wall thickness into account. Since left ventricular mass, calculated according to the American Society of Echocardiography convention was found to over-estimate the 'true' left ventricular mass, all values based on the American Society of Echocardiography convention were corrected by the regression equation as suggested by Devereux et al.\(^\text{[16]}\), left ventricular mass=

\[0.8 \times \text{ (ASE cube left ventricular mass)} + 0.6 \times \text{ g} \]

Left ventricular global systolic function was estimated by calculating ejection fraction, fractional fibre shortening and mid-wall fractional fibre shortening\(^\text{[17]}\).

To estimate cardiac preload, the end-diastolic volume index was calculated\(^\text{[18]}\). End-systolic wall stress was determined as a parameter for cardiac afterload\(^\text{[19]}\). Left ventricular diastolic filling was determined by pulse-wave Doppler sonography of left ventricular inflow\(^\text{[19]}\). This was performed from the apical four-chamber view with the volume sample placed between the mitral leaflet and the Doppler beam aligned parallel with the mitral flow. The signal was optimized by audio and visual feedback in order to obtain the recording with the maximum velocity, the least spectral dispersion and the greatest signal-to-noise ratio. The peak early diastolic inflow velocity coincident with the E wave (Vmax E), peak late diastolic inflow velocity coincident with the A wave (Vmax A), and the ratio of peak late to early velocities (Vmax A/E) were measured. Furthermore, the ratio of velocity time integrals (velocity time integrals A/E) was assessed. The atrial contribution to left ventricular filling in percent (VH ATCO) was calculated as the velocity time integral A, divided by the velocity time integral of total diastolic inflow.

All statistical analyses were carried out using the SPSS program\(^\text{[20]}\). Differences between the hypertensive and the normotensive group were analysed with the Student’s t-test. Pearson correlation coefficients were calculated where indicated. To eliminate the influence of heart rate on diastolic filling, partial correlation analysis was performed and the results are given in the text. In addition, stepwise multiple regression analysis was applied to identify determinants of left ventricular diastolic filling.

All values, unless stated otherwise, are expressed as mean ± 1 standard deviation.

**Results**

**Clinical data**

By study design, casual and ambulatory blood pressure were both significantly elevated in hypertensive patients compared to normotensive controls (see Table 1). Similarly, left ventricular mass indexed to body surface area was higher in hypertensive patients than in normotensive controls, but still within normal limits. Left ventricular end-diastolic diameter and left atrial diameter were similar and within normal limits in the hypertensive and in the normotensive group. The parameters for diastolic filling velocity time integrals A/E, Vmax A/E and VH ATCO were all greater in hypertensive patients than in controls, indicating impaired diastolic filling in hypertensive patients. Mid-wall fractional fibre shortening as a sensitive parameter of left ventricular systolic function was lower in the hypertensive group; ejection fraction and fractional fibre shortening as parameters of global systolic function was similar in hypertensive patients and in controls.

**Left ventricular function**

In our patients with mild essential hypertension, urinary sodium excretion was correlated with the parameters of
diastolic filling of the left ventricle. The higher the urinary sodium excretion, the greater were velocity time integrals A/E (partial r= -0.49, P<0.001) (Fig. 1), VH ATCO (partial r=0.52, P<0.001), and to a lesser extent Vmax A/E (partial r=0.27, P=0.07). Thus, high urinary excretion sodium was linked to diastolic filling abnormalities of the left ventricle in patients with early essential hypertension.

In contrast to this are the findings in the normotensive subjects, which showed an inverse correlation of sodium excretion with the parameters of diastolic filling: velocity time integrals A/E (partial r= -0.49, P<0.001) (Fig. 2), VH ATCO (partial r= -0.49, P<0.001), and Vmax A/E (partial r= -0.52, P<0.001). The higher the urinary sodium excretion, the better was diastolic filling in normotensive control subjects.

Stepwise multiple regression analysis confirmed the contrasting results in diastolic filling between hypertensive and normotensive individuals. In the hypertensive group, velocity time integrals A/E was inversely determined by sodium excretion (R²=0.49, β= +0.57, P=0.0001) (Table 2). In the normotensive group, sodium excretion also emerged as an equally independent determinant of velocity time integrals A/E (R²=0.40, β= -0.43, P=0.0028) but in reverse. Another independent determinant of velocity time integrals A/E was heart rate in both groups (β= +0.55, P=0.0002 in hypertensive patients and β= +0.34,
impaired left ventricular diastolic filling in hypertensive subjects.

Mid wall fractional fibre shortening did not correlate in patients, whereas the opposite was found in normotensive subjects. Similarly, left ventricular mass and body mass index were found to be a determinant of diastolic filling in the normotensive or hypertensive group.

The left ventricular end-diastolic volume index as a parameter for cardiac preload or end-systolic wall stress as a parameter for afterload did not significantly determine diastolic filling in our patients with normal-sized left ventricles (Table 3). Similar results were found in hypertensive patients when the influence of sodium excretion on VH ATCO was analysed by stepwise multiple regression analysis ($R^2 = 0.48$, $\beta = -0.56$, $P < 0.0001$). Vmax A/E was not found to be determined by urinary sodium excretion ($R^2 = 0.19$, $\beta = 0.24$, ns). Thus, high sodium excretion was related to impaired left ventricular diastolic filling in hypertensive patients, whereas the opposite was found in normotensive subjects.

Parameters of left ventricular systolic function such as ejection fraction, fractional fibre shortening and midwall fractional fibre shortening did not correlate with the rate of urinary sodium excretion.

### Left ventricular structure

Urinary sodium excretion was not correlated with septal wall thickness ($r = -0.01$, ns), posterior wall thickness ($r = 0.22$, ns), or relative wall thickness ($r = 0.01$, ns) in our patients with early essential hypertension. Similarly, left ventricular mass ($r = 0.19$, ns) and left ventricular end-diastolic diameter were not related to sodium excretion ($r = 0.05$, ns). Body mass index was correlated with left ventricular mass ($r = 0.30$, $P < 0.05$). Neither casual nor ambulatory blood pressure showed a correlation with left ventricular mass within the hypertensive group.

In normotensive subjects, no correlation was found between sodium excretion and posterior wall thickness ($r = -0.13$, ns), sepal wall thickness ($r = -0.23$, ns), relative wall thickness ($r = -0.15$, ns), left ventricular mass ($r = -0.01$, ns), or end-diastolic diameter ($r = 0.05$, ns). Body mass index showed a correlation with left ventricular mass ($r = 0.33$, $P < 0.05$).

Thus, sodium excretion was not related to left ventricular structure in either group of youthful subjects.

### Sub-analysis

In a post hoc sub-analysis, hypertensive patients (based on casual blood pressure readings as inclusion criteria)
were divided into subgroups according to their 24-h ambulatory blood pressure: those with 'confirmed essential hypertension' (ambulatory 24-h blood pressure ≥ 130 mmHg systolic or ≥ 80 mmHg diastolic') and those with 'white coat hypertension' (ambulatory 24-h blood pressure < 130/80). Patients with confirmed hypertension showed a correlation between urinary sodium excretion and velocity time integrals A/E (partial r=0.61, P<0.001), Vh ATCO (partial r=0.60, P<0.002), and Vmax A/E (partial r=0.46, P<0.05). This result was confirmed by stepwise multiple regression analysis: velocity time integrals A/E ($R^2=0.53$, $\beta=0.55$, $P<0.005$), VH ATCO ($R^2=0.52$, $\beta=0.54$, $P<0.01$) and Vmax A/E ($R^2=0.32$, $\beta=0.45$, $P<0.05$) were all determined by sodium excretion independent of heart rate, diastolic 24-h blood pressure and left ventricular mass. In this group with confirmed essential hypertension, urinary sodium excretion was correlated with posterior wall thickness ($r=0.55$, $P<0.005$) and relative wall thickness ($r=0.45$, $P<0.05$) but not with septal wall thickness ($r=0.06$, ns). Left ventricular mass and end-diastolic diameter did not correlate with urinary sodium excretion ($r=0.24$, ns, and $r=-0.03$, ns, respectively).

No correlation between urinary sodium excretion and parameters of diastolic filling could be found in the patients with white coat hypertension.

**Discussion**

In the current study we found that high dietary sodium intake is associated with altered diastolic filling of the left ventricle in patients with mild essential hypertension. Important confounding factors which have an effect on diastolic filling were eliminated in our analysis. A homogenous population was chosen to exclude influences of age', gender or any cardiovascular medication on left ventricular diastolic filling. Heart rate, which is another strong determinant of diastolic filling', was eliminated a priori by using partial correlation analysis. Sodium excretion was found to be the strongest independent determinant of left ventricular diastolic filling (as indicated by transmural flow velocity analysis), independent of heart rate, diastolic diameter, left ventricular mass, and 24-h ambulatory blood pressure. The measurement of sodium excretion is a rough but valid estimate of dietary sodium intake'. Daniels et al. have shown that a direct method of determining dietary sodium intake, namely analysis of all ingested salt per day by a trained dietitian, results in a closer correlation between salt and left ventricular hypertrophy than estimating dietary salt intake by measuring urinary sodium excretion over 24 h. Since the variation of estimating dietary sodium intake from sodium excretion over 24 h might be more marked than the direct assessment, the correlations found in the current study might in fact be even stronger if we had used the determination of all ingested salt instead of using urinary sodium excretion.

Left ventricular diastolic filling is influenced by loading conditions. However, left ventricular end-diastolic diameter and atrial size were similar in both groups. Additionally, end-diastolic volume index and end-systolic wall stress (as non-invasive substitutes for preload and afterload') were entered in the multiple regression analysis to eliminate influences of varying preload or afterload situations. Again, 24-h sodium excretion emerged as the strongest determinant of left ventricular diastolic filling.

Left ventricular hypertrophy is known to lead to diastolic dysfunction'. In our patients with mild hypertension of relatively short duration, average left ventricular mass was within the normal limits', and therefore it is not surprising that left ventricular mass was not found to be a determinant of diastolic filling. Thus, the observed correlation between a high sodium intake and an impaired diastolic filling in patients with borderline essential hypertension cannot be attributed to left ventricular hypertrophy or a change of cardiac preload or afterload. We also found an inverse correlation between 24 h diastolic blood pressure and velocity time integrals A/E, which contradicts the literature'. This relationship could not be reproduced in the correlation or partial correlation analysis. Therefore, it is unlikely that this particular result reflects a factual mechanism. In a post-hoc analysis we analysed separately those patients with essential hypertension confirmed by ambulatory blood pressure values as 'true' hypertensives. Posterior and relative wall thickness were related to urinary sodium excretion as previously described'. Again, diastolic filling abnormalities, as indicated by a high ratio of late to early filling, was linked to dietary salt intake independent of other confounding factors. This sub-analysis strengthens our finding that dietary salt intake is related to left ventricular filling abnormalities in early hypertensive heart disease. It is a striking finding that, in contrast to the hypertensive patients, in the normotensive group sodium excretion was associated inversely with diastolic filling. Considering that the diagnosis of arterial hypertension is arbitrary, one would expect no significant correlation in the normotensive group. Further studies are needed to clarify the relationship between dietary sodium intake and diastolic filling at a given blood pressure level. However, the inverse correlation found in the control group might be explained by the observation that high dietary sodium intake leads to an increased total plasma volume'. Athletes undergoing endurance training have preserved diastolic function of the left ventricle despite an elevated left ventricular mass'. Thus, an undamaged left ventricle seems to be capable of compensating for an increased preload by raising diastolic left ventricular performance.

In contrast, as indicated by our findings, at the early stage of hypertensive heart disease, high sodium intake is associated with impaired diastolic filling. In the setting of established essential hypertension, sodium intake determines the degree of left ventricular
hypertrophy\textsuperscript{[1-5]}, and, vice versa, restriction of sodium intake leads to reduction of left ventricular mass\textsuperscript{[29]}. Left ventricular hypertrophy had not yet fully developed in our patients at the early stage of hypertensive disease. Our findings, of impaired left ventricular diastolic filling in early essential hypertension, although not demonstrating a causal relationship but a correlation, strengthen the notion that even before the manifestation of left ventricular hypertrophy, changes may already have taken place in the myocardial structure leading to functional impairment prior to echocardiographically detectable morphological changes.

The pathophysiological mechanism underlying the relationship between high sodium intake and hypertensive cardiac hypertrophy has not yet been explained. It has been found in rats that arterial hypertension induces a shift of myocardial isoenzymes VI/V3 towards a lower ratio reversible by sodium restriction\textsuperscript{[30]}. Also, the involvement of sodium in the regulation of the renin-angiotensin-aldosterone system may elucidate the mechanism. The renin-angiotensin-aldosterone system has been shown to be involved in the development of myocardial fibrosis. In spontaneously hypertensive rats, basal collagen synthesis of cardiac fibroblasts is elevated compared to controls. Moreover, stimulation of collagen synthesis by angiotensin II is enhanced in this animal model\textsuperscript{[31]}. This effect of angiotensin II might be mediated by TGF-\beta\textsuperscript{[32]}. In addition, Brilla et al. have reported that high serum aldosterone concentrations lead to cardiac fibrosis in rats\textsuperscript{[33]}. Treatment with aldosterone antagonists or angiotensin-converting enzyme blockade reverses, at least in part, myocardial fibrosis\textsuperscript{[34]}. A dysregulation of the renin-angiotensin-aldosterone system in response to high sodium intake\textsuperscript{[35]} might result in inappropriately high activity of the hormone system. Thus, inappropriate high activity of the renin-angiotensin-aldosterone system in response to high sodium intake could be present in our patients with borderline essential hypertension. Also, in analogy with spontaneously hypertensive rats, patients with essential hypertension might be more susceptible to angiotensin II-mediated collagen synthesis in the myocardium. As a consequence, diastolic function might be compromised by increased myocardial fibrosis. This could explain the correlation between high sodium intake and impaired diastolic filling in patients with high sodium intake. Further studies are needed to elucidate the interaction between dietary salt intake, the renin-angiotensin-aldosterone system, and myocardial fibrosis in relation to functional performance.

In conclusion, we have found that dietary sodium intake is associated with impaired diastolic filling of the left ventricle independent of other confounding factors at the early stage of essential hypertension and even before the manifestation of left ventricular hypertrophy. This result shows that dietary sodium might be involved in the pathogenesis of hypertensive heart disease already at the early stage of essential hypertension, possibly mediated by the renin-angiotensin-aldosterone system.

\textbf{References}


