

BNP as a marker of diastolic dysfunction in the general population: Importance of left ventricular hypertrophy

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Abstract

BNP is a marker of systolic left ventricular dysfunction (LVSD) and heart failure. To assess BNP for the detection of diastolic dysfunction in the general population, we examined 1678 subjects within an age- and sex-stratified survey (MONICA Augsburg). BNP was measured using a commercially available RIA (Shionogi).

BNP increased in subjects with diastolic dysfunction (mean 20.3 ± 4.7 pg/ml vs. control 9.6 ± 0.5 pg/ml, $p < 0.001$), but to a lesser extent than in subjects with LV hypertrophy (LVH, mean 37.3 ± 49.1 pg/ml, $p < 0.001$ vs. control) or LVSD (mean 76.2 ± 23.2 pg/ml, $p < 0.001$ vs. control). Individuals with sole diastolic abnormality displayed BNP concentrations at the control level (mean 9.7 ± 1.7 pg/ml). In univariate analysis, age, BMI, systolic blood pressure, left atrial size, LV mass index, diastolic dysfunction and EF displayed a significant correlation with BNP ($p < 0.001$). However, LV mass index displaced diastolic dysfunction as a significant predictor of BNP in multivariate analysis. Upon ROC analysis, sensitivity and specificity for the detection of diastolic dysfunction by BNP were only 61% and 55%, respectively. Nevertheless, a normal BNP test virtually excluded the presence of diastolic dysfunction and concomitant LVH (NPV 99.9%).

Increased BNP concentrations in subjects with diastolic dysfunction are strongly related to LVH. Population-wide screening for diastolic dysfunction with BNP cannot be recommended although a normal BNP test usually excludes diastolic dysfunction and LV hypertrophy.

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1. Introduction

Brain natriuretic peptide (BNP), the second member of the natriuretic peptide family, is strongly expressed in myocardial tissue during heart failure (HF) [1,2]. Increased BNP plasma concentrations can be detected in patients with systolic left ventricular dysfunction (LVD)

and heart failure [3–6] and currently BNP is an approved marker for the detection of acutely decompensated heart failure [7].

Of patients with signs and symptoms of HF, up to 40% have preserved systolic function [8–10]. Clinically, the majority of these patients are assumed to suffer from diastolic HF. Upon echocardiography, a diagnosis of diastolic dysfunction requires evidence of abnormal LV filling as indicated by a panel of Doppler parameters and specific guidelines have been put forward [11]. Based upon these recommendations, our group has determined the prevalence of diastolic dysfunction in a large European population-based sample [12].

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¹ For the MONICA investigators. The MONICA Augsburg study was initiated by U. Keil and co-workers.

In addition to systolic HF, BNP has recently been suggested as a marker of diastolic dysfunction and heart failure in clinical studies [13–15]. However, in a recent population-based study, it has been suggested that BNP might be a suboptimal marker to detect diastolic dysfunction [16]. In our current study, we hypothesized that BNP is increased in LV diastolic dysfunction in the general population, but to a lesser extent than in LV systolic dysfunction. Furthermore, we hypothesized that increases in BNP associated with LV diastolic dysfunction may be associated with LV hypertrophy. In order to address this hypothesis, we determined BNP plasma concentrations in an age-stratified population-based sample, which was characterized with respect to LV systolic and diastolic function and mass by echocardiography.

2. Methods

2.1. Study population

The MONICA Augsburg study, part of the international collaborative WHO MONICA project, investigated the cardiovascular risk factor profile of randomly selected subjects from the Augsburg population in cross-sectional surveys [12,17]. This sex-age-stratified random sample of all German residents of the Augsburg study area, was chosen to contain an equal distribution of subjects of both sexes, all age classes and all social groups. The study was carried out in 1995/1996. All subjects provided information on medical history, physical activities, medication, and personal habits. Body height and weight were recorded in light clothing, and body mass index was computed as weight in kg divided by height in meter squared (kg/m^2). Blood pressure was taken as a mean of two readings on the right arm with the random zero method, measured under standardized conditions with the participant seated (after 5 min rest). Echocardiographic examinations were performed in a total of 827 males and 851 females, aged 25 to 75 years. Only subjects with optimal visualization of LV interfaces were used for assessment of LV function and mass and only subjects with sinus rhythm were evaluated for Doppler parameters of diastolic function. BNP plasma concentrations were available for 1438 subjects. A complete data set including parameters of systolic and diastolic function and BNP measurements was available for 1123 individuals. The control group ($n=556$) consisted of subjects without systolic dysfunction, diastolic abnormality, diastolic dysfunction, left ventricular hypertrophy, left atrial hypertrophy, arterial hypertension, history of myocardial infarction or atrial fibrillation.

2.2. Echocardiographic measurements

Two-dimensional echocardiograms from standard left parasternal and apical windows, derived M-mode echocardiograms, and Doppler recordings were performed by two

expert sonographers on a commercially available echocardiograph (Hewlett Packard, Sonos 1500, Andover, Mass., U.S.A.) with a 2.5 or 3.5 MHz transducer. M-mode tracings were recorded on stripchart paper at a speed of $50 \text{ mm} \cdot \text{s}^{-1}$. To reduce interobserver variability, all M-mode tracings were analysed by a single experienced observer. Measurements for M-mode guided calculation of left ventricular mass were taken just below the tip of the mitral valve. Left ventricular internal end-diastolic (LVEDD) and endsystolic diameters (LVESD) and septal (Swth) and posterior wall thickness (Pwth) were measured according to the guidelines of the American Society of Echocardiography. Left ventricular mass (LVM) was calculated according to the formula $\text{LVM}(\text{g})=0.8(1.04((\text{LVEDD}+\text{Swth}+\text{Pwth})^3-\text{LVEDD}^3))+0.6$ [18]. The rank correlation for 144 duplicate measurements by the two sonographers was 0.91 for the determination of LVM. Left ventricular mass was indexed to body surface area as left ventricular mass index (LVMI) in g/m^2 body surface area [19]. Left ventricular end-systolic and end-diastolic volumes (LVESV, LVEDV) were determined with the Teichholz equations [20]. The ejection fraction was calculated as $\text{EF}=(\text{LVEDV}-\text{LVESV})/\text{LVEDV}$. Doppler echocardiographic recordings were performed by pulsed wave Doppler with the sample volume at the tips of the mitral valve in the apical four chamber view and registered at a paper speed of $100 \text{ mm} \cdot \text{s}^{-1}$. Early (E) and late (A) diastolic velocities and ratio of early and late velocities (E/A) were determined as previously described [21]. Isovolumetric relaxation time (IVRT) was determined as the interval between the end of the aortic outflow signal and the start of the mitral inflow signal. The definitions used in this study were as follows: a preserved left ventricular systolic function was a calculated ejection fraction of $\geq 45\%$ [8]. This also represents the mean minus 2 SD as obtained in 897 healthy subjects. Diastolic abnormalities were defined as proposed by the European Study Group on Diastolic Heart Failure [8]. Specifically, an abnormal E/A-ratio was considered when E/A < 50 years was < 1, or E/A > 50 years was < 0.5, or IVRT < 30 years was > 92 ms, or IVRT 30–50 years was > 100 ms, or IVRT > 50 years was > 105 ms in the presence of a preserved ejection fraction. The term diastolic dysfunction refers to echocardiographically derived diastolic abnormalities in the presence of current diuretic therapy and/or left atrial enlargement. Left atrial enlargement was a left atrial diameter of more than 45 mm or a left atrial maximal area of more than 20 cm^2 . Hypertension was considered at a blood pressure of > 140/90 mmHg, current intake of antihypertensive medication, or both. Diabetes mellitus was defined as a history of diabetes. LV hypertrophy was defined as LV mass indexed to a body surface area of > $134 \text{ g}/\text{m}^2$ in men and $110 \text{ g}/\text{m}^2$ in women [22].

2.3. Biochemical measurements

Blood was drawn after subjects were in a supine resting position for at least 30 minutes. The samples were

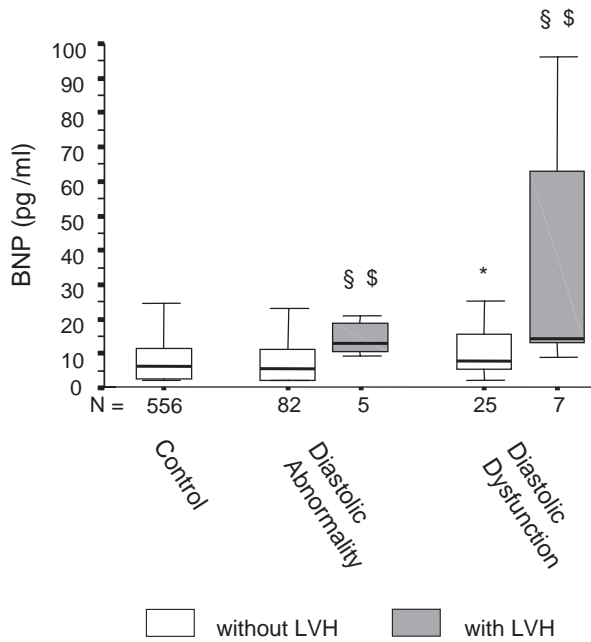


Fig. 1. BNP in subjects with Diastolic Abnormality or Dysfunction, stratified to LVH (Left ventricular hypertrophy). * denotes $p=0.056$ vs. Control; § denotes $p<0.05$ vs. Control; \$ denotes $p<0.05$ vs. subjects without LVH.

chilled, centrifuged and the plasma was stored at -80°C until measurement. Samples were stored without thawing/freezing cycles prior to BNP measurements which were performed in 2001/2002. BNP was measured by standard radioimmunoassay from 100 μl non-extracted plasma samples with a commercially available RIA-kit (Shionogi, Osaka, Japan) without cross-reactivity to ANP [23]. Intra- and inter-assay variabilities of BNP measurements were

8% respectively. All measurements were carried out in duplicate and no corrections were made for inter-assay variability.

2.4. Statistics

BNP values are given as mean and median and standard error of the mean. Differences between mean BNP concentrations in subgroups as compared to control were tested for statistical significance by Mann Whitney U-test since BNP was markedly skewed. BNP concentrations in Fig. 1 are depicted as “box and whiskers” plots, where the centre horizontal line is drawn at the sample median, the bottom and the top edges of the box are drawn at the sample 25th and 75th percentiles (interquartile range), and the vertical lines extend from the box as far as the data extend, to a distance of, at most, 1.5 interquartile ranges. Hemodynamic and anthropometric data were tested for statistical significance by two-tailed t-test. Differences between groups with categorical data were compared by chi-square test. Univariate and multivariate regression analysis was performed in order to identify statistically significant and independent correlations between BNP and a number of anthropometric and cardiac structural and functional parameters. Together with the multivariate correlation coefficients, the corresponding beta coefficients were computed. The beta coefficient is an adjusted measure for the increase or decrease in BNP that can be attributed to a given change of one unit in the corresponding independent parameter. Receiver operator characteristic (ROC) analysis was carried out to determine sensitivity, specificity, positive predictive value and negative predictive value in relation to a number of cutoff values of BNP

Table 1
Baseline demographics

	CTRL <i>n</i> =556	Diastolic dysfunction <i>n</i> =38	Systolic dysfunction (EF<45%) <i>n</i> =16	Preserved LV-function <i>n</i> =1069
Prevalence (%)	53.7	3.3	1.3	95.4
Age (years, range)	45±13 25–75	57±10*,** 37–75	57±4*,** 25–75	49±14 25–75
Gender (% female)	55	42	38	51
aHT (%)	0	87*,**,***	56*,**	24
MI (%)	0	2.6*	0	0.8
BMI (kg/m ²)	25±3.4	29±4*,**	28±5*	26±4
RR sys	121±11	148±27*,**,***	133±20*	132±19
RR dia	75±8	87±16*,**	81±11*	80±11
HR	68±11	71±12	77±17*,**	69±11
aHT therapy (%)	0	53*,**	31*,**	13
LVEDD (mm)	48±4	50±6*,**	53±9*,**	48±5
LA size (mm)	37±4	42±6*,**	43±7*,**	38±5
EF (%)	64±7	65±9***	41±5*,**	65±7
LVMI	77±14	108±31*,**	108±35*,**	84±19

CTRL denotes control; aHT, arterial hypertension; MI, myocardial infarction; BMI, body mass index; RR sys, systolic blood pressure; RR dia, diastolic blood pressure; LVEDD, left ventricular diastolic diameter; LA size, left atrial size; EF, ejection fraction; LVMI, left ventricular mass index.

* p vs. CTRL <0.05.

** p vs. preserved LV-function <0.05.

*** p vs. systolic dysfunction <0.05.

Table 2
Uni- and multivariate analyses

Parameter	Univariate analysis		Multivariate analysis	
	r value	p value	β coefficient	p value
Age	0.32	0.01	0.53	0.001
BMI (g/m ²)	0.05	0.05	-0.54	0.001
RR sys	0.14	0.01	0.02	ns
LA size	0.23	0.01	0.18	ns
LVMI	0.28	0.01	0.2	0.001
DiaDys	0.11	0.01	4.2	ns
EF	-0.10	0.01	-42.5	0.001

ns denotes not significant.

BMI denotes body mass index; RR sys, systolic blood pressure; LA size, left atrial size; LVMI, left ventricular mass index; DiaDys, Diastolic Dysfunction; EF, ejection fraction.

for diastolic dysfunction, systolic dysfunction and LV hypertrophy. P-values below 0.05 were defined as statistically significant.

3. Results

3.1. Study population

Anthropometric, hemodynamic and echocardiographic characteristics are depicted in Table 1, according to systolic and diastolic function. In the current population, the prevalence of diastolic dysfunction was 3.3%, and that of systolic dysfunction (EF<45%) 1.3%. Individuals with diastolic or systolic dysfunction were significantly older, had a higher prevalence of hypertension, a higher BMI and higher systolic and diastolic blood pressures. Left ventricular enddiastolic diameter, left atrial size and left ventricular mass index were significantly increased in subjects with systolic or diastolic dysfunction with no significant differences between the two groups.

3.2. BNP and LV diastolic and systolic dysfunction

The individuals in the control group had a mean BNP plasma concentration of 9.6 ± 0.5 pg/ml (median 6.2 pg/ml). The mean BNP concentration in subjects with diastolic

dysfunction was significantly increased with 20.3 ± 4.7 pg/ml (median 12.0 pg/ml, $p < 0.001$ vs. control). Those individuals with systolic dysfunction presented with a mean BNP value of 76.2 ± 23.2 pg/ml (median 19.9 pg/ml, $p < 0.001$ vs. control). When systolic dysfunction was defined as an EF of <40%, the mean BNP concentration rose to 123.5 ± 51.4 pg/ml (median 95.0 pg/ml, $p < 0.001$ vs. control and diastolic dysfunction).

3.3. Uni- and multivariate analyses

In univariate analysis, age, BMI, systolic blood pressure, left atrial size, LVMI, diastolic dysfunction and EF displayed a significant correlation with BNP whereas gender, heart rate and diastolic blood pressure displayed no significant correlation (Table 2). When the significant univariate predictors were entered into several multivariate models (with diastolic dysfunction not entering the same model as EF or LA size), age, BMI, LV mass index and EF remained statistically significant and independent predictors of BNP, while systolic blood pressure, left atrial size and diastolic dysfunction did not remain significant. When the significant univariate predictors were entered in a stepwise fashion, LVMI displaced diastolic dysfunction as a significant predictor of BNP.

3.4. Contribution of diastolic function and LV mass

In a subgroup analysis stratified to left ventricular hypertrophy, subjects presenting with sole diastolic abnormality showed no increase in BNP concentrations (mean 9.7 ± 1.7 pg/ml, median 5.5 pg/ml) in comparison to the control group. Individuals with sole diastolic dysfunction only displayed slightly increased BNP concentrations (mean 12.4 ± 2.3 pg/ml, median 7.6 pg/ml, $p = 0.056$ vs. control; Fig. 1). Of notice, these individuals already presented with a significantly elevated LVMI despite the absence of formal LVH (mean LVMI 97.6 ± 4.4 g/m² vs. control 76.9 ± 0.6 g/m², $p < 0.001$).

In contrast, the BNP concentration in individuals with diastolic abnormality and concomitant LVH was noticeably increased in relation to control (mean 14.4 ± 21.4 pg/ml, median 12.9 pg/ml, $p < 0.05$ vs. control and vs. diastolic

Table 3
ROC analysis

Condition	Cases (n)/ Prevalence (%)	ROC area (95% CI)	Sensitivity/ Specificity (%)	PPV/NPV (%)	BNP cutoff (pg/ml)
Diastolic abnormality (w/o DiaDys)	97/8.5	0.45 (0.39–0.51)	50.5/42.2	7.5/90.2	6.0
Diastolic dysfunction	38/3.3	0.63 (0.55–0.72)	60.5/54.5	4.3/97.6	8.7
Diastolic dysfunction w/ LVH	7/0.6	0.82 (0.71–0.93)	85.7/73.3	1.9/99.9	12.8
LVH	65/5.6	0.76 (0.70–0.82)	80.0/60.6	10.8/98.1	10.2
LV systolic dysfunction (EF<40%)	5/0.4	0.88 (0.72–1.0)	80.0/89.6	3.1/99.9	27

DiaDys denotes diastolic dysfunction.

LVH denotes left ventricular hypertrophy.

PPV denotes positive predictive value.

NPV denotes negative predictive value.

abnormality without LVH). The highest BNP concentrations were observed in individuals with diastolic dysfunction accompanied by LVH (mean 47.3 ± 21.4 pg/ml, median 14.2 pg/ml, $p < 0.05$ vs. control and vs. diastolic dysfunction without LVH). Of notice, these subjects had a markedly increased left ventricular mass index of 150.1 g/m^2 .

3.5. Predictive values

The predictive values of BNP for the diagnosis of sole LV diastolic abnormality and dysfunction and in combination with LVH were determined by ROC analysis in comparison to systolic dysfunction. The area under the ROC curve and the values for sensitivity and specificity, as well as the positive and negative predictive values for individually defined BNP cutoff levels are displayed in Table 3. Of those individuals with diastolic abnormality or dysfunction, subjects with diastolic dysfunction and concomitant LVH reached acceptable predictive values. The highest predictive values were observed in subjects with systolic LV dysfunction.

4. Discussion

The current study assesses the association between BNP and impaired diastolic function on a population-wide basis. Left ventricular diastolic dysfunction was associated with an overall increase in mean BNP of 110% as compared to control. Subgroup analyses demonstrated that this association was most pronounced in subjects with concomitant LV hypertrophy where median BNP was increased by 490%. This increase compares to a 790% increase in subjects with systolic LV dysfunction. Of notice, diastolic but not systolic LV dysfunction was displaced by LV mass index as a statistically significant and independent predictor of BNP concentrations when univariate predictors were entered into a multivariate model.

4.1. Effects of impaired diastolic function and LV hypertrophy on BNP

In our current study, impaired diastolic function was classified either as diastolic abnormality or diastolic dysfunction. Subjects were assigned to diastolic abnormality when abnormal Doppler recordings were obtained as proposed by the European study group on diastolic heart failure [8]. Diastolic dysfunction was assigned in the presence of a diastolic Doppler abnormality in combination with left atrial enlargement or diuretic therapy, which both suggest chronically elevated preload as a cardinal feature of diastolic dysfunction.

BNP was slightly elevated in subjects with isolated diastolic dysfunction. Of notice, LV mass was significantly elevated in these patients ($+27\%$ vs. control), despite the lack of formal LV hypertrophy. In contrast, BNP concen-

trations remained at the control level in the presence of an isolated diastolic abnormality. This finding suggests that impaired relaxation and/or compliance per se is not sufficient to trigger cardiac BNP secretion.

Contrary to that, markedly elevated BNP concentrations were observed in subjects with diastolic abnormality or dysfunction and concomitant LV hypertrophy. Since LV hypertrophy is a well known stimulus for cardiac BNP secretion [3,24–27] and is often associated with impaired diastolic function, it therefore appears that the observed elevations of BNP are predominantly caused by myocyte hypertrophy. The assumption that the observed increases in BNP with diastolic dysfunction are mostly related to increases in LV mass are also supported by our results from multivariate analysis. Here, diastolic dysfunction displayed a statistically significant correlation with BNP only in univariate analysis while it was displaced as a predictor of BNP by LV mass index in multivariate analysis. This is in contrast to LV systolic dysfunction, which remained a statistically significant and independent predictor of BNP even after adjustment for LV mass index. This latter association supports the hypothesis that unlike in diastolic dysfunction, BNP secretion in systolic dysfunction is not only dependent on myocardial mass but also on altered hemodynamics, particularly on increased wall stress. Indeed, experimental studies have demonstrated that cardiac BNP expression is closely associated with LV systolic wall stress in heart failure even when major changes in LV mass are lacking [28].

4.2. Predictive values of BNP for abnormal diastolic function

With respect to the diagnosis of impaired LV diastolic function in the general population, relatively low sensitivities and specificities were observed for BNP. In contrast, satisfactory predictive values were obtained for the diagnosis of more severe LV systolic dysfunction. Of notice, the predictive values for the diagnosis of LV diastolic abnormality as well as the diagnosis of LV diastolic dysfunction were lower as compared to those for the diagnosis of LV hypertrophy. This finding again indirectly indicates a superior importance of hypertrophic LV remodelling as compared to diastolic functional parameters and confirms and extends a previous study by Yamamoto et al. In this clinical study, diastolic function was measured invasively through assessment of the time constant of LV relaxation (τ) or LV enddiastolic filling pressure. Similarly to our study, the predictive values of BNP for the detection of LV hypertrophy exceeded those for the detection of diastolic dysfunction and the authors concluded that BNP best reflects LV structural abnormalities rather than abnormal loading conditions [23]. Of notice, the current predictive values increased slightly for the combination of LV diastolic dysfunction and hypertrophy. Regarding the high negative predictive values, LV diastolic dysfunction alone or in

combination with LV hypertrophy can be virtually excluded in the presence of a normal BNP result. Nevertheless, population-wide screening for diastolic dysfunction by BNP cannot be recommended because of its low prevalence and the low sensitivity of BNP to detect diastolic dysfunction. This observation and interpretation is consistent with a very recent publication by Redfield et al. [16], who also report a limited utility of BNP for the detection of diastolic dysfunction, with a high rate of confirmatory testing needed.

Our current results in mostly asymptomatic subjects differ from a recent clinical study which reported very satisfactory predictive values in a clinical sample of mostly symptomatic patients with LV diastolic dysfunction [13]. In this latter study, Lubien et al. found a sensitivity of 85% and a specificity of 83% for the detection of diastolic dysfunction by BNP as well as a correlation between BNP and the severity of diastolic dysfunction. However, 34% of all patients with diastolic dysfunction had a very severe pattern of diastolic dysfunction (restrictive-like filling). This observation demonstrates that in patients with signs and symptoms of heart failure, the BNP test may perform differently than as a screening tool in the general population. Of notice, patients with LV hypertrophy and concomitant left atrial enlargement were characterized by a similar increase in BNP as patients with diastolic dysfunction in the study by Lubien et al. This finding again supports the hypothesis that BNP reflects LV structural abnormalities rather than abnormal filling per se.

Our current results confirm our previous observation that LV systolic function and mass index are independent predictors of BNP [3] in a second and larger population. Our results regarding the predictive values of BNP for LV systolic dysfunction further confirm and extend previous population-based studies [3,6,29,30] which have also demonstrated a satisfactory sensitivity and specificity for more severe LV systolic dysfunction even in the population-based setting. However, due to the prevalence of this condition, which is even lower than that of diastolic dysfunction, and due to the low positive predictive value, population-wide screening for LV systolic dysfunction by BNP cannot be recommended based on the current results. Nevertheless, because of the high negative predictive value, LV systolic dysfunction, similarly to diastolic dysfunction, can be virtually excluded in the presence of a normal BNP result.

4.3. Limitations

Because of our population-based study design, only a limited number of diastolic function parameters could be obtained and more refined parameters such as pulmonary venous flow, tissue doppler velocity, and dynamic studies of mitral inflow (Valsalva) had to be omitted. Consequently, a pseudonormalized pattern of diastolic dysfunction could have been overlooked. However, since the more severe pseudonormalized pattern should be much

less prevalent in the general population than an abnormal E/A ratio, it is very unlikely that the predictive values for the detection of diastolic dysfunction would improve much. Also, a more precise classification of diastolic dysfunction would most likely not alter our central finding which is the observation that increased BNP in subjects with evidence of diastolic dysfunction appears to be predominantly associated with hypertrophic LV-remodelling. Nevertheless, future studies with a more precise classification of diastolic dysfunction are warranted. In addition it has been demonstrated that the lack of consistency of echocardiographic parameters in identifying the condition of diastolic dysfunction can be a limitation to studies concerning this diagnosis [31]. Another limitation may be that we used the Teichholz-method for the determination of ejection fraction. We may have thus overlooked regional or mildly impaired systolic dysfunction. However, the present and other population surveys are consistent with respect to a relatively low prevalence of systolic dysfunction such that a relevant misclassification appears unlikely.

4.4. Summary

In the general population, LV diastolic dysfunction is associated with a mild-to-moderate increase in BNP which is strongly related to hypertrophic LV-remodelling. In contrast to clinical diastolic heart failure, the predictive values of BNP are insufficient to recommend population-wide screening for LV diastolic dysfunction. Nevertheless, a normal BNP test virtually excludes LV diastolic dysfunction and/or LV hypertrophy.

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