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Diagnosing heart failure in centenarians

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5Max-Planck Odense Center on the Biodemography of Aging, University of Southern Denmark, Odense, Denmark

Abstract

Background As a consequence of the demographic development with increasing proportion of older people, the prevalence of heart failure (HF) is expected to rise with considerable economic and societal costs. However, knowledge on cardiac structure and function among population-based samples of the exceptional old is lacking. Methods Population-based study of all persons (no exclusion criteria) living in the western part of Denmark and turning 100 years in the year 2015. In-home face-to-face interviews were conducted, and echocardiography and blood sampling for plasma Brain Natriuretic Peptide (BNP) were offered to those who were able to give consent. Results Out of 303 eligible, 238 (79%) participated, of which 125 (53%) accepted echocardiography. Left ventricular (LV) dysfunction was present in 68 (54%) of the participants of whom less than half had HF symptoms. Pulmonary hypertension was present in 31 (42%) with no correlation to LV function. The well-known association between increased level of BNP and the prevalence of LV dysfunction could not be confirmed. Conclusions This in-home echocardiographic study shows that more than half of the participants had LV dysfunction, although mostly asymptomatic. There was no association between heart failure symptoms and LV dysfunction. Furthermore, BNP seems to have lost its biomarker potential to rule out heart failure in centenarians. Due to the latter, and the questionable symptom validity among centenarians, the current criteria to diagnose HF might be less valid in a centenarian population than in younger olds.


Keywords: Brain Natriuretic Peptide; Centenarian; Heart failure; In-home echocardiography; Left ventricular dysfunction

1 Introduction

In older people, cardiovascular diseases (CVD) are very common1,2 and they are also the leading cause of death.3 Particularly heart failure (HF) is common, probably reflecting that the aging heart is exposed to age-related alterations, e.g., physiological aging of the cardiomyocytes leading to cardiac dysfunction.4,5

Although it is widely accepted that HF is associated with functional decline and mortality,6,7 the diagnosis of HF in older people may be a challenge as it relies on the combination on characteristic symptoms and objective markers of cardiac function.8 Especially, symptoms in older people can be ambiguous and/or masked by other conditions, e.g., lung diseases or physical deconditioning, or may even be misinterpreted as aging-related physiological changes. In addition, the echocardiographic evaluation may be challenging as only half of patients with heart failure have reduced left ventricular (LV) ejection fraction (EF).9-11 In the remaining, the diagnosis of HF with preserved EF depends on the demonstration of LV structural changes with increased LV filling pressures, either by echocardiography or elevated natriuretic peptides. However, the use of these markers has mainly been validated among younger persons and may not apply to the oldest-old.

The use of natriuretic peptides to detect HF in people ≥75 years has recently been questioned,12 as potential and commonly occurring confounding variables should be taken into account when interpreting them, e.g., high age and female gender13,14 renal function,15 and hemoglobin.16 The use of echocardiographic variables may also provide some challenges as changes in LV relaxation may depend on age rather than disease per se.
The study of centenarians may provide insights into the association between age and LV function; accordingly, various studies have been conducted on this topic. However, most are limited by the lack of comprehensive echocardiographic data and only include patients able to attend healthcare clinics.\cite{17-20} The latter may lead to underestimation of HF rates due to selection bias. Indeed, recent in-home studies among ≥85-year-old participants demonstrated that significant systolic and diastolic dysfunction was more common than previously suggested in these age groups\cite{22,23} (supplemental material, Table 1S).

In the United States, it is estimated that the prevalence of HF will increase rapidly during the next centuries.\cite{24} As a consequence of the demographic development with increasing number and proportion of older people\cite{25} as well as improved survival with HF,\cite{26,27} the prevalence of HF is expected to rise further with considerable economic and societal costs.\cite{28,29} Thus, investigating HF and its precursor, LV dysfunction, is found to be highly relevant. The aim of this study was therefore to describe LV structure and function in an unselected population of 100-year olds based on in-home echocardiography and to correlate systolic and diastolic function to the natriuretic peptides and to heart failure symptoms.

2 Methods

2.1 Study population

Eligible centenarians were identified through the Danish Civil Registration System (CRS), which keeps a record of all people living in Denmark.\cite{30} Included were persons born between January 1, 1915 and December 31, 1915, alive on their 100th birthday, and living in the western part of Denmark, i.e., west of the Great Belt. A description has been reported in detail previously.\cite{31} There were no exclusion criteria. If a centenarian would or could not participate in-person, proxy interviews were allowed. An informed consent was signed by each participant or proxy before initiating the interview. The survey received approval from the Committee on Health Research Ethics (trial number S-20140099) and the Danish Data Protection Agency (trial number 2016-41-4552). The study (including all examinations) was conducted by a single survey team consisting of a medical doctor (SHR) and a research nurse. All visits and clinical examinations were carried out in the participants’ homes, including nursing homes, consecutively as they turned 100 years.

2.2 Echocardiography

A standardized transthoracic echocardiography (TTE) using the Philips CX-50 portable echocardiograph was carried out according to Danish guidelines,\cite{32} which conform to the guidelines of the American Society of Echocardiography.\cite{8} Systolic function was determined by left ventricular ejection fraction (LVEF) using wall motion index (WMI) score and/or by using eyeballing, whenever either method was possible. A cut-off point of less than 50% was set for LVEF to define systolic dysfunction.

The 2016 guidelines were used to assess the diastolic properties, e.g., mitral inflow (E-wave), lateral and septal mitral valve annulus (e’), and were based on the following four parameters presented with cut-off values. Diastolic dysfunction was present if more than two of the parameters were abnormal: (1) lateral e’ < 10 cm/sec and/or septal e’ < 7 cm/sec; (2) average E/e’ > 14 (or E/e’ lateral > 13, E/e’ septal > 15); (3) left atrial volume (LA), (indexed by body surface area) > 34 mL/m2; and (4) peak tricuspid velocity > 280 cm/s.\cite{33} Additional measurements included cardiac output,\cite{34} LV hypertrophy (evaluated by indexed LV mass (LVMi))\cite{35} and pulmonary hypertension, the latter defined as pulmonary artery systolic pressure (PASP) ≥ 40 mmHg.\cite{36} In addition information on the valves was recorded.

Additional information on e.g., LV hypertrophy, pulmonary hypertension, and the valves can be found in the supplemental material. All echocardiograms were evaluated by SHR and a blinded highly experienced specialist consultant in cardiology (SG).

2.3 Brain natriuretic peptide

Blood samples were collected by venipuncture in connection with the in-home visit. Hemoglobin was analyzed on fresh blood after the interview, while brain natriuretic peptide (BNP) and creatinine were analyzed collectively from frozen plasma using Architect equipment (Abbott, Illinois, USA) with dedicated reagents from the manufacturer. BNP measurements were performed with a two-step sandwich immunoassay using monoclonal antibodies specific for human BNP with detection limits 10-5000 pg/mL. Threshold concentrations of 35 pg/mL and 100 pg/mL were applied according to guidelines.\cite{8}

2.4 Heart failure symptoms

Symptoms were collected through self-report according to the New York Heart Association (NYHA) classification of dyspnoea divided by severity of symptoms into the four groups; NYHA I-IV.\cite{37}

2.5 Statistical analyzes

To analyze data, the STATA statistical software package
14.2 was used. Data was presented with $P$-values and 95% CI. A $P$-value < 0.05 was considered statistically significant. Fisher’s exact test was used with respect to categorical variables, the unpaired $t$-test was used with respect to normally distributed numeric data and in non-normally distributed data the non-parametric Wilcoxon rank sum test was used. Assessments of normality were evaluated by quantile-quantile plots and histograms, and in testing for homogeneity of variance the $F$-test was used. The normally distributed data were presented with mean and standard deviation (SD). The median and the interquartile range (IQR), [25th, 75th percentile] were used for non-normally distributed data. A binomial regression model was chosen to estimate the association of BNP with the risk of LV dysfunction (systolic and diastolic dysfunction) to allow for confounder adjustment. The latter included that BNP was dichotomized into < 35 / $\geq$ 35 (“BNP 35”) pg/mL and into < 100 / $\geq$ 100 (“BNP 100”) pg/mL, respectively.

3 Results

Out of 303 eligible persons, 238 participated (79%) of whom 83% were women (Figure 1). Participants ($n = 238$) and non-participants ($n = 65$) did not differ with respect to gender, but differed regarding to the type of housing, e.g., a higher proportion of non-participants lived in their own homes and correspondingly fewer in nursing homes.[38] All visits were conducted within three months from the participant’s 100th birthday. Direct face-to-face interviews rea-
ched 185 (78%) of all interviews, while 53 participants were interviewed through a proxy (proxy interview), mainly due to severe cognitive impairment. The latter group was not considered able to give informed consent to having an echocardiographic assessment. Of the 185 eligible for echocardiographic assessment, 125 (68%) accepted, of whom the majority (n = 98) were women. The “echo group” was more likely to be independent in basic activities of daily living (BADL) and to receive cardiovascular medication than the “non-echo group” (supplemental material). Thus, the “echo group” appeared to be healthier in BADL than the “non-echo group”.

### 3.1 Left ventricular function and structure

The median LVEF was 55% (IQR = 50%–60%) with significantly lower median LVEF among men than women (men: median LVEF = 50%, IQR = 45%–55% vs. women: median LVEF 55%, IQR = 50%–60%, P = 0.002).

LVEF ≤ 50% was a rare finding, occurring only in 15 participants (12%) and only 2 demonstrated severe reduced LV function (LVEF ≤ 30%). A reduced systolic function was significantly more frequent among men than women (26% vs. 8%, P = 0.019). In patients with LVEF ≥ 50%, diastolic dysfunction was found in 53 (42%) participants, with grade two diastolic function being the most prevalent pattern (Figure 1). Thus, 68 (54%) had LV dysfunction (systolic or diastolic dysfunction) with no statistically significant gender differences (Table 1). There was no association between LV function and comorbidities as demonstrated in Table 1. Compared to those with normal LV function, participants with LV dysfunction had larger end-systolic LV diameter (LVIDs), larger LA volume, higher E/e' (septal, lateral, average) and lower e' (Table 2).

Pulmonary hypertension was present in 31 (42%) of the participants with no difference between genders. The proportion of pulmonary hypertension in those with and without LV dysfunction was almost equal, being 41% and 44%, respectively (P = 0.82). There was no association between pulmonary hypertension and E/e' (lateral); the median E/e' was 13 in both those with and without pulmonary hypertension, and with similar IQR (not shown). Furthermore, there was no correlation between pulmonary hypertension and BNP; median BNP (and IQR) were similar being 83 pg/mL and 81 pg/mL in those with and without pulmonary hypertension, respectively.

Overall, 40 (33%) of the participants had LV hypertrophy, with a higher prevalence in those with LV dysfunction (38%) compared to those with normal LV function (25%), although this difference was not significant (P = 0.18). Of these, 12 (48%) had pulmonary hypertension, which did not

### Table 1. Characteristics in centenarians of the 1915-West birth cohort study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>LV dysfunction (n = 68)</th>
<th>Normal LV function (n = 57)</th>
<th>Total (n = 125)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male participation)</td>
<td>16 (24%)</td>
<td>11 (19%)</td>
<td>27 (22%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>100.1 (0.4–1.2)</td>
<td>100.1 (0.5–1.0)</td>
<td>100.1 (0.5–1.1)</td>
<td>0.81</td>
</tr>
<tr>
<td>1 Hypertension</td>
<td>44 (67%)</td>
<td>32 (58%)</td>
<td>76 (63%)</td>
<td>0.35</td>
</tr>
<tr>
<td>2 Atrial fibrillation/flutter</td>
<td>16 (24%)</td>
<td>10 (18%)</td>
<td>26 (21%)</td>
<td>0.51</td>
</tr>
<tr>
<td>3 Heart failure</td>
<td>4 (9%)</td>
<td>4 (11%)</td>
<td>8 (10%)</td>
<td>1.00</td>
</tr>
<tr>
<td>4 Angina pectoris</td>
<td>3 (7%)</td>
<td>4 (11%)</td>
<td>7 (9%)</td>
<td>0.41</td>
</tr>
<tr>
<td>5 Myocardial infarction</td>
<td>3 (7%)</td>
<td>2 (5%)</td>
<td>5 (6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>6 Stroke</td>
<td>6 (13%)</td>
<td>5 (13%)</td>
<td>7 (9%)</td>
<td>1.00</td>
</tr>
<tr>
<td>7 Chronic obstructive pulmonary disease</td>
<td>2 (5%)</td>
<td>2 (5%)</td>
<td>4 (5%)</td>
<td>1.00</td>
</tr>
<tr>
<td>8 Diabetes mellitus</td>
<td>7 (15%)</td>
<td>1 (3%)</td>
<td>8 (10%)</td>
<td>0.07</td>
</tr>
<tr>
<td>9 Obesity</td>
<td>4 (6%)</td>
<td>5 (9%)</td>
<td>9 (7%)</td>
<td>0.73</td>
</tr>
<tr>
<td>10 Cardiovascular medication</td>
<td>56 (82%)</td>
<td>49 (86%)</td>
<td>105 (84%)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Data are presented as n (%) except for age which is shown as median and IQR (25th–75th percentile) in months after the 100th birthday. *Blood pressure was measured in n = 121/125 (97%) during the visits. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. †Information on atrial fibrillation/flutter was obtained from the recorded ECG in n = 118 (94%) during the visits. ‡Participants who currently or previously were diagnosed with the disease (information obtained by self-report). Only data on n = 79–84 (63%–67%). §Obesity = body mass index ≥ 30 g/m² were obtained in all 125. Similar results if also including overweight (BMI ≥ 25 g/m²). ††Cardiovascular medications were obtained in all 125, and divided into eight groups by the ATC codes; (1) diuretics (loop, thiazide, and spironolactone), (2) beta blockers (3) calcium antagonists, (4) angiotensin converting enzyme inhibitor/angiotensin receptor blocker, (5) digoxin, (6) nitrates, (7) statins, and (8) antithrombotic treatment (oral anticoagulant and antiplatelet therapy). BMI: body mass index; IQR: interquartile range; LV: left ventricular.
Moderate to severe aortic stenosis was present in 35 (30%) of the participants. Thus, moderate to severe valve pathology of either the aortic or the tricuspid valves, respectively. However, a significantly higher proportion with moderate to severe mitral valve pathology had LV dysfunction than those with normal LV function and moderate to severe mitral valve pathology, $P = 0.001$.

### Table 2. LV function and structure in centenarians of the Danish 1915-West birth cohort.

<table>
<thead>
<tr>
<th>Variables</th>
<th>LV dysfunction $n = 68$</th>
<th>Normal LV function $n = 57$</th>
<th>Total $n = 125$</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV function, $n = 125$</td>
<td>LVEF</td>
<td>55% (50%–60%)</td>
<td>55% (50%–60%)</td>
<td>55% (50–60%)</td>
</tr>
<tr>
<td>LV dimensions, $n = 117–125$</td>
<td>IVSd, mm</td>
<td>11 ± 2</td>
<td>1 ± 2</td>
<td>11 ± 2</td>
</tr>
<tr>
<td></td>
<td>LVIDd, mm</td>
<td>44 ± 7</td>
<td>42 ± 6</td>
<td>43 ± 7</td>
</tr>
<tr>
<td></td>
<td>LVIDs, mm</td>
<td>30 ± 7</td>
<td>28 ± 7</td>
<td>29 ± 7</td>
</tr>
<tr>
<td></td>
<td>LVPWd, mm</td>
<td>10 ± 2</td>
<td>9 ± 2</td>
<td>9 ± 2</td>
</tr>
<tr>
<td>CO, $n = 108$</td>
<td>CO, min/L</td>
<td>3.6 ± 1.0</td>
<td>3.6 ± 1.2</td>
<td>3.6 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>CO/BSA, L/min/m²</td>
<td>2.3 ± 0.7</td>
<td>2.3 ± 0.8</td>
<td>2.3 ± 0.8</td>
</tr>
<tr>
<td>Diastolic measures, $n = 100–117$:</td>
<td>LA-volume/BSA, mL/m²</td>
<td>44 (38–55)</td>
<td>32 (25–53)</td>
<td>42 (32–54)</td>
</tr>
<tr>
<td>all variables except</td>
<td>E, cm/s</td>
<td>80 (6–105)</td>
<td>70 (58–91)</td>
<td>77 (64–100)</td>
</tr>
<tr>
<td>$n = 68–74$: Septal e', E/e'(septal)</td>
<td>A, cm/s</td>
<td>104 (94–121)</td>
<td>97 (80–107)</td>
<td>100 (89–116)</td>
</tr>
<tr>
<td>and E/e'(average)]</td>
<td>Lateral e', cm/s</td>
<td>6.1 (4.8–7.5)</td>
<td>6.7 (5.3–8.4)</td>
<td>6.3 (5.1–7.7)</td>
</tr>
<tr>
<td>E/e' (lateral)</td>
<td>13.5 (10.5–17.8)</td>
<td>11.2 (8.6–13.6)</td>
<td>12.7 (9.3–15.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>E/e'(septal)</td>
<td>17.6 (14.6–23.1)</td>
<td>14.7 (11.8–17.7)</td>
<td>16.8 (13.3–20.3)</td>
<td>0.006</td>
</tr>
<tr>
<td>E/e'(average)</td>
<td>15.6 (13.3–22.5)</td>
<td>14.0 (11.7–16.4)</td>
<td>14.5 (12.7–19.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>TRVmax, cm/s</td>
<td>272 (235–310)</td>
<td>257 (233–309)</td>
<td>259 (233–309)</td>
<td>0.49</td>
</tr>
<tr>
<td>Pulmonary, $n = 73$</td>
<td>PASP, mmHg</td>
<td>38 (30–43)</td>
<td>36 (27–48)</td>
<td>38 (27–46)</td>
</tr>
<tr>
<td>LV mass, $n = 123–124$</td>
<td>LVMi (indexed by BSA), g/m²</td>
<td>93 (79–109)</td>
<td>81 (68–101)</td>
<td>87 (69–107)</td>
</tr>
<tr>
<td></td>
<td>Relative wall thickness</td>
<td>0.42 (0.35–0.52)</td>
<td>0.45 (0.37–0.53)</td>
<td>0.44 (0.37–0.52)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or median (IQR). $P$-values were obtained by the unpaired $t$-test and Wilcoxon rank sum test, respectively. BSA: body surface area; CO: cardiac output; IQR: interquartile range; LV: left ventricular; LVIDd: left ventricular internal diameter end diastole; LVIDs: LV ejection fraction; LVIDs: left ventricular internal diameter end systole; IVSd: Interventricular septal end diastole; LVPWd: left ventricular posterior wall end diastole; PASP: pulmonary artery systolic pressure.

Differ from those without LV hypertrophy and pulmonary hypertension 19 (40%), (missing data, $n = 15$). Men had a significantly higher LVMi compared to women (men: median LVMi 99, IQR = 84–112, women: median LVMi 84, IQR = 67–103, $P = 0.03$).

### 3.2 Valve pathology obtained by echocardiography

No prosthetic valves were found when evaluating the echocardiograms. The valve pathology was shown in Table 2S (supplemental material). Moderate regurgitation was present in 1 (1%) of the aortic, 3 (2.5%) of the mitral, and 10 (9%) of the tricuspid valves, respectively. None of the participants had severe regurgitation in either valve. Moderate to severe calcification was found in 36 (29%) and 29 (23%) of the aortic and mitral valves including annulus, respectively. Moderate to severe aortic stenosis was present in 35 (30%) of the participants. Thus, moderate to severe valve pathology (regurgitation and/or calcification and/or stenosis) was found in 69 (55%, 95% CI: 46%–64%) of the participants. There was no statistically significant difference between LV dysfunction and having moderate to severe valve pathology (the combined aortic, mitral, and tricuspid valves, $n = 69$). Nor were there any differences between LV dysfunction and moderate to severe valve pathology of either the aortic or the tricuspid valves, respectively. However, a significantly higher proportion with moderate to severe mitral valve pathology had LV dysfunction than those with normal LV function and moderate to severe mitral valve pathology, $P = 0.001$.

### 3.3 Brain natriuretic peptide

Overall, the median of BNP was 75 pg/mL (IQR = 54–110) with no differences between genders (men; median 81 pg/mL, IQR = 51–112 and women; median 74 pg/mL, IQR = 54–108), $P = 0.87$. There was a non-significantly lower median BNP (68 pg/mL, IQR = 52–98) in those with LV dysfunction than in participants with normal LV function (median 88 pg/mL, IQR = 58–127), $P = 0.12$. In addition, the division of BNP into the groups $< 55$ pg/mL, $55–99$ pg/mL, and $\geq 100$ pg/mL showed a similar E/e’ (lateral) in these three groups being 14, 13, and 12, respectively. Furthermore, the distribution of the three BNP groups by NYHA class and LV function, respectively, showed no correlations (Figures 2 & 3).
A BNP value above the suggested cut-off values of respectively 35 pg/mL and 100 pg/mL\cite{8} was negatively, but non-significantly, associated with LV dysfunction, i.e., there were 17% fewer centenarians with LV dysfunction among those with BNP ≥ 100 pg/mL compared to those with BNP < 100 pg/mL. Thus, a higher proportion with normal LV function had a BNP ≥ 100 pg/mL compared to those with LV dysfunction. Similarly, there were 8% fewer centenarians with LV dysfunction among those with BNP ≥ 35 pg/mL compared to BNP < 35 pg/mL (Table 3). Even after adjusting for gender, hemoglobin, and creatinine, the results were similar.

The negative predictive values of BNP with cut-off value of 100 and 35 pg/mL were 39% and 36%, respectively. Overall, 66 (63%) participants were treated with at least one type of diuretics (loop, thiazide, or spironolactone). Participants on diuretic treatment had non-significantly higher median BNP (median 88 pg/mL, IQR = 58–125) than those not treated with diuretics (median BNP 77 pg/mL, IQR = 41–110), \( P = 0.51 \). In addition, there was no association between treatment with diuretics and having LV-dysfunction; a higher proportion with normal LV function was treated with diuretics (69%, 95% CI: 54%–81%) compared to those with LV dysfunction (57%, 95% CI: 43%–71%), \( P = 0.23 \).

### 3.4 Heart failure symptoms

Overall, 44 (37%) reported symptoms of dyspnoea (NYHA II-IV) of whom 17%, 12%, and 8% were classified in NYHA II, III, and IV, respectively. The NYHA distribution of the participants by LV function is illustrated in Figure 4. The proportional distribution in the four NYHA groups was similar in participants with LV dysfunction and normal LV function, respectively. Furthermore, there was no association between having BNP above threshold and the NYHA distribution (Figure 2).

### 4 Discussion

This is the first in-home echocardiography study performed in centenarians. It offers insights into the prevalence

![Figure 2. The distribution of BNP by NYHA groups I-IV.](image)

**Figure 2.** The distribution of BNP by NYHA groups I-IV. BNP: brain natriuretic peptide; NYHA: New York Heart Association classification of heart failure symptoms.

![Figure 3. The distribution of BNP by left ventricular function.](image)

**Figure 3.** The distribution of BNP by left ventricular function. BNP: brain natriuretic peptide; LVEF: left ventricular ejection fraction.

<table>
<thead>
<tr>
<th>BNP ≥ threshold vs. BNP &lt; threshold</th>
<th>PD</th>
<th>95% CI</th>
<th>( P )-value</th>
<th>( n )</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP (ref: &lt; threshold)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>-0.17</td>
<td>-0.38–0.04</td>
<td>0.11</td>
<td>100</td>
</tr>
<tr>
<td>Adjusted for sex</td>
<td>-0.17</td>
<td>-0.38–0.04</td>
<td>0.11</td>
<td>100</td>
</tr>
<tr>
<td>Adjusted for sex, hemoglobin, and creatinine</td>
<td>-0.16</td>
<td>-0.38–0.05</td>
<td>0.11</td>
<td>98</td>
</tr>
<tr>
<td>BNP ≥ 100 pg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>-0.08</td>
<td>-0.36–0.19</td>
<td>0.54</td>
<td>100</td>
</tr>
<tr>
<td>Adjusted for sex</td>
<td>-0.08</td>
<td>-0.36–0.19</td>
<td>0.54</td>
<td>100</td>
</tr>
<tr>
<td>Adjusted for sex, hemoglobin, and creatinine</td>
<td>-0.13</td>
<td>-0.40–0.14</td>
<td>0.36</td>
<td>98</td>
</tr>
</tbody>
</table>

\( \text{PD}: \) prevalence difference; \( \text{CI}: \) confidence interval; \( \text{participants, n}: \) number of participants.

*The number of participants varied due to missing values. BNP: brain natriuretic peptide; CI: confidence interval; PD: prevalence difference.

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4.1 Left Ventricular function and structure

The prevalence of systolic dysfunction was only 12% in our study, and it much lower compared to the two in-home studies on octogenarians where systolic dysfunction was found to be 44% and 32%, respectively.[22,23] The lower prevalence among the Danish centenarians may be explained by a selection towards the healthier, i.e., a survival bias, as those with systolic dysfunction would die before attaining the age of 100 years. Yet, the classification methods differed between the studies, which might also partly explain the different prevalence of systolic dysfunction.

The prevalence of diastolic dysfunction was 42% in the present study compared to 32% in the Israeli study[22] and 88% in the Newcastle study.[23] However, these two studies reported the prevalence of diastolic dysfunction irrespective of LVEF. In the Newcastle study, looking only at those with normal LVEF, like in the present study, the prevalence of diastolic dysfunction decreased from 88% to 61% (the majority having mild diastolic dysfunction). Relevant data from the Israeli study could not be retrieved for comparison, but the study population seems to be more selected as it did not include nursing home residents, which may explain the lower prevalence of diastolic dysfunction. Furthermore, classification methods (criteria) for assessing diastolic function also differed. In the Newcastle study three criteria were used compared to one criterion in the Israeli study and four criteria in the current 1915-West cohort study (supplemental material, Table 1S). Only one of these criteria was similar between these three in-home studies, namely measurement of mitral inflow (E/e'). To define normal diastolic function by mitral inflow E/e’ < 10 (lateral), E/e’ ≤ 13 (average), and E/e’ ≤ 14 (average) were applied in the Newcastle, Israeli, and the 1915-West study, respectively. Hence, when looking at this one criterion, a potentially higher prevalence of diastolic dysfunction in the Newcastle study would be expected compared to the two other studies.

4.2 Brain natriuretic peptide

The cut-off levels for BNP to rule out heart failure have been debated previously.[42] European guidelines have suggested threshold concentrations to be 100 pg/mL and 35 pg/mL.[8] However, the guidelines do not differentiate by age and gender. In particular, age has been shown to influence BNP levels with higher BNP concentrations at increasing age.[13,14] The negative predictive values in the 1915-West study were much lower than the previously reported negative predictive values > 97% in populations > 45 years old.[43] Thus, the well-known high negative predictive
value to rule out HF could not be confirmed when threshold values of either 100 pg/mL or 35 pg/mL were applied. An association between high BNP values and LV dysfunction could not be confirmed in the present study, which was in line with results from another Danish centenarian study.[44] These results entail that BNP might not be a useful screening tool to rule out HF in centenarians. A loss of biomarker potential has also been shown for risk factors at older age, e.g., smoking and obesity,[45] cancer and myocardial infarction,[46] and low-density lipoprotein cholesterol.[47]

The BNP level may have been lower in participants with LV dysfunction due to treatment with diuretics, thus lowering the filling pressure leading to a reduced BNP release. However, this could not be demonstrated as the median BNP was higher among participants treated with diuretics than those not receiving diuretic treatment. Whether this indicates a true lack of association, or is a reflection of severity of LV dysfunction remains unclear; those treated with diuretics might have a more severe cardiac condition and might also be subject to under-treatment. Furthermore, the prescription indications were unclear and might have been due to non-cardiac conditions. Still, there was a higher proportion with normal LV function in treatment with diuretics vs. those treated with diuretics and having a normal LV function.

4.3 Heart failure

Reduced LVEF and preserved LVEF with diastolic dysfunction constituted the two types of heart failure: HF with reduced EF and HF with preserved EF. The diagnosis of HF includes present or previous symptoms of HF at rest or during exercise.[8,48] Still, disentangling the difference between HF and LV dysfunction can be very difficult in older people due to masked symptomatology, aging physiological changes in the columna and lungs, and concomitant diseases.[49,50] In the present 1915-West study, the majority of the participants with LV dysfunction were asymptomatic. In addition, this information on symptomatology (dyspnea) was obtained through self-report, which may cause an information bias as symptoms by self-reporting in centenarians have been shown to be under-reported.[51] Furthermore, some centenarians are less physically active and more sedentary, and may therefore never reach a sensation of dyspnea, which otherwise would have been reached if physically more actively. Thus, the symptom validity may be considered questionable in centenarians. Distinguishing between the grades of diastolic dysfunction may also be taken into account when defining HF, as mild diastolic dysfunction (Grade 1) can be considered a part of the normal aging of the heart.[23] The prognostic importance of moderate to severe diastolic function has been shown but it remains less clear with respect to mild diastolic dysfunction.[52] Only three participants were classified with grade 1 diastolic dysfunction in the 1915-West study, and excluding these resulted in apparent LV dysfunction in 65 (52%) irrespective of symptoms; 15 with systolic dysfunction and 50 with diastolic dysfunction. This prevalence of LV dysfunction might be considered as a "best case scenario" as diagnosing diastolic dysfunction resulted in 12 inconclusive who were excluded from the calculations.

All in all, LV dysfunction is a common finding in centenarians, with no association between LV dysfunction and heart failure symptoms, or between LV dysfunction and BNP. Estimating LV dysfunction, namely diastolic dysfunction, can be difficult in this population due to the challenges of disentangling disease-related diastolic dysfunction from aging per se. The assessment of diastolic dysfunction is still subject to debate, and many different criteria have been used. Furthermore, HF with preserved EF may be considered a complex geriatric syndrome affecting both cardiac and non-cardiac organs rather than solely a cardiac syndrome.[53] Also, it can be difficult to assess heart failure symptoms as already discussed. Although BNP was interpreted both with and without confounder adjustment, other age-related factors may also influence the release of BNP to help explain the inverse relationship between BNP and LV function that was demonstrated in this study.

Thus, the current criteria to diagnose HF might be less valid in a centenarian population than in younger old persons, due to the challenges in assessing LV dysfunction, the questionable symptom validity, and the lack of BNP association with LV dysfunction. Hence, the true prevalence of HF might therefore be underestimated.

4.4 Limitations

Despite our best intention to conduct a study in an unselected population, echocardiography was only carried out in 53% (125/238) of all the participants. However, due to ethical considerations, only 78% (n = 185) of the study population were eligible for clinical examinations, and more than two-thirds (68%, n = 125) of the eligible participants underwent an echocardiography.

Analyzes showed that the “echo group” was more independent in BADL compared to the “non-echo group” causing a potential healthy selection bias in those who underwent echocardiography. It is possible that echocardiographic pathologies would be more prevalent in the more BADL...
dependent “non-echo group”. If true, the results from the “echo group” represent a best-case scenario of the prevalence of cardiac function in centenarians. Nevertheless, in the present study, the high overall participation rate (79%) and register-based identification minimize this potential healthy selection bias, which otherwise can be observed in studies with low participation rates. Furthermore, the study is strengthened by the methodology, i.e., population-based, no selection criteria, and conducting in-home face-to-face interviews including nursing home residents.

The higher use of cardiac medication in those who underwent echocardiography compared to those with no cardiac assessment may be explained by a relatively better health in the “echo group” and thus these participants were subject to more aggressive treatment.

To carry out standard echocardiography normally requires a proper examination bed with dimmed light in a clinical setting in order to optimize the positioning of the participants. The in-home environment was not always optimal, as the examinations were carried out on couches or in soft beds. This may have hampered the optimal positioning of the participants, thereby affecting the results due to a poorer echocardiographic image quality. This has resulted in several examinations with one or more inconclusive measurements and thus missing values. However, our results show that it is feasible to do in-home echocardiographic assessment, thereby yielding a higher participation rate compared to an examination in a clinical setting, which would likely be declined by many of the centenarians for various reasons. Furthermore, the present study is the largest echocardiographic study on centenarians, and also the first study to carry out an in-home echocardiography in a centenarian population. The results of this sample may therefore be more representative for the general centenarian population than those found in the previous centenarian echocardiographic studies.

4.5 Conclusions

This in-home echocardiographic study shows that more than half of a centenarian population has LV dysfunction when applying the most recent guidelines. However, most centenarians were asymptomatic, and we did not find any association between LV dysfunction and NYHA functional class. Furthermore, BNP seems to have lost its biomarker potential to rule out HF in centenarians. Due to the latter, the challenges in assessing LV dysfunction, and the questionable symptom validity among centenarians, the current criteria to diagnose heart failure might be less valid in a centenarian population than in younger olds.

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