Tissue Doppler echocardiography for the diagnosis of new-onset heart failure with normal ejection fraction: Influence of serum protein concentration on clinical interpretation in elderly patients

Échographie doppler tissulaire dans le diagnostic des insuffisances cardiaques récentes avec fraction d’éjection ventriculaire gauche normale : influence de la concentration de la protéine sérique dans l’interprétation chez des patients âgés

Stéphane Arques, Pierre Ambrosi, Emmanuel Roux, Pascal Sbragia, Richard Gelisse, Bertrand Pieri, Roger Luccioni

Department of Cardiology, Aubagne Hospital, avenue des Sœurs-Gastine, 13400 Aubagne, France
La Timone University of Medicine, Marseille, France

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Summary
Introduction. — According to Starling’s law, low serum colloid osmotic pressure related to hypoproteinaemia is likely to modulate the pulmonary capillary hydrostatic pressure threshold of pulmonary oedema formation. We therefore examined the clinical relevance of bedside tissue Doppler echocardiography in the emergency diagnosis of new-onset heart failure with normal ejection fraction (HFnlEF) according to serum protein concentration.

Methods. — A total of 105 consecutive elderly patients presenting with acute severe dyspnoea were prospectively enrolled. B-type natriuretic peptide (BNP) concentration and spectral tissue Doppler-derived septal E/E' ratio were obtained at presentation. Serum protein concentration was measured immediately after clinical stabilization, with a value of less than 6 g/dL defining hypoproteinaemia.

Results. — The diagnostic performance of E/E' was excellent in normoproteinaemic patients (n=71; area under the receiver-operating characteristic [ROC] curve 0.97; p<0.001) and...
Introduction

Acute shortness of breath is a frequent cause of emergency hospital admission in developed countries. Rapid and accurate diagnosis of acute congestive heart failure (HF) is essential to target therapy at presentation, especially for elderly patients with severe symptoms at high risk for adverse hospital outcome [1,2].

The clinical diagnosis of acute HF syndromes is challenging in the emergency care setting [3] and usually requires additional diagnostic methods such as B-type natriuretic peptide (BNP) and bedside Doppler echocardiography [4,5]. In this respect, noninvasive evidence of a left ventricular (LV) ejection fraction less than 40–50% readily identifies congestive HF [4] and spectral tissue Doppler echocardiography, a widespread noninvasive technique for assessing LV diastolic pressures in daily practice, provides incremental diagnostic information in patients with preserved LV systolic function [4]. However, there is experimental [6,7] and clinical [8,9] evidence that low serum colloid osmotic pressure related to hypoproteinaemia plays a role by favouring pulmonary congestion at a less increased pulmonary capillary pressure. Accordingly, we hypothesized that serum protein concentration is likely to influence the clinical interpretation of tissue Doppler results in elderly patients hospitalized for suspected HF at high risk for presenting with such a comorbidity. The aim of the present study was to examine the clinical relevance of bedside tissue Doppler echocardiography in the emergency diagnosis of new-onset HF with normal ejection fraction (HFnEF) in elderly patients presenting with acute severe dyspnoea according to serum protein concentration.

MOTS-CLÉS
Doppler tissulaire ; Insuffisance cardiaque à fraction d’éjection ventriculaire gauche normale ; Âgés ; Peptides natriurétiques
Methods

Patients

A total of 105 consecutive elderly patients who referred to our institution for acute severe dyspnea (NYHA class IV) were prospectively enrolled after informed consent had been obtained. Exclusion criteria were as follows:

- age less than 65 years (n = 23);
- history of congestive HF (n = 63);
- LV ejection fraction less than 50% (n = 27);
- arrhythmias other than permanent atrial fibrillation (n = 6);
- paced-rhythm (n = 4);
- left bundle branch block (n = 3);
- moderate to severe left-sided valve disease (n = 6);
- unstable angina and acute myocardial infarction with ST elevation (n = 5).

A blood sample was taken at presentation to measure BNP concentration. The patients underwent bedside Doppler echocardiography, at presentation at the time of therapy initiation.

At discharge, two cardiologists and one chest physician, both blinded to the results of BNP and tissue Doppler echocardiography, established either a HFnlEF or a non-cardiac cause as the primary origin of acute shortness of breath, according to the data collected at admission and during hospitalization, which included the clinical response to appropriate medical therapy. In particular, complete relief of symptoms under intravenous diuretics with or without nitrates was a necessary condition for the diagnosis of HFnlEF at discharge. Data collected at presentation by a senior emergency physician were analysed retrospectively by a cardiologist to calculate the Boston score for congestive HF [10]. This score is based on symptoms (0–4 points), physical examination (0–4) and chest radiography (0–4) [10]. Since all of the patients presented with dyspnoea at rest (4 points), their score ranged from 4 to 12.

Laboratory measurements

Plasma BNP concentration was measured at our institution’s laboratory with a Triage Meter Plus® system, a point-of-care test based on fluorescence immunoassay (Biosite Inc., San Diego, California; range: 5–5000 pg/mL). The middle range was defined as concentrations ranging from 100 to 400 pg/mL [11]. Serum protein concentration was measured using the reflectometry method, with a Vitros 950® system (Johnson & Johnson Clinical Diagnostics Inc., New York, USA), once clinical stabilization had been achieved (one to two days after admission) to avoid either haemococoncentration or volume overload at the acute phase [8]. Hypoproteinaemia was defined as a value of less than 6 g/dL. Serum sodium, creatinine and haematocrit were measured from the same blood sample after clinical stabilization.

Bedside tissue Doppler echocardiography

An Aloka SSD 5500 PHD® ultrasound system (Aloka Co. Ltd., Tokyo, Japan) with a 2.5 MHz harmonic transducer was used to perform all Doppler echocardiography studies at the bedside by an experienced cardiologist who was blinded to the data. LV ejection fraction was measured using Simpson’s biplane method. Teichholz’s method was used in association with a visual estimate in patients with inadequate two-dimensional images in apical views. Peak early and late diastolic mitral velocities (E and A, cm/s) and the deceleration time of mitral early filling (DTE, ms) were recorded placing the pulsed-wave Doppler sample volume between the tips of the mitral leaflets. The sample volume was then placed at the septal side of the mitral annulus and the peak early diastolic velocity (E, cm/s) measured by spectral tissue Doppler [4]. Optimal Doppler gain and filter settings were carefully adjusted to avoid under- or overestimation of spectral peak E, A and E’ velocities. Three consecutive beats were averaged for all Doppler parameters in sinus rhythm and five in atrial fibrillation. The septal E/E’ ratio was calculated for each patient and used a noninvasive Swan-Ganz catheter regardless of rhythm [12,13]. A value greater than 15 for septal E/E’ was used as a hallmark of critical increase in pulmonary capillary pressures greater than 18–20 mmHg [12–15]. Numerical images from 10 consecutive patients were stored and analysed offline by the operator and a second cardiologist. Intra- and interobserver variability for E/E’ was 4% ± 6 and 7% ± 8, respectively. The restrictive mitral filling pattern was defined as previously proposed by Logeart et al. (E/A ratio > 2 and/or DTE < 130 ms) [5].

Statistical analysis

Descriptive data are given as mean ± standard deviation. Intergroup comparison used the analysis of variance test, the chi-square test, Fisher’s exact test with bilateral formulation and the Mann–Whitney test. The diagnostic performance of the Boston score, BNP and E/E’ for predicting HFnlEF was assessed by univariate and multivariable logistic regression analyses. Log-transformed data were used for BNP concentrations in the logistic regression model. The diagnostic performance was also evaluated using the area under the receiver-operating characteristic (AUC) curve, which is provided with its 95% confidence interval (CI). The optimal cut-off corresponded to the value with the greatest accuracy. A p-value less than 0.05 was considered statistically significant.

Results

The diagnosis at discharge was HFnlEF in 51 patients, 31 of whom had a normal serum protein concentration and a non-cardiac cause in 54 patients, 40 of whom had a normal serum protein concentration. The final diagnosis was acute exacerbation of chronic pulmonary disease in 25 patients with a non-cardiac cause, pulmonary infectious disease in 22, acute pulmonary embolism in four and lung cancer in three.

The baseline clinical characteristics of the study population are listed in Table 1 according to diagnosis at discharge and serum protein concentration. The mean delay between presentation and Doppler echocardiography was 0.7 ± 1.3 h, without non-significant difference, according to the final diagnosis (p = 0.4).
Table 1 Baseline characteristics of patients at presentation according to the diagnosis at discharge.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal serum protein concentration ≥ 6 g/dL</th>
<th>Decreased serum protein concentration &lt; 6 g/dL</th>
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<tbody>
<tr>
<td></td>
<td>Heart failure (n = 31)</td>
<td>Heart failure (n = 20)</td>
</tr>
<tr>
<td></td>
<td>Non-cardiac (n = 40)</td>
<td>Non-cardiac (n = 14)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>82 ± 6</td>
<td>84 ± 6</td>
</tr>
<tr>
<td>Women (%)</td>
<td>21 (68)</td>
<td>13 (65)</td>
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<tr>
<td>Sinus rhythm (%)</td>
<td>23 (74)</td>
<td>14 (70)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>168 ± 28&lt;sup&gt;a&lt;/sup&gt;</td>
<td>142 ± 31&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>89 ± 23</td>
<td>94 ± 20</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25 ± 5</td>
<td>26 ± 7</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>64 ± 7</td>
<td>61 ± 10</td>
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<tr>
<td>Boston score</td>
<td>10 ± 1.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.7 ± 1.6&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lung crackles or wheezing (%)</td>
<td>24 (81)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18 (90)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Venous pressure elevation (%)</td>
<td>10 (32)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Interstitial and/or alveolar radiographic pulmonary oedema (%)</td>
<td>26 (84)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14 (70)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>B-type natriuretic peptide concentration (pg/mL)</td>
<td>401 [257–625]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>995 [643–2150]&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum protein concentration (g/dL)</td>
<td>6.8 ± 0.4</td>
<td>5.4 ± 0.4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Septal E′/E ratio</td>
<td>20 [17.1–23.5]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15.7 [12–20.3]&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Restrictive mitral filling (%)</td>
<td>12 (39)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4 (20)</td>
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<tr>
<td>History of coronary artery disease (%)</td>
<td>8 (26)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>23 (74)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9 (64)</td>
</tr>
<tr>
<td>History of chronic pulmonary disease (%)</td>
<td>6 (19)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 (10)&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>History of diabetes mellitus (%)</td>
<td>6 (19)</td>
<td>7 (35)</td>
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<tr>
<td>Chronic diuretic therapy (%)</td>
<td>18 (58)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 (30)</td>
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<tr>
<td>Haematocrit (%)</td>
<td>35 ± 6</td>
<td>33 ± 4</td>
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<tr>
<td>Serum sodium (mmol/L)</td>
<td>139 ± 4</td>
<td>138 ± 6</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>44 ± 18&lt;sup&gt;a&lt;/sup&gt;</td>
<td>38 ± 23&lt;sup&gt;c&lt;/sup&gt;</td>
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</table>

Mean ± S.D. or median (25th to 75th percentiles) when appropriate.

<sup>a</sup> p < 0.05 for patients with normal serum protein concentration, heart failure versus non-cardiac cause.
<sup>b</sup> p < 0.05 for patients with heart failure, low versus normal serum protein concentration.
<sup>c</sup> p < 0.05 for patients with low serum protein concentration, heart failure versus non-cardiac cause.
<sup>d</sup> p < 0.05 for patients with non-cardiac cause, low versus normal serum protein concentration.

By regression analysis performed in patients with HFn-Hf,L EF, E′/E was predicted by serum protein concentration (p = 0.0026; Fig. 1), but not by age, sex, systolic blood pressure, rhythm, heart rate, LV ejection fraction, serum haematocrit or serum creatinine (p > 0.1 for all). None of these variables was found to predict E′/E in patients with a non-cardiac cause of dyspnoea (p > 0.1 for all). Hypoproteinaemia, evidenced after clinical stabilization to avoid false-positives related to volume overload, was mainly related to severe chronic malnutrition in 47% of patients and to severe sepsis (C-reactive protein greater than 100 mg/L) in 53%.
Tissue Doppler echocardiography for the diagnosis of new-onset heart failure with normal ejection fraction

Diagnostic accuracy of diagnostic variables in overall population

By logistic regression analysis, Boston score (odds-ratio [OR] 1.9, 95% CI 1.5–2.4; p < 0.001), BNP (OR 15, 95% CI 5–47; p < 0.001) and E/E′ (OR 1.5, 95% CI 1.3–1.8; p < 0.001) were univariate predictors of HFnLEF. By multivariable stepwise logistic regression analysis, Boston score (p = 0.017), BNP (p = 0.003) and E/E′ (p < 0.001) independently predicted HFnLEF. The optimal cut-off value for E/E′ was 13.3 (AUC 0.90, 95% CI 0.83–0.95; p < 0.001, sensitivity 88%, specificity 85%); E/E′ > 15 was 78% sensitive and 91% specific.

Thirty-eight patients had BNP levels in the middle range (inconclusive for the diagnosis; p = 0.1), 16 of whom had a diagnosis of HFnLEF at discharge. E/E′ was a good predictor of HFnLEF in this subset of patients (OR 1.5, 95% CI 1.2–1.9; p = 0.0019) with an optimal cut-off value of 12.6 (AUC 0.88, 95% CI 0.83–0.95; p < 0.001; sensitivity 94%, specificity 77%); E/E′ > 15 was 81% sensitive and 82% specific.

Diagnostic accuracy of E/E′ in patients with normal serum protein concentration

Boston score (OR 2, 95% CI 1.4–2.8; p < 0.001), BNP (OR 11.9, 95% CI 3.2–45; p < 0.001) and E/E′ (OR 2.2, 95% CI 1.5–3.2; p < 0.001) were univariate predictors of HFnLEF in patients with normal serum protein concentration. By stepwise regression analysis, including Boston score, BNP and E/E′, the Boston score (p = 0.038) and E/E′ (p < 0.001) independently predicted HFnLEF. The optimal cut-off value for E/E′ was 14.8 (AUC 0.97, 95% CI 0.90–0.99; p < 0.001; sensitivity 97%, specificity 92%; Fig. 2); E/E′ > 15 was 93% sensitive and 92% specific.

Twenty-seven patients had BNP levels in the middle range, 13 of whom had a diagnosis of HFnLEF at discharge. E/E′ was a good predictor of HFnLEF in this subset of patients (OR 1.65, 95% CI 1.15–2.37; p = 0.007) with an optimal cut-off value of 14.4 (AUC 0.91, 95% CI 0.74–0.98; p < 0.001, sensitivity 92%, specificity 79%); E/E′ > 15 was 85% sensitive and 79% specific.

As shown in Fig. 1, when European Society of Cardiology (ESC) recommendations were tested in all patients with normal protein levels to confirm the diagnosis of HFnLEF established at discharge, BNP greater than 200 pg/mL offered incremental information over tissue Doppler only in one of the two patients with E/E′ < 15 [16]; the overall sensitivity and specificity in the diagnosis of HFnLEF were 97 and 70%, respectively, for the presence of one of the following criteria, E/E′ > 15 or 8 < E/E′ ≤ 15 associated with BNP greater than 200 pg/mL [16].

Diagnostic accuracy of E/E′ in patients with low serum protein concentration

Boston score (p = 0.005), BNP (p = 0.0022) and E/E′ (p = 0.008) were univariate predictors of HFnLEF in patients with hypoproteinaemia. However, E/E′ did not offer independent diagnostic information over the Boston score and BNP (p > 0.1). The optimal cut-off value for E/E′ was 10.9 (AUC 0.83, 95% CI 0.66–0.93; p < 0.001, sensitivity 85%, specificity 71%; Fig. 3). Over half (55%) of the patients with HFnLEF and hypoproteinaemia had E/E′ > 15 (for a specificity of 86%) compared with 93% of patients with HFnLEF and normal serum protein concentration (p = 0.0017).

Figure 1. Scatter plot of relationship between E/E′ and serum protein concentration in patients with heart failure and normal ejection fraction. Solid circles correspond to patients with B-type natriuretic peptide (BNP) greater than 200 pg/mL (E/E′ range: 8–30), open circles correspond to patients with BNP less than 200 pg/mL (E/E′ range: 13.4–20.6). According to the European Society of Cardiology (ESC) recommendations, evidence of E/E′ > 15 and/or a BNP greater than 200 pg/mL associated with E/E′ > 8 defines HFnLEF in the setting of signs or symptoms of heart failure and left ventricular ejection fraction greater than 50% [16]. Using the combination of these two criteria, 90% of patients with hypoproteinaemia had confirmed HFnLEF according to the ESC consensus compared with 97% of patients with normoproteinaemia.

Figure 2. Area under the receiver-operating characteristic curve (AUC) evaluating the performance of the septal E/E′ ratio for the diagnosis of new-onset heart failure with normal ejection fraction in patients with normal serum protein concentration. The E/E′ performed well in differentiating heart failure from non-cardiac causes of acute dyspnoea, with an AUC of 0.97 (95% CI 0.90–0.99; p < 0.001). The optimal cut-off value was 14.8, with a sensitivity of 97% and a specificity of 92%. The arrow indicates the optimal cut-off value for E/E′.
Doppler in seven of the nine patients with BNP greater than 200 pg/mL offered incremental information over tissue Doppler echocardiography was able to offer additional diagnostic information over intermediate, inconclusive BNP concentrations in this subset of patients. Conversely, when the ESC criteria were applied [16], the combination of BNP and \( E/E' \) slightly increased the sensitivity in establishing HFnLEf compared with \( E/E' \) alone (93—97%), but specificity was substantially lower (70% versus 92%). Consistent with previous clinical studies [8,9,29—31], critical increase in filling pressures was not observed in about half of the patients with HFnLEf and hypoproteinemia. Such a result confirms that low plasma oncotic pressure due to hypoproteinemia is likely to favour pulmonary congestion at less increased pulmonary capillary pressures [6—8]. Spectral tissue Doppler was still able to differentiate HFnLEf from non-cardiac causes of acute dyspnoea with reasonable accuracy in patients with low serum protein concentration. The observed optimal cut-off value of 10.9 is consistent with abnormal LV diastolic filling and exercise intolerance related to diastolic dysfunction in stable patients [17—19]. When the ESC criteria were used [16], the combination of BNP with \( E/E' \) substantially improved the detection of HFnLEf compared with \( E/E' \) alone (55—90%), but the specificity was significantly lower (64% versus 86%). BNP therefore appears to be a helpful additional diagnostic complement to tissue Doppler in this setting, assuming the relatively worse consequences of failing to treat false-negative patients than of treating those who are false-positive.

Hypoproteinemia is a common comorbid condition in frail, elderly patients and is related primarily to malnutrition and inflammation [31]. Taking into consideration that serum protein concentration is likely to improve the clinical interpretation of tissue Doppler in elderly patients with suspected HFnLEf in daily practice, septal \( E/E' > 15 \) is clinically relevant for the diagnosis of HFnLEf in acutely dyspnoeic patients with both normal LV ejection fraction and serum protein concentration. In patients with a low serum protein concentration, this haemodynamic condition may be absent in a significant proportion of cases; the diagnosis of HFnLEf is independently associated with reduced exercise performance [17—19] and a value greater than 13 reliably predicts HFnLEf in the acute setting [4]. Tissue Doppler evidence of basal or exercise-induced pulmonary capillary hypertension is recommended as a hallmark of HFnLEf irrespective of clinical presentation [4,16,20].

In the present study, spectral tissue Doppler echocardiography provided useful information for the diagnosis of new-onset HFnLEf in the acute care setting. A critical increase in hydrostatic pulmonary capillary pressures greater than 18—20 mmHg is regarded as the main haemodynamic condition that characterizes acute HF syndromes [27,28]. We observed such critically elevated pulmonary capillary pressures, well defined by a spectral tissue Doppler-derived \( E/E' > 15 \), in 93% of patients with HFnLEf and a normal serum protein concentration; further, tissue Doppler echocardiography was able to offer additional diagnostic information over intermediate, inconclusive BNP concentrations in this subset of patients. Conversely, when the ESC criteria were applied [16], the combination of BNP and \( E/E' \) slightly increased the sensitivity in establishing HFnLEf compared with \( E/E' \) alone (93—97%), but specificity was substantially lower (70% versus 92%). Consistent with previous clinical studies [8,9,29—31], critical increase in filling pressures was not observed in about half of the patients with HFnLEf and hypoproteinemia. Such a result confirms that low plasma oncotic pressure due to hypoproteinemia is likely to favour pulmonary congestion at less increased pulmonary capillary pressures [6—8]. Spectral tissue Doppler was still able to differentiate HFnLEf from non-cardiac causes of acute dyspnoea with reasonable accuracy in patients with low serum protein concentration. The observed optimal cut-off value of 10.9 is consistent with abnormal LV diastolic filling and exercise intolerance related to diastolic dysfunction in stable patients [17—19]. When the ESC criteria were used [16], the combination of BNP with \( E/E' \) substantially improved the detection of HFnLEf compared with \( E/E' \) alone (55—90%), but the specificity was significantly lower (64% versus 86%). BNP therefore appears to be a helpful additional diagnostic complement to tissue Doppler in this setting, assuming the relatively worse consequences of failing to treat false-negative patients than of treating those who are false-positive.

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### Discussion

Currently, Doppler echocardiography is regarded as the single most useful diagnostic test for assessing LV ejection fraction and cardiac abnormalities in patients referred for suspected congestive HF. Numerous clinical studies have established the usefulness of the spectral tissue Doppler-derived \( E/E' \) for the diagnosis of congestive HF, as well as for risk stratification in multiple clinical settings. This is due, at least in part, to the reasonable accuracy of \( E/E' \) as a noninvasive surrogate for LV diastolic pressure in patients with cardiac disease [4]. Noninvasive assessment of LV diastolic pressures offers the ability to establish the cause-and-effect relationship of structural heart disease with symptoms and signs compatible with the diagnosis of HF, especially for patients with normal LV ejection fraction [4]. Septal \( E/E' > 10 \) at rest or during exercise is independently associated with reduced exercise performance [17—19] and a value greater than 13 reliably predicts HFnLEf in the acute setting [4]. Tissue Doppler evidence of basal or exercise-induced pulmonary capillary hypertension is recommended as a hallmark of HFnLEf irrespective of clinical presentation [4,16,20]. Furthermore, septal \( E/E' > 15 \) is associated with high risk of adverse cardiovascular outcome in the setting of structural heart disease irrespective of rhythm and LV systolic function [21—23], in the setting of acute myocardial infarction [24,25] and chronic congestive HF [26]. Consequently, establishing relevant cut-off values for \( E/E' \) according to clinical setting is of critical importance in appropriately interpreting tissue Doppler results in daily practice.

In the present study, spectral tissue Doppler echocardiography provided useful information for the diagnosis of new-onset HFnLEf in the acute care setting. A critical increase in hydrostatic pulmonary capillary pressures greater than 18—20 mmHg is regarded as the main haemodynamic condition that characterizes acute HF syndromes [27,28]. We observed such critically elevated pulmonary capillary pressures, well defined by a spectral tissue Doppler-derived \( E/E' > 15 \), in 93% of patients with HFnLEf and a normal serum protein concentration; further, tissue Doppler echocardiography was able to offer additional diagnostic information over intermediate, inconclusive BNP concentrations in this subset of patients. Conversely, when the ESC criteria were applied [16], the combination of BNP and \( E/E' \) slightly increased the sensitivity in establishing HFnLEf compared with \( E/E' \) alone (93—97%), but specificity was substantially lower (70% versus 92%). Consistent with previous clinical studies [8,9,29—31], critical increase in filling pressures was not observed in about half of the patients with HFnLEf and hypoproteinemia. Such a result confirms that low plasma oncotic pressure due to hypoproteinemia is likely to favour pulmonary congestion at less increased pulmonary capillary pressures [6—8]. Spectral tissue Doppler was still able to differentiate HFnLEf from non-cardiac causes of acute dyspnoea with reasonable accuracy in patients with low serum protein concentration. The observed optimal cut-off value of 10.9 is consistent with abnormal LV diastolic filling and exercise intolerance related to diastolic dysfunction in stable patients [17—19]. When the ESC criteria were used [16], the combination of BNP with \( E/E' \) substantially improved the detection of HFnLEf compared with \( E/E' \) alone (55—90%), but the specificity was significantly lower (64% versus 86%). BNP therefore appears to be a helpful additional diagnostic complement to tissue Doppler in this setting, assuming the relatively worse consequences of failing to treat false-negative patients than of treating those who are false-positive.

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should be carefully considered in the setting of intermediate values for $E/E'$. In addition to BNP, further studies will address the usefulness of left atrial enlargement as well as the analysis of pulmonary venous flow as diagnostic complements to an intermediate $E/E'$ ratio in patients with suspected HFnEF and hypoproteinemia [16].

**Limitations of the study**

The main limitation of this prospective, single-centre study is the small number of patients, especially those with hypoproteinemia. Nevertheless, the population was homogeneous and significant results have been achieved. HFnEF is acknowledged to affect primarily older patients [32] and we specifically addressed the imbalance of Starling’s forces in such patients with acute severe symptoms because of specific therapeutic and prognostic issues [1,2]. Hypoproteinemia is far less common in young patients and pulmonary congestion of cardiac origin is related mainly to a critical increase in hydrostatic pulmonary capillary pressure in this setting [33]. It is of high clinical importance to highlight that our results cannot be extrapolated to patients in NYHA class II–III, since critical increases in pulmonary capillary pressures may be unmasked only during exercise in this setting [15,19]. Further studies will therefore delineate the clinical relevance of serum protein determination in stable patients with symptoms on exertion, along with pulmonary capillary hypertension at rest and/or during exercise [34]. $E/E'$ was measured at the septal side of mitral annulus because this method has been validated in sinus rhythm as well as in permanent atrial fibrillation with similar results [4,9,12,13] and is extensively used in the setting of HFnEF [35].

**Conclusion**

Septal $E/E'$ offers the ability to provide useful information at the bedside for the diagnosis of new-onset HFnEF in elderly patients hospitalized for acute severe dyspnoea. However, while the standard cut-off value of 15 for $E/E'$, which well defines critical elevation in LV filling pressures, is clinically relevant for patients with normal serum protein concentration, lower abnormal values should be strongly considered predictive of HFnEF in the setting of hypoproteinemia.

**References**


