Prevalence of thoracic vertebral fractures in hospitalized elderly patients with heart failure

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Abstract

Objective: Heart failure (HF) has been associated with increased risk of fragility fractures. Indeed, most literature data on fractures were based on an historical and clinical approach focused on the identification of peripheral fractures, whereas the risk of vertebral fractures in this clinical setting is still unclear.

Design: Cross-sectional study.

Aim: To evaluate the prevalence and determinants of radiological thoracic vertebral fractures in patients with HF.

Methods: The study includes 1031 elderly hospitalized patients (491 females and 540 males; median age, 75 years; range, 65–90; 430 patients with HF) who were evaluated for the presence of thoracic vertebral fractures by quantitative morphometric analysis, using chest X-ray routinely performed in the diagnostic work-up of HF.

Results: Vertebral fractures were found in 166 patients (16.1%), the prevalence being significantly higher in patients with HF as compared with those without HF, both in females (30.9 vs 15.8%; \(P<0.001\)) and in males (16.4 vs 7.4%; \(P<0.001\)). The association between HF and vertebral fractures remained statistically significant (odds ratio, 2.14; 95% CI, 1.25–3.66; \(P<0.01\)) even after adjustment for age, sex, loop diuretic therapy, anticoagulant therapy, proton pump therapy, coexistent chronic obstructive pulmonary disease, diabetes mellitus, renal insufficiency, and chronic liver diseases. In patients with HF, vertebral fractures were positively correlated with female sex, duration of HF, ischemic heart disease, cigarette smoking, and treatment with anti-osteoporotic drugs, and inversely correlated with left ventricular ejection fraction.

Conclusions: Hospitalized patients suffering from HF are at higher risk of vertebral fractures than patients without HF in the same clinical context.

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Introduction

Heart failure (HF) is a chronic progressive condition which affects a large number of subjects in the western countries, approaching an incidence of 10/1000 population after age 65 (1). Among various causes of chronic illness and disability, HF is noteworthy for its frequency and burden of care, and for implications in terms of mortality, morbidity, and quality of life (2, 3).

Osteoporosis is a skeletal disorder characterized by a decrease in bone mineral density (BMD) and loss of structural and biomechanical properties of the skeleton leading to an increased risk of fragility fractures (4). It is estimated that about half of the women at age 50 or older will have an osteoporotic fracture during their lifetime causing disability, increased mortality, and financial burden (5, 6).

Over the recent years, there has been growing evidence to suggest the existence of correlation between HF and skeletal fragility (7). More than 50% of patients with HF have been reported to have low BMD (8) with an increase in osteoporotic hip fracture risk ranging from 1.5 to 6 times as compared with the general population (9, 10, 11, 12). The advanced age of the patients may itself be a predisposing factor, considering that both HF and bone loss are common conditions in elderly subjects. Moreover, co-morbidities, such as diabetes mellitus and chronic renal failure frequently observed in patients suffering from HF, may play a role in favoring the onset of osteoporosis in this clinical setting (12, 13, 14). Beyond these general points, there are specific factors related to HF, as secondary hyperaldosteronism and chronic treatment with loop diuretics, that may be responsible for the frequent detection of osteoporosis and fractures in patients with HF (15, 16, 17, 18). Moreover, genetic factors were suggested to be involved in determining the association between osteoporosis and cardiovascular diseases in the general population (10, 19). All these factors could explain the finding of high prevalence of fragility fractures in patients with HF. Indeed, most of literature data on this hard end-point were based on an historical
and clinical approach focused on the identification of peripheral fractures (9, 10, 11), whereas the risk of vertebral fractures in this clinical setting is still unclear (20, 21, 22). As vertebral fractures are often asymptomatic and largely underdiagnosed based upon clinical records, the radiological and morphometric approach has emerged as the method of choice for evaluating the true prevalence of fractures in population studies (23, 24). Although population-based screening for vertebral fractures is not currently recommended (25), the chest radiograph may be a valuable case-finding tool in ‘at-risk’ patients, such as those with HF (26, 27). Vertebral fractures are clinically important because they impact the clinical outcome of patients with osteoporosis in terms of development of new fractures and increase in morbidity and mortality (28, 29). These aspects may be of clinical relevance in frail patients, such as the elderly with HF (30).

In this cross-sectional study, we evaluated for the first time the prevalence of radiological thoracic vertebral fractures using routine chest X-rays performed in elderly hospitalized patients with HF as compared with subjects coming from the same clinical setting. Moreover, we investigated whether the association between HF and vertebral fractures was influenced by coexistent chronic diseases and/or therapies.

Materials and methods

Subjects

This study was conducted on hospitalized patients consecutively admitted to our Medicine and Geriatric Units in the period between February 2010 and March 2011. The inclusion criteria were: i) age ≥ 65 years; ii) availability of lateral chest X-rays; and iii) availability of clinical information of patients for at least 5 years before the enrollment. Exclusion criteria were: i) neoplastic diseases in progression; ii) chronic autoimmune diseases except for Hashimoto’s thyroiditis and Graves’ disease; iii) chronic therapy (> 3 months) with oral and parenteral glucocorticoids; iv) chronic immobilization; v) trauma; vi) severe renal insufficiency (creatinine clearance < 30 ml/min per 1.73 m²); and vii) previous clinical history of HF without specific symptoms at the time of enrollment.

Patient selection was initially performed using the International Classification of Diseases, Ninth Revision (ICD-9) codes (31). By this approach, 1498 patients older than 65 years were screened and 256 did not meet the eligibility criteria (Fig. 1). In the 1242 remaining patients, complete clinical file records were carefully reviewed and 211 were excluded from the study for different reasons: 64 patients had no available lateral chest X-ray, 20 were on chronic glucocorticoid therapy, 103 were chronically immobilized, 20 had history of trauma, and four patients had a previous history of HF which was not clinically present at the time of the study (Fig. 1). The remaining 1031 patients (491 females and 540 males; median age, 75 years; range, 65–90) were enrolled after obtaining oral informed consent. The study was approved by the Local Ethical Committee.

For identifying patients with HF, the following ICD-9 codes were considered: 428.0–428.4, 428.9, 402.11, 404.01, 404.11, 404.13, 404.91, and 404.93. The diagnosis of HF was then confirmed by the revision of clinical records according to available guidelines (32). Specifically, the diagnosis of HF was based on the presence of dyspnea and/or fatigue and coexistent clinical and/or radiological signs of fluid retention (32). In all patients with HF, echocardiography showed signs of systolic (decreased left ventricular ejection fraction) or diastolic dysfunction (preserved left ventricular ejection fraction) (32). Four hundred and thirty patients (41.7%) had a diagnosis of HF at the time of enrollment. According to the New York Heart Association (NYHA) staging (32), 322 patients (74.9%) were in class IV whereas the remaining 108 patients were in class III. Among patients with HF, 229 were
admitted to hospital for the first time for this reason (HF as primary diagnosis), 64 for the second time, while the remaining 137 had been already admitted at least three times. The median duration of symptoms of HF (classes NYHA 2–4) was 23 months (range, 1–120). Comorbidities and medications were identified by revision of clinical records, based on clinical criteria and historical assessment. For the purpose of this study, we considered only therapies with duration longer than 6 months.

In the remaining 601 patients, who acted as the control group, HF was excluded by clinical, radiological, and ecocardiographic evaluations. Specifically, HF was excluded primarily with clinical assessment. In patients with clinical signs possibly consistent with HF, diagnosis was excluded by echocardiography, chest X-ray, and by measurement of serum pBNP values.

**Assessment of vertebral fractures**

Vertebral fractures were detected on lateral chest X-rays using a qualitative evaluation of vertebral shape and quantitative morphometric assessment of centrally digitized images using dedicated morphometry software (Spine-X Analyzer; ICAM Diagnostics, Milan, Italy). Using a translucent digitizer and a cursor, six points were marked on each vertebral body to describe vertebral shape. Anterior (Ha), middle (Hm), and posterior (Hp) vertebral heights were measured and height ratios (Ha/Hp, Hm/Hp, Hp/Hp of the upper vertebrae, and Hp/Hp of the lower vertebrae) were calculated for each vertebral body from T4 to T12. According to the method initially proposed by Genant et al. (24), the fractures were defined as mild, moderate, and severe on the basis of height ratio decreases of 20–25, 25–40, and more than 40% respectively. We defined a priori that a clinically important vertebral fracture was one that was at least moderate to severe, translating into a 25% or greater loss of vertebral body height with wedge, crush, or biconcave morphology. The morphometric analysis was performed by one operator (G Mazziotti) who was blinded to the identity of patients. The intra-observer coefficient of variation, evaluated on a series of 10 measurements, was between 4 and 8%. Operationally, chest radiographs of all patients were bookmarked in the hospital's digital archiving system. This allowed the study reviewer to independently view radiographs but blinded him to official radiologist reports as well as other clinical data.

**Measurement of BMD**

Femoral neck and total hip BMD were measured in 464 patients by dual-energy X-ray absorptiometry (QDR-1000; Hologic, Inc., Waltham, MA, USA) in the last 24 months prior to their enrollment. BMD was expressed as T-score, comparing the results of each subject with those obtained in a sex-matched young US population. Osteopenia and osteoporosis were defined with T-score equal or below −1.0 s.d. and equal or below −2.5 s.d. respectively.

**Statistical analysis**

All data were expressed as the median and range. Unpaired data were compared using Mann–Whitney U test. Frequencies were compared using χ²-test with Fisher correction, when appropriate. A logistic regression model was used in the statistical analysis of risk factors for the occurrence of vertebral fractures. Statistical significance was assumed when P values were ≤0.05.

**Results**

**Clinical characteristics**

Patients with HF were significantly older, more frequently males, with higher prevalence of ischemic heart disease and chronic obstructive pulmonary disease, lower rate of liver disease and they were more often undergoing anticoagulant, loop diuretic, thyroxine, and anti-osteoporotic therapy as compared with those not suffering from HF. Moreover, patients with HF had reduced left ventricular ejection fraction than patients without HF (Table 1).

**Prevalence of vertebral fractures**

Vertebral fractures were found in 166 out of 1031 patients in the total study population (16.1%). The fractures were severe in 65 patients (6.3%) and multiple in 95 patients (9.2%). In fractured patients in whom BMD was measured (123 cases), 75.6% had osteoporosis and 24.2% osteopenia at femoral neck and/or total hip. Anti-osteoporotic drugs were taken by 27.1% of patients with vertebral fractures and 10.1% of those who did not have fracture (P<0.001).

The prevalence of vertebral fractures was significantly higher in patients with HF as compared with those without HF (21.9 vs 12.6%; χ² 18.1; P<0.001), the difference remaining statistically significant even when the analysis was performed separately for females (30.9 vs 15.8%; χ² 14.9; P<0.001) and males (16.4 vs 7.4%; χ² 10.6; P=0.001) and also when only severe and multiple fractures were considered (Fig. 2).

**Correlations**

In multivariate analysis, the association between HF and vertebral fractures remained statistically significant even after adjustment for the different covariates, such as age, sex, cigarette smoking, alcohol use, ischemic heart disease, chronic obstructive pulmonary disease, diabetes mellitus, chronic liver disease, chronic renal insufficiency (mild to moderate), hyperthyroidism, chronic treatment...
with loop diuretics, oral anticoagulants, proton pump inhibitors, and thyroxine, potentially influencing vertebral fracture risk (Table 2). The association between HF and vertebral fractures was still significant even when only severe fractures (odds ratio (OR), 6.01; 95% CI, 2.05–17.68; \( P < 0.001 \)) were considered as the dependent variable in the multivariate analysis.

### Determinants of vertebral fractures in patients with HF

Fractured patients with HF were more often females and smokers and suffered more frequently from ischemic heart disease, hyperthyroidism, chronic liver disease, and diabetes mellitus, with longer duration of HF symptoms and lower left ventricular ejection fraction compared with patients who did not have fracture (Table 3). The prevalence of vertebral fractures was significantly higher in patients in class NYHA IV than patients in class NYHA III (24.8 vs 12.9%; \( P < 0.001 \)). Moreover, the prevalence, severity, and number of vertebral fractures were related to the increasing number of hospital admissions for HF patients (\( P < 0.001 \)). Finally, patients who had experienced vertebral fractures were more frequently on therapy with anti-osteoporotic drugs and proton pump inhibitors as compared with non-fractured patients. However, the percentage of fractured patients taking bone-active drugs was <40% (Table 3). In the subgroup of patients in whom femoral BMD data were available, higher prevalence of osteoporosis and lower prevalence of normal BMD occurred in fractured patients as compared with those who did not have fracture (Table 3).

In a multivariate analysis, vertebral fractures maintained a significant correlation with female sex (OR, 3.93; 95% CI, 2.07–7.46; \( P < 0.001 \)), duration of HF (OR, 1.04; 95% CI, 1.03–1.05; \( P < 0.001 \)), ischemic heart disease (OR, 2.64; 95% CI, 1.36–5.13; \( P = 0.004 \)), left ventricular ejection fraction (OR, 0.94; 95% CI, 0.89–0.99; \( P = 0.02 \)), and treatment with proton pump inhibitors (OR, 2.18; 95% CI, 1.17–4.08; \( P = 0.01 \)).

### Discussion

This cross-sectional study showed that about 20% of patients with HF had prevalent single or even multiple vertebral fractures assessed by a morphometric approach. Prevalence of vertebral fractures in HF was significantly greater than in non-HF patients from the same clinical setting. Vertebral fractures in HF were correlated to the severity of disease, in terms of left ventricular fraction ejection impairment and duration of clinical manifestations, presence of ischemic heart disease, and female sex. Moreover, interestingly, vertebral fractures were found to be associated with the number of hospital admissions for HF. Finally, our study showed that <40% of HF patients with vertebral fractures were undergoing specific anti-osteoporotic therapies.

It has been suggested that patients with HF are predisposed to develop fragility fractures (7, 9, 10, 11, 12).
vertebrae was not directly investigated by the studies, is likely to lead to a highly heterogeneous study approach could lead to an underestimation of global fracture risk, as vertebral fractures are often (≈ 50%) not diagnosed being frequently asymptomatic or only mildly symptomatic (23). In the last decade, the radiological and morphometric approach has emerged as the method of choice for evaluating the true prevalence of vertebral fractures in population studies (24, 33). Only a few previous studies conducted a radiological and morphometric evaluation of vertebral fractures in patients with HF, without definitive conclusions on the existence of a real increase in the risk of vertebral fractures in this clinical setting (20, 21, 22). These limitations span from small study populations (21) to absence of a control population (22). Moreover, in one of these studies, presence of vertebral fractures was not directly investigated by the researchers but relied on routine external radiological evaluations (22), while it is well known that vertebral fractures are often not reported in this setting. Finally, use of registers for recruiting patients, as in previous studies, is likely to lead to a highly heterogeneous study population. Our study is the first which includes an homogenous control population, and is therefore able to give relevant information on the actual risk of vertebral fractures in patients with HF. Furthermore, our study provides a morphometric analysis of the chest X-rays by an expert in the research team. In order to avoid misclassification of vertebral deformities, we choose to exclude mild spine deformities from the analysis. Using this approach, it was possible to demonstrate the presence of thoracic vertebral fractures in about 20% of elderly patients suffering from HF, a prevalence about double vs the control population, and comparable with those found in populations known to be at the highest risk for vertebral fractures, such as post-menopausal women in chronic glucocorticoid treatment (34). Moreover, about 10% of these patients had severe and/or multiple vertebral fractures. These numbers are of clinical relevance, considering the frailty of elderly patients with HF (2) and the prognostic aspects related to vertebral fractures in the general populations (28, 29, 35, 36, 37). Indeed, vertebral fractures, even when mild or asymptomatic, are a negative prognostic factor for further vertebral and nonvertebral fractures (35). Symptomatic vertebral fractures are also a major cause of disability with consequent significant limitations in daily living activities (36).

Our study confirmed that female patients with HF may predispose to vertebral fractures (22). However, our data would also suggest that males with HF are still at higher risk to develop vertebral fractures as compared with subjects without HF. This finding may be of clinical interest, considering that HF tends to occur more frequently in males than in females (37).

In our patients with HF, vertebral fractures were associated with lower left ventricular ejection fraction

### Table 3 Demographical and clinical differences between fractured and non-fractured patients with heart failure (HF).

<table>
<thead>
<tr>
<th>Heart failure</th>
<th>No fractures</th>
<th>Fractures</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (n)</td>
<td>336</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>78.5 (65–95)</td>
<td>81.5 (65–95)</td>
<td>0.24</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>112/224</td>
<td>50/44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>105 (31.3%)</td>
<td>44 (46.8%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>35 (20–45)</td>
<td>31 (22–40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD</td>
<td>51 (15.2%)</td>
<td>18 (19.1%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>67 (19.9%)</td>
<td>28 (29.8%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>79 (23.5%)</td>
<td>16 (17.0%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>8 (2.4%)</td>
<td>14 (14.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>7 (2.1%)</td>
<td>8 (8.5%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Treatment with:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>loop diuretics</td>
<td>271 (80.7%)</td>
<td>79 (84.0%)</td>
<td>0.46</td>
</tr>
<tr>
<td>anticoagulants</td>
<td>173 (51.5%)</td>
<td>47 (50.0%)</td>
<td>0.79</td>
</tr>
<tr>
<td>proton pump inhibitors</td>
<td>99 (29.5%)</td>
<td>40 (42.6%)</td>
<td>0.02</td>
</tr>
<tr>
<td>thyroxine</td>
<td>47 (14.0%)</td>
<td>15 (16.0%)</td>
<td>0.63</td>
</tr>
<tr>
<td>anti-osteoporotic drugs*</td>
<td>47 (14.0%)</td>
<td>32 (34.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>69 (20.6%)</td>
<td>31 (32.9%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Alcohol</td>
<td>53 (15.8%)</td>
<td>12 (12.8%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Duration of HF (months)</td>
<td>3 (1–100)</td>
<td>32 (16–89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal BMD</td>
<td>40 (29.6%)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>46 (34.1%)</td>
<td>19 (30.6%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>49 (36.3%)</td>
<td>43 (68.4%)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease.
*Anti-osteoporotic drugs included bisphosphonates, strontium ranelate, teriparatide, and 1–84 parathyroid hormone.
*These frequencies were calculated in 197 patients with HF (62 with fractures and 135 without fractures) in whom BMD was measured.
Our study has some limitations. First, even if the enrollment of patients was consecutive, the study was cross sectional. Such a study design did not allow us to evaluate the timing of occurrence of vertebral fractures in patients with HF, but the significant correlation between duration of HF clinical symptoms and prevalence of vertebral fractures would suggest a time-dependent effect on the occurrence of fractures. Secondly, many of our HF patients were not investigated for bone metabolism and BMD. The lack of this information did not allow us to clarify the relationship between BMD and vertebral fractures in this clinical setting, which was previously shown to be a variable in secondary forms of osteoporosis (48, 49, 50, 51, 52). However, some of our results supported the hypothesis that vertebral fractures could be caused by skeletal fragility in patients with HF. In fact, in the subgroup of patients in whom BMD data were available, vertebral fractures were associated with osteoporosis. Moreover, in the global study population we observed a significant correlation between vertebral fractures and different clinical conditions, such as diabetes mellitus, chronic obstructive pulmonary disease, hyperthyroidism, and chronic therapy with proton pump inhibitors, which are shown to predispose to skeletal fragility (14, 18, 53, 54). A third limitation of our study was related to the mode of analysis of vertebral fractures, which was based only on evaluation of chest radiographs. This approach allowed us to identify only thoracic vertebral fractures with likely underestimation of true prevalence of vertebral fractures in this clinical context. In fact, the prevalence of radiological lumbar fractures in patients with HF is still unknown and it is unclear whether HF patients and control subjects had a comparable ratio of thoracic-to-lumbar fractures. However, thoracic fractures are the most common osteoporotic fractures (55) and the high prevalence observed in our patients with HF may have important clinical implications. Fractures involving the thoracic spine can cause an impairment of lung capacity which implies relevant consequences, including potential worsening of HF (56). As a matter of fact, the finding of an association between number of hospitalizations of patients with HF and prevalence and severity of thoracic vertebral fractures seems to suggest a potential influence of fractures on the clinical outcome of HF. Specifically, one could hypothesize that thoracic vertebral fractures, probably through a reduction of lung capacity, may be a contributing factor to deterioration of cardiopulmonary performance which may require frequent hospital admissions.

In conclusion, our study shows for the first time that patients suffering from HF are at higher risk of radiological vertebral fractures than patients without HF in the same clinical context. In those patients, vertebral fractures are likely a marker of frailty. Based on our data, HF patients should be actively evaluated for their bone health including at least a morphometric evaluation of thoracic chest X-ray. In the case of a prevalent fracture, densitometric and biochemical evaluation will be needed to establish an adequate anti-osteoporotic treatment.
Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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