Relationship between Depression, BNP Levels and Ventricular Impairment in Heart Failure

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Abstract

Background: Depression is a common comorbidity in heart failure (HF); however, the mechanisms related to a poorer outcome of depressed patients with HF remain unclear.

Objective: To evaluate the role of severe depression in the outcome of patients with decompensated HF.

Methods: A total of 43 patients with advanced HF, EF < 40.0%, and hospitalized for cardiac compensation were consecutively studied. After history taking and physical examination, the patients underwent laboratory tests including BNP determination. After the diagnosis of depression was made, the Hamilton-D scale was applied. Severe depression was defined by a score equal to or greater than 18. The clinical and laboratory variables according to the presence or absence of severe depression were analyzed using logistic regression. The ROC curve defined the cut-off point for BNP.

Results: Severe or very severe depression was identified in 24 (55.8%) patients. Severely depressed patients did not differ from non-depressed patients as regards age, gender and renal function, but showed less cardiac impairment (EF 23.4 ± 7.2% vs 19.5 ± 5.2%; p = 0.046) and higher BNP levels (2,582.8 ± 1,596.6 pg/ml vs 1,206.6 ± 587.0 pg/ml; p < 0.001). However, patients with BNP levels higher than 1,100 pg/ml had a 12.0-fold higher chance (odds ratio [95% CI] = 2.61 - 55.26) of developing severe depression.

Conclusion: Patients with severe depression showed a higher degree of neurohormonal stimulation despite their lower degree of ventricular dysfunction. The pathophysiological changes related to depression, leading to increased neurohormonal stimulation and cytokines, probably contributed to this more intense clinical manifestation even in the presence of less cardiac damage. (Arq Bras Cardiol 2010;95(6):732-737)

Keywords: Depression; comorbidity; heart failure; natriuretic peptides/analysis.

Introduction

Heart failure (HF) is known to be a syndrome accompanied by high morbidity and mortality. Both morbidity and mortality are influenced by the comorbidities of the patients, and patients with comorbidities, among which is depression, have a poorer outcome. In the overall population, from 5.0% to 10.0% of the individuals have criteria for the diagnosis of depression. Among patients with heart failure seen in outpatient clinics, this prevalence is of between 11.0% and 25%, and among those hospitalized with HF, the rate increases to the range of 35.0% to 70.0%. The wide variation in the incidence results from the different techniques used for the diagnosis, as well as from the characteristics of the study populations, considering age, gender and severity of HF. Anyway, a strong association between HF and depression is observed.

HF and depression share common pathophysiological aspects, both increasing the stimulation of the hypothalamus-pituitary-adrenal axis and the sympathetic activity, as well as increasing the levels of circulating inflammatory cytokines. Depression can contribute to the development of HF in susceptible populations and aggravate the manifestations of HF in those with existing disease, and is predictive of rehospitalizations and mortality.

The high morbidity and mortality may be related to the synergistic action between HF and depression on neurohormonal activation; to inflammatory factors; and to hypercoagulability. Depression also has a negative influence on the course of HF, for being associated with patient non-compliance with medical recommendations, especially as regards the use of medications. Patients with HF and depression are more symptomatic, presenting with more advanced functional class and frequently a poorer quality of life.

In view of these findings, we sought to verify the role of severe depression in the clinical presentation of patients with advanced HF admitted in a tertiary hospital for cardiac compensation.
Methods

In a large tertiary hospital in the city of São Paulo, we conducted a cross-sectional study including 43 consecutive patients hospitalized for compensation of heart failure and for whom psychiatric evaluation had been requested by the clinician. Psychiatric evaluation is performed at the discretion of the patient’s clinician, and not routinely for all patients.

At hospital admission, all patients were clinically assessed and underwent laboratory tests including complete blood count, hematocrit, and determination of serum levels of BUN, creatinine, sodium, potassium, and B-type natriuretic peptide (BNP).

Patients with left ventricular ejection fraction < 0.40 for whom a psychiatric evaluation had been requested by the clinician were included in the study. The exclusion criteria were delirium; dementia; psychosis; bipolar affective disorders; sepsis; neoplasias; and baseline creatinine > 3.0 mg/dl.

Left ventricular ejection fraction (LVEF) was calculated by means of echocardiographic study using the Teichholz method or Simpson’s rule performed within six months prior to hospitalization. BNP was determined by chemiluminescence immunoassay, ADVIA Centaur™ system (Roche Inc.), and was expressed as pg/ml.

Patients meeting the inclusion criteria and not meeting the exclusion criteria underwent depression assessment using the 17-item version Hamilton-D depression assessment rating scale. In this scale, the patients were classified as follows:
- from 0 to 7 points, normal;
- from 8 to 13 points, patients with mild depression;
- from 14 to 18 points, moderate depression;
- from 19 to 22 points, severe depression; and
- 23 or more points, very severe depression.

According to the result of the assessment of presence of depression, the patients were divided into two groups: group 1 - comprising patients with less than 18 points in the Hamilton scale (euthymia or mild and moderate depression), and group 2 - comprising patients with a score higher than 18 (severe or very severe depression).

Statistical analysis

Categorical variables were expressed as proportion and percentage, and continuous variables as mean and standard deviation.

Comparisons between continuous variables were made using the Student’s t test. The chi square test or Fisher’s exact test were used to analyze the categorical variables. The ROC curve was constructed to analyze the best cut-off point between BNP levels and the assessment of intensity of depression. Univariate and multiple logistic regression analyses were used to determine predictors of depression. Variables with p < 0.200 in the univariate analysis were included in the multivariate analysis. The final model was constructed using the stepwise forward procedure. In the final model, variables with p < 0.05 were maintained.

In the comparisons, differences with p values < 0.05 were considered significant.

Results

Table 1 shows the main clinical characteristics of the patients.

The mean age of the patients was 54.3 ± 15.9 years.

In this population, all patients were in NYHA functional class IV, the mean LVEF was 21.6 ± 6.6, and the mean BNP level was 1,974 ± 1,421.9 pg/ml. These findings characterize the participants as patients with advanced HF.

It was also observed that most of the patients with HF and systolic ventricular dysfunction hospitalized for compensation presented with severe or very severe depression (24 patients - 55.8%).

Results of the variables according to the presence or absence of severe or very severe depression are shown in Table 2.

Patients with severe or very severe depression did not differ from those without depression or with mild and moderate depression as regards age, gender, and renal function, but they presented with less cardiac impairment (LVEF 23.4 ± 5.2% vs 19.5 ± 5.2%; p = 0.046) and higher BNP levels (2,582.8 ± 1,596.6 pg/ml vs 1,206.6 ± 587.0 pg/ml; p < 0.001).

In face of the difference in BNP levels between the patients with severe or very severe depression and the others, an ROC curve was constructed which identified the BNP level of 1,100 pg/ml as the best cut-off point (Area under the curve = 0.79), with sensitivity = 87.5% and specificity = 63.2%.

In the logistic regression analysis, BNP was the only independent variable related to an increased risk of severe depression, and patients with BNP ≥ 1,100 pg/ml had a 12-fold higher chance of developing severe depression (Table 3).

Table 1 - Main clinical characteristics of the study population (frequency, mean and standard deviation)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>43</td>
</tr>
<tr>
<td>Age (mean and standard deviation)</td>
<td>54.3 ± 15.9</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>26 (60.5%)</td>
</tr>
<tr>
<td>White</td>
<td>23 (53.5%)</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>14 (32.6%)</td>
</tr>
<tr>
<td>Chagas cardiomyopathy</td>
<td>14 (32.6%)</td>
</tr>
<tr>
<td>FC IV</td>
<td>43 (100%)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>21.6 ± 6.6</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.9 ± 2.2</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>39.3 ± 6.8</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>65.3 ± 27.4</td>
</tr>
<tr>
<td>Creatinine(mg/dl)</td>
<td>1.5 ± 0.4</td>
</tr>
<tr>
<td>Sodium (mEq/l)</td>
<td>132.2 ± 6.6</td>
</tr>
<tr>
<td>Potassium (mEq/l)</td>
<td>4.5 ± 0.8</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>1,974 ± 1,421.9</td>
</tr>
<tr>
<td>Hamilton D</td>
<td>18.1 ± 9.9</td>
</tr>
</tbody>
</table>
Table 2 - Variables according to the presence or absence of severe or very severe depression

<table>
<thead>
<tr>
<th>Variable</th>
<th>≥18</th>
<th>&lt; 18</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>24 (55.8%)</td>
<td>19 (44.2%)</td>
<td>0.055</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.4 ± 16.4</td>
<td>55.4 ± 15.6</td>
<td>0.761</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>14 (58.3%)</td>
<td>12 (63.1%)</td>
<td>0.856</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>23.4 ± 7.2</td>
<td>19.5 ± 5.2</td>
<td>0.046</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.8 ± 2.2</td>
<td>13.1 ± 2.3</td>
<td>0.596</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>38.9 ± 6.8</td>
<td>39.9 ± 6.8</td>
<td>0.614</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>61.3 ± 27.4</td>
<td>70.6 ± 27.3</td>
<td>0.271</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.5 ± 0.4</td>
<td>1.6 ± 0.45</td>
<td>0.596</td>
</tr>
<tr>
<td>Sodium (mEq/l)</td>
<td>136.4 ± 3.8</td>
<td>136.0 ± 3.8</td>
<td>0.584</td>
</tr>
<tr>
<td>Potassium (mEq/l)</td>
<td>4.5 ± 0.8</td>
<td>4.6 ± 0.8</td>
<td>0.786</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>2,582.8 ± 1,596.6</td>
<td>1,206.6 ± 587.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Log BNP</td>
<td>7.7 ± 0.6</td>
<td>7.0 ± 0.5</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

In the study population, 12/43 (27.9%) patients died during hospitalization; 3/19 (15.7%) were from the group with mild to moderate depression and 9/24 (37.5%) from the group with severe or very severe depression (p = 0.115). In the follow-up 90 days after hospitalization, three more deaths were observed, one in the group with mild to moderate depression and two in the group with more severe depression. In all, by the end of 90 days, 15/43 (34.8%) patients died, 4/19 (21.0%) in the group with mild to moderate depression and 9/24 (37.5%) from the group with severe or very severe depression (p = 0.090).

Discussion

High morbidity and mortality are observed in advanced forms of HF. The presence of comorbidities may worsen the outcome of the patients, thus further increasing morbidity and mortality, which are already high.

The presence of anemia, atrial fibrillation, thyroid dysfunction, chronic obstructive pulmonary disease and depression are known to be factors associated with a poorer prognosis.

Depression is a multifaceted condition. Hovranek et al identified four independent factors associated with the development of depression: living alone, alcohol abuse, financial losses, and worsening of HF. The loss of social support is identified as one of the most important factors for depression, increasing its risk by 3.2 times in men and 8 times in women.

Depression has not been systematically analyzed in patients with HF, but, when studied, it is verified to be relatively common among these patients. In patients without HF, major depressive manifestations are described in 14.0%-26.0% of the individuals; however, in patients with HF, this incidence rises to 24.0%-85.0% of the patients. The prevalence of depression increases with age, but is clearly aggravated by the presence of HF. Not only does the incidence of depression increase with the presence of HF, but it is also related to its severity, being more frequent in more symptomatic HF.

Thus, the frequency of depressive disorders is higher among cohorts of hospitalized patients than among outpatients, probably as a reflex of the greater severity of HF in hospitalized patients. Mild depression may be found in most of the patients hospitalized for cardiac decompensation, affecting 85.0% of them. Severe depression is less frequent.

Not only is depression commonly seen in patients with HF; but also patients with HF and depression have a two to three-fold higher risk of death. Depressed patients are also hospitalized approximately three times more frequently, and depression does not resolve in one third of the patients in the first year of follow-up. Depression increases the costs of treatment by 25.0%-40.0%, as well as hospitalization rates, and is associated with worsened functional class and impaired daily activities.

In the present study, we sought to evaluate the relationship between HF and depression in patients with advanced HF. The diagnosis of depression is made by means of a psychiatric assessment, and the Hamilton-D scale helps classify the severity of the disease by turning the assessment into figures, which is useful in scientific research. With this test, the severity of depression is scored; the higher the score, the more severe the disease. In the present study, we applied the Hamilton-D scale because of its accuracy in the diagnosis of depression and its easy way to graduate depression, as well as for having demonstrated (in several studies) that it evaluates the degree of severity in crises of depression.

Our case series comprised patients with advanced HF. In Hospital Auxiliar de Cotoxo, a severity bias occurs, because only patients who could not be compensated or who did not improve in the emergency room are admitted. In this population, 55.8% of the patients presented with signs.
of severe or very severe depression, as identified by the Hamilton-D scale which showed scores higher than 18.

When we compared our data to those of the literature, we observed that the incidence of severe depression among our patients was higher than that described in published studies on patients with HF.12,15 The characteristics of our population comprised of patients with very advanced HF may be an explanation to this finding, because of the strong correlation between severity of HF and the incidence and severity of depression. The pathophysiology, with aspects common to HF and depression, may explain this finding, since both HF and depression lead to the elevation of neurohormone and cytokine levels so that, by acting together, they enhance the pathophysiological changes, which, in turn, exacerbate clinical manifestations, morbidity and mortality.13-17,19

However, in our study, when patients with severe depression (Hamilton-D score > 18) were compared to those without depression or with mild to moderate depression, it was interesting to observe that those with severe or very severe depression showed higher BNP levels (2,582.8 ± 1,596.6 pg/ml vs 1,206.6 ± 587.0 pg/ml; p < 0.001). This indicates more severe manifestations of congestion, in contrast to higher ejection fraction values (33.4 ± 7.2% vs 19.5 ± 5.2%; p = 0.046), which indicates less ventricular impairment.12,13,17,19 These data may be considered as a documentation of the previously mentioned synergy between HF and depression in the genesis of the clinical manifestations of patients with the disease.

It is important to point out that there were no differences between the two groups as regards gender, age, anemia, and renal function, which are factors known to exert influence on the clinical manifestations and BNP levels.

In relation to some aspects these results are different from those described in the literature. In the HF-ACTION study, a relationship was observed between clinical manifestations (more severe) in patients with depression in comparison to non-depressed patients, but no correlation was observed between objective measurements of the cardiac function and the presence of depression.20 However, in our study, we verified a clear relationship between the presence of severe depression and objective signs of more severe congestion (high BNP levels). The synergistic action between HF and depression, as well as the presence of a greater number of cases of severe depression, may possibly have exacerbated the clinical manifestations to the point of making them statistically different.

To a certain extent, this lesser myocardial impairment and the documentation of more severe congestion (higher BNP levels) show the importance of depression in the exacerbation of the clinical manifestation of depressed patients because even with less cardiac impairment they present with more clinical manifestations. This explains why depressed patients are more frequently hospitalized than non-depressed patients.

The attitude of the patients in relation to their disease also contributes to the genesis of the manifestations. Depressed patients are less compliant with non-pharmacological advices (salt ingestion and fluid restriction) as well as with the pharmacological treatment.15,16 Non-compliance with treatment is increasingly described as being associated with a poorer outcome.20-23

The pool of data strongly suggests that HF exacerbates or triggers depression, but the converse is also true. May et al studied 13,708 patients with coronary artery disease without HF or depression and observed that HF developed in 3.6% of the non-depressed patients and in 16.4% of the depressed patients during the follow-up. Depression was associated with a 1.5-fold higher risk of the patient further presenting with HF in relation to non-depressed patients.6

In our study, we could also demonstrate HF as the cause of depression. When BNP levels and their relation to the incidence of severe depression were analyzed, we could verify a strong correlation between higher BNP levels and a higher incidence of severe or very severe depression. Using the ROC curve, we identified that BNP levels higher than 1,100 pg/ml were associated with a higher prevalence of depressive symptoms, with a 12.0-fold higher chance of these patients with HF developing severe depression in comparison to those with lower BNP levels (Figure 1).

Considering that depression exacerbates the clinical manifestations and worsens the outcome of patients with HF, we clinicians should pay more attention to it, and never fail to investigate whether patients with HF also present with depression. The importance of this approach has increasingly being considered, and now there are studies showing that, by treating depression, improvement of symptoms and a better quality of life for the patients are achieved. Some studies also showed that treating depression with antidepressant drugs may

![Figure 1 - ROC curve for the determination of the cut-off point of BNP levels for the presence of severe depression in patients with HF. BNP ≥ 1,100 pg/ml, sensitivity of 87.5% and specificity of 63.5%.](image-url)
reduce the morbidity and mortality of patients with HF.21,24)

The possibility of changing the natural history of the HF by treating depression is worthy of attention. In our case series of patients with advanced HF, in-hospital mortality was high (27.9%); among patients with severe or very severe depression it was 2.38 times higher than among those with mild or moderate depression (37.5% vs. 15.7%; p = 0.115). Despite the difference in mortality, it was not statistically significant. These results should be carefully considered in view of the sample size; however, they are consistent with reports of the literature regarding the worse outcome of patients with depression.

Our results showed that severe depressive manifestations are frequent among patients with advanced HF and that their presence exacerbates the symptoms of cardiac decompensation as well as its severity. This study showed a relationship between depression and more neurohormonal stimulation in HF as assessed by BNP with depression exacerbating the neurohormonal stimulation and HF worsening depression.25

In conclusion, the prevalence of depression in advanced HF is high; patients with depression show higher BNP levels than non-depressed patients; and the more decompensated the patient, the higher their chance of developing severe or very severe depression. Given the small sample size, these findings should be considered as preliminary.

Investigation of the presence of depression has been overlooked among patients with HF and this should be changed, since the identification and treatment of depression may improve both the quality of life and the outcome of patients with HF.

Potential Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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Study Association
This study is not associated with any post-graduation program.

References

