**Is Blood Pressure Response to the Valsalva Maneuver Related to Neurohormones, Exercise Capacity, and Clinical Findings in Heart Failure?**

Hans P. Brunner-La Rocca, MD; Daniel Weilenmann, MD; Hans Rickli, MD; Ferenc Follath, MD; and Wolfgang Kiowski, MD

**Objectives:** To investigate the relationship of the BP response to the Valsalva maneuver (VM) to parameters of congestive heart failure (CHF) other than hemodynamic measures.

**Design:** Comparison of neurohormones (atrial natriuretic peptide [ANP], brain natriuretic peptide [BNP], norepinephrine [NE]), parameters of spiroergometry, and clinical parameters with BP response to the VM.

**Setting:** Tertiary care center.

**Patients:** Forty-five patients with stable CHF (ejection fraction, 28 ± 7%).

**Measurements:** Pulse amplitude ratio (PAR) calculated between the end and the beginning of the VM using the last two and the first three beats of the straining phase. Failure of the systolic BP to fall below the resting level during the VM.

**Results:** Patients in the New York Heart Association class III (n = 15) had a higher PAR than those in class II (0.82 ± 0.21 vs 0.63 ± 0.20; p < 0.01). There was a close correlation between PAR and ANP (r = 0.76) and BNP (r = 0.62), whereas other parameters were less well correlated (eg, for peak VO₂, r = -0.35; p < 0.05). Patients with failure of the systolic BP to fall below the resting level (n = 24) had higher neurohormones (mean ANP, 246 ± 158 vs 84 ± 43 pg/mL; mean BNP, 282 ± 289 vs 81 ± 85 pg/mL; p < 0.001; mean NE, 3.9 ± 1.7 vs 3.4 ± 1.5 nmol/L; nanosecond), lower exercise capacity (19.8 ± 5.2 vs 23.0 ± 3.7 mL/kg/min; p < 0.05), and their quality of life (Minnesota questionnaire) was more compromised (31 ± 19 vs 18 ± 15; p < 0.05).

**Conclusions:** The BP response to the VM is related to a broad range of clinical and neurohumoral parameters of CHF. Whether or not it is also related to prognosis remains to be determined. Nevertheless, this easily applicable test should be part of the assessment of patients with CHF.

*(CHEST 1999; 116:861–867)*

**Key words:** congestive heart failure; exercise testing; neurohormones; symptoms; Valsalva maneuver

**Abbreviations:** ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; CHF = congestive heart failure; EF = ejection fraction; NYHA = New York Heart Association; PAR = pulse amplitude ratio; PETCO₂ = partial pressure of end-tidal CO₂; VE/VCO₂ = ventilatory equivalent of CO₂; VM = Valsalva maneuver; VO₂ = oxygen consumption
Materials and Methods

Patient Population

The study population comprised 45 patients (43 men, 2 women) aged 33 to 74 years old (mean age, 55 ± 10 years old) with mild to moderate chronic CHF (ie, diagnosis ≥ 6 months prior to study inclusion) secondary to coronary artery disease (as documented by coronary angiography) in 26 patients (58%), dilated cardiomyopathy in 16 patients (36%), and valvular heart disease in 3 patients (7%). All patients had an ejection fraction (EF) ≤ 40% (mean, 28 ± 7%) and were in stable condition for at least 3 months (ie, no hospitalization and no changes in medical therapy). The EF was determined within 3 months of study inclusion and was performed by echocardiography in 22 patients (49%) and by angiography in 23 patients (51%) using biplane area-length calculations. All patients were on angiotensin-converting enzyme inhibitors and diuretics, 26 were on digitalis, and 19 were on amiodarone. Patients whose exercise capacity was limited by reasons other than CHF were excluded from the study. The protocol was approved by the local ethics committee, and patients gave informed consent to participate in the study.

Evaluation Criteria

All patients were examined in the morning. A history of symptoms of CHF was elicited by a standard questionnaire, and severity of dyspnea, orthopnea, ankle edema, and nocturia were judged on a scale from 0 to 3. In addition, impairments that patients related to their CHF and the severity of dyspnea, orthopnea, ankle edema, and nocturia were judged on a scale from 0 to 3. All patients had an ejection fraction (EF) ≤ 40% (mean, 28 ± 7%) and were in stable condition for at least 3 months (ie, no hospitalization and no changes in medical therapy). The EF was determined within 3 months of study inclusion and was performed by echocardiography in 22 patients (49%) and by angiography in 23 patients (51%) using biplane area-length calculations. All patients were on angiotensin-converting enzyme inhibitors and diuretics, 26 were on digitalis, and 19 were on amiodarone. Patients whose exercise capacity was limited by reasons other than CHF were excluded from the study. The protocol was approved by the local ethics committee, and patients gave informed consent to participate in the study.

BP Recording and VM

Subsequently, heart rate and peripheral BP at rest and during the VM were continuously measured by means of noninvasive equipment (Finapres; Ohmeda; Liberty Corner, NJ). This instrument is based on the volume clamp method of Peñaz and the physical criteria of Wesseling, which has been shown to accurately reflect intra-arterial BP changes. The data were transferred to and recorded on an IBM-compatible computer and analyzed off-line by a person who was blind to the other results.

Ergospirometry

Exercise testing was performed on a treadmill using a two step protocol. ECG was monitored continuously with a CASE 12 monitor (Marquette Medical Systems; Milwaukee, WI), and gas exchange was assessed breath-by-breath using an exercise system (CPX/D; Medical Graphics; St. Paul, MN). The system was calibrated before each test. 

Laboratory Measurements

Venous blood was collected into chilled tubes containing ethylenediamine-tetracetic acid and aprotinin (500 k unit/mL blood) for assessment of natriuretic peptides, and it was collected into tubes containing lithium-heparin for assessment of norepinephrine. Plasma was separated immediately using a refrigerated centrifuge, and it was stored at −80°C until it was measured. Norepinephrine was measured using means of a high performance liquid chromatography separation method after solvent extraction. Atrial natriuretic peptide (ANP) was determined directly (ie, without prior extraction) in duplicate by a competitive radioimmunoassay with 125I as the tracer (Eiken Chemical; Tokyo, Japan). Brain natriuretic peptide (BNP) was likewise determined directly in duplicate by a solid-phase immunometric radioimmunoassay with 125I as the tracer (Shionogi Chemical; Osaka, Japan). All analyses were performed by individuals who were blind to other results.

Statistics

Values are expressed as frequencies and mean ± SD as indicated. The correlation between continuous parameters was

Clinical Investigations

862
determined by using the Pearson correlation test. For ordinal or not normally distributed data, the Spearman rank correlation test was used. Group comparisons were made by using the unpaired Student’s t test or the Mann-Whitney U test as appropriate. A two-tailed significance level of 0.05 was considered to be statistically significant. All analyses were performed using a commercially available statistical package (SPSS for Windows 6.0).

Results

Patients’ characteristics are shown in Table 1. Indexes of neurohumoral stimulation were increased in most patients and the mean EF was < 30%, although the mean peak oxygen consumption was > 20 mL/kg/min. Two thirds of the patients were in New York Heart Association (NYHA) class II, and one third were in class III. Pulse amplitude decreased by a mean of 31% during the VM; however, it increased in four patients (9%) by 2 to 6%. Heart rate increased by a mean of 8.4 ± 7.4 beats per min during the VM. In 24 patients (53%), the systolic BP at the end of the VM was above the systolic BP at rest. The pulse amplitude and the heart rate responses to the VM were significantly less in this group (PAR, 0.86 ± 0.11 [range, 0.65 to 1.08] vs 0.50 ± 0.15 [range, 0.18 to 0.72]; heart rate response, 5.8 ± 5.2% [range, −1.4 to 19.0%] vs 19.9 ± 11.7% [range, 2.8 to 46.0%]; for both, p < 0.001). Medication and etiology of CHF did not significantly influence the response of either BP or heart rate to the VM.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (± SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>55 ± 10</td>
<td>33–74</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81.4 ± 13.2</td>
<td>56–124</td>
</tr>
<tr>
<td>Symptom score</td>
<td>3.2 ± 1.3</td>
<td>1–7</td>
</tr>
<tr>
<td>Physical signs of CHF, %</td>
<td>16†</td>
<td>—</td>
</tr>
<tr>
<td>NYHA class (II/III)</td>
<td>30/15</td>
<td>2–3</td>
</tr>
<tr>
<td>Minnesota LHFQ</td>
<td>25 ± 19</td>
<td>1–76</td>
</tr>
<tr>
<td>EF, %</td>
<td>27.7 ± 7.3</td>
<td>11–40</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>117 ± 16</td>
<td>92–150</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>67 ± 10</td>
<td>54–89</td>
</tr>
<tr>
<td>Heart rate supine, beats per min</td>
<td>70 ± 12</td>
<td>50–93</td>
</tr>
<tr>
<td>PAR during VM</td>
<td>0.69 ± 0.22</td>
<td>0.18–1.06</td>
</tr>
<tr>
<td>Heart rate increase during VM, %</td>
<td>12.4 ± 11.2</td>
<td>−1.4–47.4</td>
</tr>
<tr>
<td>Systolic BP end VM &gt; systolic BP</td>
<td>53†</td>
<td>—</td>
</tr>
<tr>
<td>rest, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANP, pg/mL</td>
<td>170 ± 143</td>
<td>24–738</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>188 ± 239</td>
<td>3–1270</td>
</tr>
<tr>
<td>Norepinephrine, nmol/L</td>
<td>3.7 ± 1.6</td>
<td>1.0–7.5</td>
</tr>
<tr>
<td>Peak VO₂, mL/kg/min</td>
<td>21.3 ± 4.8</td>
<td>10.1–30.8</td>
</tr>
<tr>
<td>Peak heart rate, beats per min</td>
<td>139 ± 23</td>
<td>97–187</td>
</tr>
<tr>
<td>Duration of ramp exercise, min</td>
<td>10.4 ± 4.4</td>
<td>1.3–17.3</td>
</tr>
</tbody>
</table>

* LHFQ = Minnesota Living With Heart Failure Questionnaire.
† n = 7.
‡ The PAR indicates the ratio of pulse amplitude during phase 2 of the VM.
§ n = 24.

There was no correlation between the PAR and left ventricular EF (r = −0.06). Similarly, the EF was not different between patients with systolic BP at the end of the VM above and below the resting level. Table 2 shows the correlation of the PAR with neurohormones and exercise capacity. In addition, these parameters were compared in patients having a PAR < or > 0.8 and a systolic BP at the end of the VM below or above resting level, respectively. It shows that neurohormones were elevated and that peak oxygen consumption (VO₂) during exercise was reduced in patients with only minimal BP response to the VM. In addition, respiratory response to exercise was higher in these patients. Natriuretic peptides showed a good correlation to the PAR (Fig 1). While peak VO₂ was only fairly correlated to the PAR, the ventilatory equivalent of CO₂ (VE/VCO₂), and the partial pressure of end-tidal CO₂ (PETCO₂) were reasonably correlated, indicating hyperpnea in patients with a high PAR at both low and maximum intensity exercise.

Symptoms of CHF were generally less related to the response to the VM. Nevertheless, quality of life, as assessed by the Minnesota Living With Heart Failure Questionnaire, showed a reasonable relation to BP response (Fig 2). In addition, the PAR was significantly higher in NYHA class III patients than in NYHA class II patients (0.82 ± 0.21 vs 0.63 ± 0.20; p = 0.005), and the physical signs of CHF tended to be more common in patients with a minimal response to the VM. Finally, cough, particularly productive cough, was related to the BP response to the VM. Table 3 summarizes the results.

Discussion

Our results show that the BP response to the VM is related to a variety of clinical and biochemical markers of CHF. In particular, it was closely related to natriuretic peptides, which are considered to play an important role in the homeostasis of the cardiovascular system in CHF and are powerful prognostic markers in these patients.17–19 It has long been suggested that the BP response to the VM is useful in evaluating myocardial dysfunction. In the early 1980s, it was shown that left ventricular EF is significantly lower if the normal decrease in the pulse pressure is diminished or absent.4,5 In addition, it was found useful to distinguish the etiology of acute dyspnea.20 We did not find any correlation between EF and the pulse pressure response to the VM. Although this is in agreement with other studies that found either no correlation or a poor correlation to EF, but found a close correlation to left sided filling pressures,7,8,21
the discrepancy might be explained by the fact that we included patients with \( EF \leq 40\% \), which thereby only limited the range of this variable and the likelihood of finding a statistical correlation.

One indispensable condition for an abnormal response seems to be the maintenance of left ventricular filling throughout the course of the strain phase of the VM\(^6\) in the presence of reduced venous return.\(^{22}\) This assumption is supported by the finding that end-diastolic volume\(^{23,24}\) and left atrial dimension\(^{25}\) as assessed by echocardiography did not change during the VM in CHF patients with pulmonary congestion. Accordingly, the BP response to the VM may be useful in detecting left ventricular dysfunction accompanied with elevated filling pressure. Recent studies showed that elevated pulmonary wedge pressure may be detected with a reasonable diagnostic accuracy by pulse pressure response to the VM. In addition, changes of pulmonary wedge pressure corresponded well with changes in pulse pressure response in both studies.\(^6,9\)

Our study supports the diagnostic usefulness of the VM in that the BP response was also related to a variety of other parameters reflecting the severity of CHF. Of those, its relation to natriuretic peptides was best. This might be expected since natriuretic

\[ r = 0.75 \]

\[ r = 0.60 \]

\[ r = 0.39 \]

\[ r = 0.0001 \]
peptides are also related to left sided filling pressures. Moreover, increased natriuretic peptides are associated with a clinical progression of CHF and indicate a poor prognosis independently of other clinical variables. Thus, it is tempting to speculate that BP response to the VM may be a marker of prognosis in patients with CHF. Indeed, it has been shown that the BP response pattern to the VM predicted the prognosis in patients after myocardial infarction. However, there was also a close relation between the BP response pattern and the EF. Whereas patients with a normal response had a normal EF, patients with an abnormal response had a markedly reduced EF. Thus, it is not possible to say whether or not the BP response to the VM is an independent predictor of prognosis and whether or not the aforementioned findings also apply to patients with chronic CHF and nonischemic etiology. Obviously, larger trials would be required to address this question.

The BP response to the VM was also related to the ventilatory response to exercise. Several studies have shown that ventilatory response to exercise in patients with CHF is greater than normal for a given metabolic rate and contributes to the perception of dyspnea in these patients. It is most probably caused by high ventilation/perfusion mismatching, an increase in VCO₂ relative to VO₂ resulting from HCO₃⁻ buffering of lactic acid, and a decrease in PaCO₂ due to tight regulation of arterial pH. The underlying mechanisms are not yet completely understood. Whereas some studies showed that the ventilation/perfusion mismatching is related to an increase in pulmonary wedge pressure, others could not find such a relationship and suggested structural changes as the underlying cause. Our data suggest that an increase in central blood volume is an important contributor to the greater ventilatory response in patients with CHF. Even at very low intensity exercise corresponding to daily life activities (ie, 1 mile/h, 6% elevation), there was a clear relation between the ventilatory response and the BP response to the VM at rest. Accordingly, the BP response to the VM seems to be a good indicator of the ventilatory response to exercise and, thereby, not only a sign of intolerability of peak exercise, but also of daily life activities.

Finally, the BP response to the VM was also related to clinical symptoms and physical signs of CHF. Of these, its correlation to the Minnesota Living With Heart Failure Questionnaire score was best. This questionnaire has been shown to be a valid indicator of patients’ perspectives concerning the effects of disease and therapy in CHF and also of the therapeutic benefits of medications for CHF. Thus, an increase in the central blood pool in patients with CHF seems to contribute to the perception of the severity of the disease, and its assessment might be useful for targeting therapy according to the patient’s individual need.

**Limitations**

We did not measure left sided filling pressures invasively, and our results do not allow any conclu-

---

**Table 3—Clinical Variables in Patients With Normal and Reduced Blood Pressure Response to the VM and Correlation Between Clinical Variables and PAR**

<table>
<thead>
<tr>
<th>Variables</th>
<th>PAR</th>
<th>BP VM†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 0.8</td>
<td>&gt; 0.8</td>
</tr>
<tr>
<td>NYHA class III, %</td>
<td>—</td>
<td>18†</td>
</tr>
<tr>
<td>Physical signs of CHF, %</td>
<td>—</td>
<td>7†</td>
</tr>
<tr>
<td>Symptoms of CHF</td>
<td>0.24</td>
<td>2.5 ± 1.0</td>
</tr>
<tr>
<td>Dry cough score</td>
<td>0.22</td>
<td>1.3 ± 1.7</td>
</tr>
<tr>
<td>Productive cough score</td>
<td>0.32**</td>
<td>1.0 ± 2.0</td>
</tr>
<tr>
<td>LHFQ score</td>
<td>0.39‖</td>
<td>18 ± 15</td>
</tr>
</tbody>
</table>

* p < 0.05. Values are given as percent or mean (± SD). See Table 1 for abbreviation.
† Refers to systolic BP at the end of the VM or at rest.
‡ n = 5.
§ n = 10.
¶ n < 0.01.
‖ n = 2.
# n = 13.
** p < 0.05.
†† n = 1.
‡‡ n = 16.
sion as to whether or not the relation between natriuretic peptides and the PAR was independent of the relation of natriuretic peptides to left sided filling pressures.

Furthermore, EF was measured using two different methods, and it was not measured on the same day that the rest of the tests were performed. This might have negatively influenced its correlation to the BP response to the VM. However, only the patients who had remained stable since the EF was assessed were included in the study. In addition, apart from similar findings in other studies,7,8,21 the BP response to the VM seems to depend mainly on the central blood volume.23,39 Obviously, systolic dysfunction is only one reason for such an increase and is a particularly important factor in a patient population with a broad range of EFs.4,5,29 which is different from our patient population.

In addition, many of our patients were on drugs that influence the autonomic nervous system. Accordingly, we cannot exclude our findings being influenced by drug therapy; however, we did not find such an influence statistically. Nevertheless, we did not include the phase 4 response of the VM in our analysis because it is influenced by baroreceptors.

Finally, it might be argued that measurements of BP and its changes were not accurate enough because we did not measure BP invasively. However, prior to the study, we tested the Finapres device against invasive recordings of the pressure in the radial artery, which did not show a significant difference between the two methods (unpublished data). In addition, it has been shown that the Finapres device can be used to reliably measure BP and its changes during the VM.13

CONCLUSION

The BP response to the VM, assessed either by the pulse amplitude response or by the failure of the systolic BP to fall below the resting level, is related to a broad range of clinical parameters and, in particular, measures of neurohumoral activation, as well as the patient’s perception of the severity of the disease in chronic stable CHF. In view of the prognostic importance of elevated neurohormones in chronic CHF, it is tempting to speculate that this easily performed, noninvasive maneuver may not only aid in the assessment of the severity of CHF but also relate to its prognosis. This contention would have to be tested in an appropriately designed larger trial.

REFERENCES

8 Schmidt DE, Shah PK. Accurate detection of elevated left ventricular filling pressure by a simplified bedside application of the Valsalva maneuver. Am J Cardiol 1993; 71:462–465
11 Rector TS, Kubo SH, Cohn JN. Patients’ self-assessment of their congestive heart failure: II. Content, reliability and validity of a new measure, the Minnesota Living With Heart Failure Questionnaire. Heart Failure 1987; 3:198–209
17 Keogh AM, Baron DW, Hickie JB. Prognostic guides in patients with idiopathic or ischemic dilated cardiomyopathy assessed for cardiac transplantation. Am J Cardiol 1990; 65:903–908

866

Clinical Investigations
symptomatic left ventricular dysfunction. Circulation 1997; 96:509–516
20 Zema MJ, Masters AP, Margouleff D. Dyspnea: the heart or the lungs? Differentiation at bedside by use of the simple Valsalva maneuver. Chest 1984; 85:59–64
38 Rector TS, Kubo SH, Cohn JN. Validity of the Minnesota Living with Heart Failure questionnaire as a measure of therapeutic response to enalapril or placebo. Am J Cardiol 1993; 71:1106–1107