Acute Effects of Continuous Positive Air way Pressure on Pulse Pressure in Chronic Heart Failure

Mônica Quintão[1,2], Sérgio Chermont[1,2], Luana Marchese[1,2], Lúcia Brandão[2], Sabrina Pereira Bernardez[1], Evandro Tinoco Mesquita[1], Nazareth de Novaes Rocha[1], Antônio Claudio L. Nóbrega[1]

Programa de Pós-graduação em Ciências Cardiovasculares/Universidade Federal Fluminense[1]; Clínica de Insuficiência Cardíaca (CLIC)/Centro Universitário Serra dos Órgãos[2], Teresópolis, RJ - Brazil

Abstract

Background: Patients with heart failure (HF) have left ventricular dysfunction and reduced mean arterial pressure (MAP). Increased adrenergic drive causes vasoconstriction and vessel resistance maintaining MAP, while increasing peripheral vascular resistance and conduit vessel stiffness. Increased pulse pressure (PP) reflects a complex interaction of the heart with the arterial and venous systems. Increased PP is an important risk marker in patients with chronic HF (CHF). Non-invasive ventilation (NIV) has been used for acute decompensated HF, to improve congestion and ventilation through both respiratory and hemodynamic effects. However, none of these studies have reported the effect of NIV on PP.

Objective: The objective of this study was to determine the acute effects of NIV with CPAP on PP in outpatients with CHF.

Methods: Following a double-blind, randomized, cross-over, and placebo-controlled protocol, twenty three patients with CHF (17 males; 60 ± 11 years; BMI 29 ± 5 kg/cm², NYHA class II, III) underwent CPAP via nasal mask for 30 min in a recumbent position. Mask pressure was 6 cmH_2O, whereas placebo was fixed at 0-1 cmH_2O. PP and other non invasive hemodynamics variables were assessed before, during and after placebo and CPAP mode.

Results: CPAP decreased resting heart rate (Pre: 72 ± 9; vs. Post 5 min: 67 ± 10 bpm; p < 0.01) and MAP (CPAP: 87 ± 11; vs. control 96 ± 11 mmHg; p < 0.05 post 5 min). CPAP decreased PP (CPAP: 47 ± 20 pre to 38 ± 19 mmHg post; vs. control: 42 ± 12 mmHg, pre to 41 ± 18 post p < 0.05 post 5 min).

Conclusion: NIV with CPAP decreased pulse pressure in patients with stable CHF. Future clinical trials should investigate whether this effect is associated with improved clinical outcome.(Arq Bras Cardiol. 2014; 102(2):181-186)

Keywords: Heart Failure; Pulse Pressure; CPAP.

Introduction

Heart failure (HF) is one of the main public burdens in developing countries, and despite medical advances, the mortality of HF remains elevated [1]. Neurohumoral activation in HF leads to left ventricular dysfunction and reduced mean arterial pressure (MAP). Compensatory mechanisms to maintain MAP causes vasoconstriction, which increases peripheral vascular resistance and conduit vessel stiffness [2]. These effects increase pulse pressure (PP), which reflects a complex interaction of the heart with the arterial and venous systems [3,4]. Pulse pressure is determined by two hemodynamic components: a direct component, which is a product of ventricular ejection (stroke volume and ventricular ejection swiftness) and great vessel viscoelastic property interactions, as well as an indirect component resulting from the pulse wave [5,6]. As increased PP expresses progression of HF, it is has been related to increased ventricular afterload [7] and myocardial oxygen demand [8], impaired ventricular relaxation [9], and subendocardial ischemia [10]. Therefore, increased PP is an important risk marker for subsequent cardiovascular events in patients with chronic HF (CHF)[11,12]. Previous studies have reported that a PP of 50 mm Hg is the mean normal value for clinic reference in both men and women [13], and above 53 mm Hg it increases risk of cardiovascular events [14,15].

Noninvasive ventilation (NIV) has been used in decompensated HF to decrease pulmonary congestion and improve ventilation through both mechanical and hemodynamic effects [16,17]. In patients with stable CHF, NIV has not been extensively studied. Naughton et al [18] have shown that the administration of continuous positive airway pressure (CPAP) to patients with stable HF at rest acutely improved cardiac performance and also reduced the work of breathing. Others have shown increases in cardiac output and stroke

Mailing Address: Sergio Chermont •
Estrada da Prata s/n. Prata. CEP 25976-340, Teresópolis, RJ – Brazil
E-mail: schermont@yahoo.com.br
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volume along with decreased systemic vascular resistance among patients with CHF and elevated left ventricular filling pressure [19,20]. However, none of these studies has reported the effect of NIV on PP, which is an independent risk marker in patients with stable HF [11,12].

In the present study, we hypothesized that in patients with CHF, NIV would decrease pulse pressure by unloading the ventilatory muscles and improving cardiac performance. Therefore, the aim of the present study was to determine the effects of a single session of NIV with CPAP on pulse pressure in patients with stable CHF.

Methods

The study included patients with systolic CHF from the University Hospital Heart Failure Clinics. The inclusion criteria were: 1) CHF of either ischemic or idiopathic etiology for at least 3 months, 2) left ventricular ejection fraction (LVEF) ≤ 45% within the previous 3 months, documented by echocardiography or radioisotope ventriculography, 3) New York Heart Association class II or III; 4) stable disease with no hospital admission in the previous 3 months. Clinical stability was defined as the absence of change in symptoms, clinical status, or medications in the preceding 3 months. Patients were excluded from the study if they had significant obstructive lung disease ($FEV_1/FVC < 75\%$ predicted), unstable angina, significant cardiac arrhythmias, or myocardial infarction within the previous 3 months. The subjects completed a screening visit that included a clinical examination and pulmonary function testing (Marquette Hellige, Germany). This protocol was approved by the Human Research Ethics Committee and all patients gave informed consent before entering the study.

The study protocol consisted of a double-blind, randomized, cross-over, and placebo-controlled investigation of the hemodynamic effects of NIV in a controlled environment. Twenty-three patients were recruited and the experiments were performed on two different days with an interval of 3-5 days. The patient had no knowledge of prior randomized ventilation mode and the principal investigator was not present at the scene of NIV. A preliminary NIV session was performed for adaptation and determination of mask size, tolerance to the method and the individual pressure of CPAP to be used in the experiment. The sensation of respiratory discomfort was gauged during all tests by using an arbitrary comfort score (0 = no discomfort, up to 5 = very uncomfortable). This parameter was used to limit the increase or to decrease mask pressure whenever the rating reached 4 or 5 in the NIV adaptation sessions.

On CPAP day, patients underwent a protocol using the predetermined mask pressure and CPAP time. On the control day, patients underwent placebo CPAP consisting of the application of a fixed pressure of ≤ 1 cmH_2O for 30 min by means of a bypass valve (Figure 1).

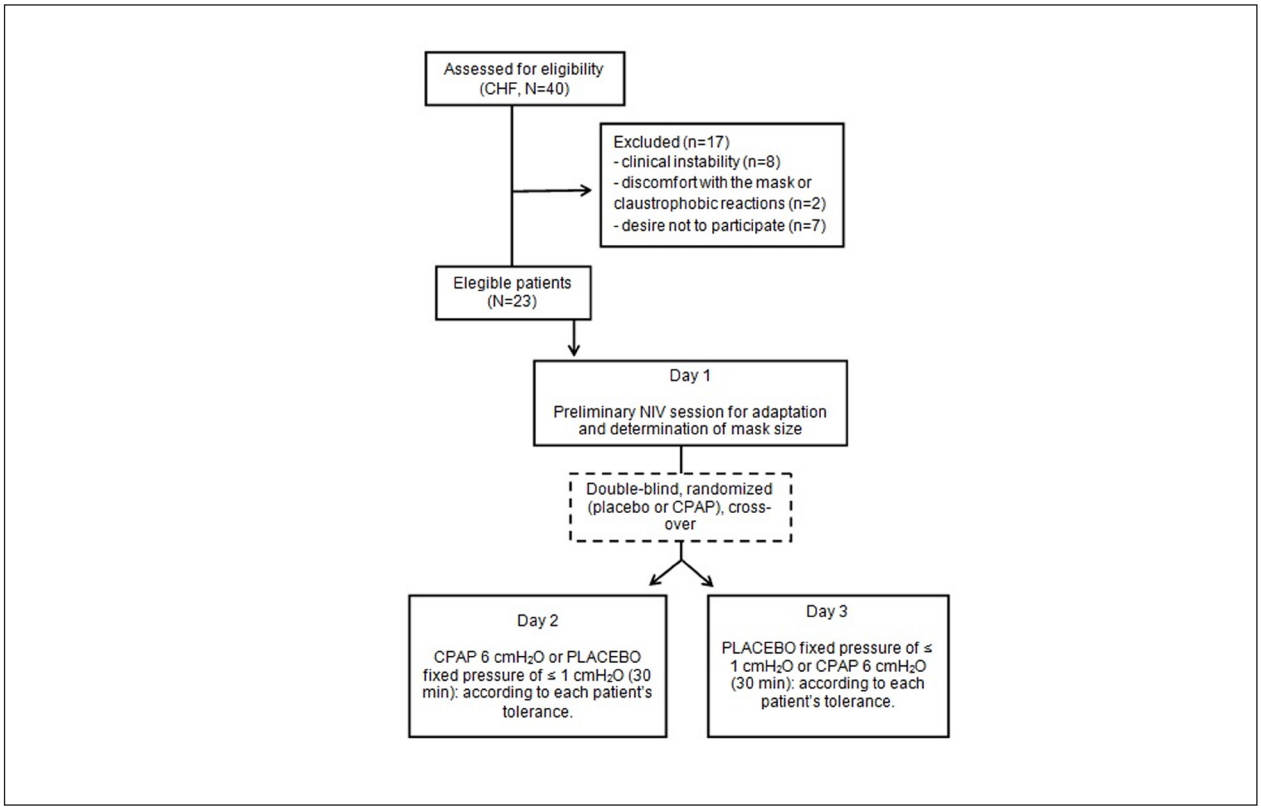

Figure 1 - *Flowchart of the study design. CHF: chronic heart failure; NIV: non-invasive ventilation; CPAP: continuous positive airway pressure.*

Table 1 - Characteristic of heart failure patients participating in the study

Sample size	23 (17M / 6F)
Age (years)	60 ± 10
Weight (kg)	78 ± 18
Height (cm)	160 ± 0,1
BMI (kg/cm^2)	29 ± 6
HF Etiology	12/11
NYHA	13 class II/ 10 class III
Medications	
ACEI	83%
Diuretics	75%
Digoxin	33%
Nitrates	16%
β-blockers	66%

BMI: body mass index; NYHA: New York Heart Association; M: male; F: female; ACEI: Angiotensin converting enzyme inhibitors.

NIV in the CPAP mode (Tranquility, Healthdyne, USA), was applied via nasal mask (Sealflex, Caradyne, USA) for 30 min in the recumbent position, preceded by a resting steady state period of 15 min of spontaneous breathing. Mask pressure was initially set to 3 cmH_2O for 5 min followed to 6 cmH_2O, according to each patient's predetermined tolerance.

During NIV, heart rate (HR) and oxygen saturation (SpO_2) by pulse oximetry (Healthdyne, Marietta, GA) were continuously monitored, and blood pressure (BP) was measured manually at the end of the resting period and at 5, 10, 20, and 30 min of NIV (auscultatory method obtained by trained researcher using a standard mercury sphygmomanometer on the left arm). Respiratory rate (RR) and SpO_2 were recorded, at these same intervals. In order to test whether the effect of CPAP persisted after cessation of NIV, the hemodynamic variables were measured 5 min after discontinuation of NIV (post).

Statistical Analysis

All data were assessed by the Kolmogorov-Smirnov test to determine whether they followed normal distribution. Temporal changes in hemodynamic and respiratory variables (randomized, placebo controlled experiment) were compared during NIV and placebo by two-way ANOVA with repeated measures, where ventilatory mode (NIV or placebo) and time were the main variables. When F values were significant, pairwise comparisons were performed with the Bonferroni post-hoc test. The number of subjects to be studied was calculated from the PP response obtained from previous studies, where the minimal detectable difference in means was 7 mmHg and the expected standard deviation of residuals was 5 mmHg. For this expected size effect and deviation and establishing the statistical power at 0.8 and alpha error at 0.05, the minimum sample size was determined to be of at least 9 subjects. All results are expressed as means ± SEM and $p < 0.05$ was considered significant.

Results

Forty patients were invited to take part in the study and twenty-three of them agreed to participate and were effectively enrolled in the present study. The characteristics of the subjects are shown in Table 1.

A controlled experiment was added following a randomized, placebo controlled and cross-over protocol to reduce bias in the analysis of the hemodynamic effects of acute NIV in patients with CHF. Of the 40 patients, 17 had to be excluded from the study due to: 1) clinical instability; 2) discomfort with the mask or claustrophobic reactions; or, 3) unwillingness to participate. Consequently the experiments involved 23 patients, whose characteristics are depicted in Table 1.

The results showed a decrease in HR, systolic blood pressure (SBP), PP, and RR with NIV and CPAP when compared to pre-CPAP values ($p < 0.05$). Values for SBP, diastolic blood pressure (DBP), and MAP during CPAP were lower than controls ($p < 0.05$). PP progressively declined, reaching the lowest value at 20 min post CPAP ($p < 0.05$). On the other hand, HR decreased at 5 min of CPAP and remained lower than pre- values until the end of the analysis (Table 2).

The behavior of pulse pressure during and after CPAP mode against placebo, are shown in Figure 2.

Discussion

Previous studies evaluated the hemodynamic effects of CPAP in patients with acute HF [21,22] while others evaluated the clinical relevance of PP [23,24], but few studies have studied the effects of CPAP in patients with chronic HF [18,25]. Therefore, it is not surprising that some of the present findings are similar to previous publications involving patients with decompensated HF [26,27] and may reflect direct heart-lung interactions leading to an overall improvement in cardiac performance and decreased respiratory effort [22]. However, the main purpose of the study was to determine specifically the effects of NIV with CPAP on PP since it is a useful hemodynamic indicator of conduit artery vascular stiffness [28,29], has a direct interdependence with key hemodynamic factors, such as stroke volume and peak aortic blood flow [11,30], and carries an independent predictive power for the development of left ventricular dysfunction [31] and CHF in previously healthy subjects [32]. In addition, there is a direct relationship between elevated PP and adverse outcome in patients with asymptomatic LV dysfunction [31] and HF [33].

Aronson [11] in his study observed that a lower PP in patients with decompensated HF determined greater risk of death. Also, he concluded that PP depends on the patient's clinical setting, as a high PP in patients with decompensated HF conferred preserved contractility and in outpatients, it confers a higher risk of events. The patients in this study had been in NYHA class II and III for at least 3 months without admission to the emergency room or hospital and therefore, clinically stable.

Verdecchia et al [14] found a higher risk for cardiovascular events when pulse pressure was greater than 53 mmHg. In this study, patients showed an initial PP close to 50 mmHg and CPAP reduced this parameter continuously, which persisted after the withdrawal of NIV.

The present study showed a PP decrease in patients with stable CHF submitted to NIV with CPAP associated with other hemodynamic changes, both in the open study, as well as in the double-blinded controlled cross-over protocol. The patients enrolled in the present study had LVEF ≤45% and high basal PP, which denotes left ventricular dysfunction and a reduction in arterial compliance or distensibility, with an increase in vessel stiffness. These results may have direct clinical implications, as the decrease in PP produced by CPAP may represent improved left ventricular ejection and reduced adverse outcomes.

In addition to the effects on PP, NIV with CPAP also caused a marked effect on other hemodynamic and respiratory variables, which may reflect changes in autonomic modulation rather than or in addition to ventricular loading and venous return [34]. The decreased respiratory rate might reflect improved ventilation, explaining the subjective sensation of all the patients who reported greater respiratory comfort. Regarding the hemodynamic variables, there are a number of autonomic reflex links between the pulmonary and circulatory systems that include reflex responses to changes in chest wall and/or respiratory mechanoreceptors, and reflex responses to changes in arterial gas tensions [35]. Indeed, lung inflation can lead to systemic vasodilatation via a vagal mediated reflex, which could result in decreases in cardiac volume secondary to decreased LV afterload [36]. The blood pressure reduction observed under NIV could be explained by increased airway and intrathoracic pressure leading to increased lung volume and subsequent decreases in transmural left ventricular pressure and afterload [36].

Table 2 - Effects of non-invasive ventilation with continuous positive airway pressure or placebo on hemodynamic variables in heart failure patients (n = 23)

Moment	HR		SBP		DBP		MAP		PP		RR	
	CPAP	CTRL	CPAP	CTRL	CPAP	CTRL	CPAP	CTRL	CPAP	CTRL	CPAP	CTRL
Pre	72 ± 9	69 ± 9	117 ± 17	115 ± 17	70 ± 12	73 ± 10	86 ± 10	87 ± 10	47 ± 20	42 ± 18	19 ± 4	20 ± 3
5min	68 ± 11*	69 ± 11	112 ± 16†	118 ± 19	71 ± 12†	75 ± 10	85 ± 11†	89 ± 12	41 ± 17	43 ± 16	17 ± 3*	20 ± 3
10min	67 ± 11*	71 ± 12	113 ± 17†	118 ± 20	71 ± 11†	75 ± 11	85 ± 11†	90 ± 13	42 ± 18	43 ± 16	17 ± 3*	20 ± 3
20min	68 ± 11*	70 ± 12	111 ± 17*†	117 ± 19	73 ± 10	75 ± 11	86 ± 10†	89 ± 12	38 ± 17* †	42 ± 14	17 ± 3*	19 ± 3
30min	67 ± 11*	70 ± 12	112 ± 16*†	116 ± 20	74 ± 9†	75 ± 9	86 ± 9†	88 ± 11	39 ± 16* †	41 ± 16	18 ± 3	19 ± 3
Post5min	67 ± 10*	72 ± 12	113 ± 18*†	118 ± 20	74 ± 10	77 ± 12	87 ± 10†	90 ± 12	38 ± 19* †	41 ± 18	19 ± 3	19 ± 3

** p < 0.05 vs. Pre for the same mode; † p < 0.05 CPAP vs. Placebo at the same moment; CPAP: continuous positive airway pressure; CTRL: control; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PP: pulse pressure; RR: respiratory rate.*

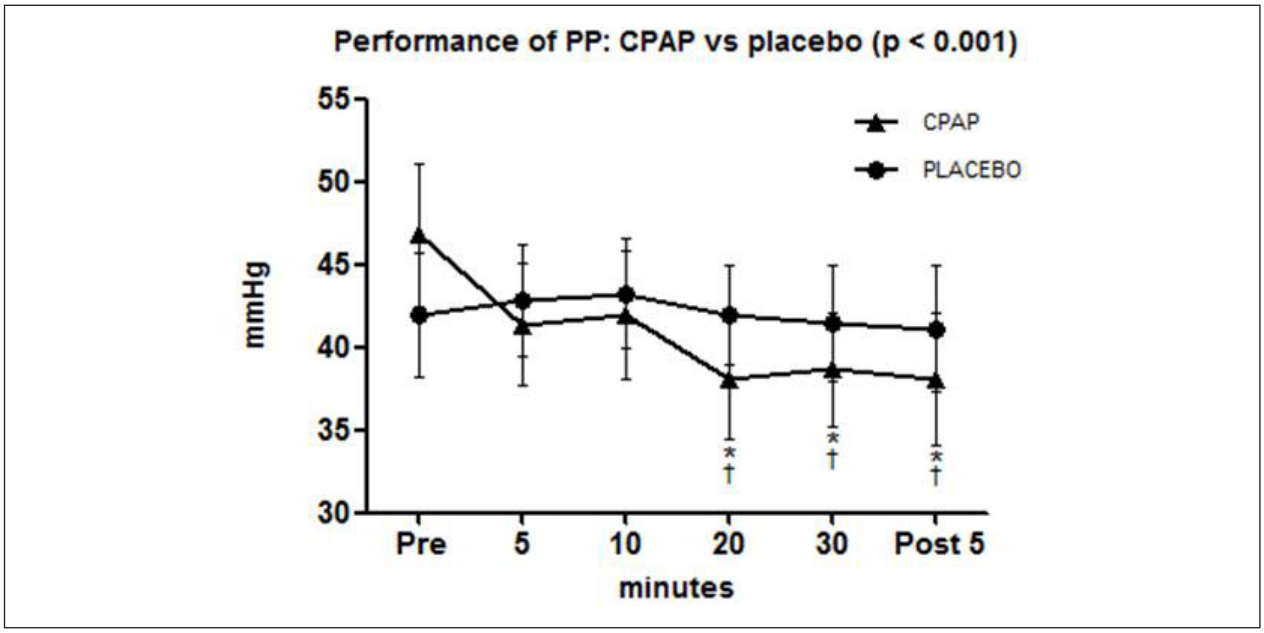

Figure 2 - *Pulse pressure (PP), of patients with chronic heart failure (n = 23) measured at 5, 10, 20, and 30 minutes of non-invasive ventilation with continuous positive airway pressure (CPAP; triangle symbols) or Placebo (circle symbols) * p < 0.01 vs. PRE for the same mode of ventilation; † p < 0.001 vs. Placebo at the same moment.*

NIV is a safe and feasible ventilation method easily applied in the ambulatory setting, but its effectiveness is critically dependent on patient comfort and acceptance [25,27]. Therefore, in the present study, a preliminary NIV session (phase 1) for adaptation and determination of the mask was performed. This preliminary session was also employed to determine the individual CPAP pressure to be used in the subsequent experiments, which was determined to be the lowest pressure that resulted in greater hemodynamic responses, while being comfortable for the patient. The CPAP pressure level that resulted in significant hemodynamic responses was close to 6 cmH_2O. These values of CPAP pressure were similar to those in previous studies that demonstrated improved cardiac output with low CPAP levels [19,37]. As previous publications had shown myocardial ischemia in patients with ischemic heart failure during the administration of bilevel positive airway pressure (Bipap)[38,39], the CPAP mode was chosen in order to decrease the occurrence of potential adverse outcomes. Accordingly, there were no events triggered by CPAP in the patients participating in the present study.

Limitations

In our study it was not possible to determine the exact mechanism responsible for the hemodynamic changes; however, it is already known from previous studies that increases in cardiac output with CPAP might be explained by systemic vasodilatation, possibly on a reflex basis, leading to a decrease in the left ventricular afterload and consequent increased stroke volume and cardiac output [35]. We observed that the hemodynamic effects of NIV with CPAP remained up to five minutes after CPAP withdrawal; however, we understand that further studies are needed to determine the duration of these effects after CPAP cessation. Although in the present study clinic outcomes were not measured, in a previous study an improvement was observed in the exercise tolerance with CHF patients after NIV with CPAP (placebo vs. CPAP)[40].

Conclusions

We conclude that NIV with CPAP is an effective non-pharmacological method to reduce pulse pressure in patients with stable chronic heart failure with potential clinical implications for the management of this group of patients.

Author contributions

Conception and design of the research: Quintão M, Chermont S, Mesquita ET, Nóbrega ACL; Acquisition of data: Quintão M, Chermont S, Rocha NN; Analysis and interpretation of the data: Quintão M, Chermont S, Marchese L, Brandão L, Bernardez SP, Mesquita ET, Rocha NN, Nóbrega ACL; Statistical analysis: Quintão M, Chermont S, Nóbrega ACL; Writing of the manuscript: Quintão M, Chermont S, Marchese L, Bernardez SP, Mesquita ET, Nóbrega ACL; Critical revision of the manuscript for intellectual content: Quintão M, Chermont S, Marchese L, Brandão L, Bernardez SP, Mesquita ET, Nóbrega ACL.

Potential Conflict of Interest

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

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Study Association

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