

## Haemodynamic effects of nasal continuous positive airway pressure in severe congestive heart failure

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**ABSTRACT:** Nasal continuous positive airway pressure (NCPAP) during sleep may be a useful adjunct to medical therapy in patients with stable severe congestive heart failure (CHF), particularly when there is a coexisting respiratory sleep disorder. However, the direct haemodynamic effects of NCPAP in patients with severe stable CHF have not yet been adequately assessed.

Right heart catheter studies were performed in seven awake males (aged 51–75 yrs) with stable CHF, before, during and after the application of 5 cmH<sub>2</sub>O NCPAP over 3 h. All patients had left ventricular ejection fractions  $\leq 30\%$  and baseline pulmonary capillary wedge pressures  $>12$  mmHg, and six patients were in atrial fibrillation.

Cardiac index fell from baseline in all patients whilst on NCPAP, with the greatest fall at 2 h (from  $3.3 \pm 0.3$  (mean  $\pm$  SEM) at baseline to  $2.8 \pm 0.2$  l min<sup>-1</sup> m<sup>-2</sup>) and rose back to baseline after NCPAP withdrawal. Systemic vascular resistance (SVR) increased during NCPAP application ( $1,268 \pm 108$  to  $1,560 \pm 82$  dyn·s<sup>-1</sup>·cm<sup>5</sup>), with baseline SVR showing a significant negative correlation vs percentage fall in cardiac index (CI) at 2 h on multiple linear regression analysis ( $r^2=0.8$ ).

These data indicate that domiciliary nocturnal NCPAP should not be prescribed as part of the therapy in severe CHF without first determining the individual patient's cardiac response to such therapy.

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Nasal continuous positive airway pressure (NCPAP) is an effective therapy for obstructive sleep apnoea [1, 2] and some forms of central sleep apnoea [3]. Positive airway pressure has also been reported to reduce left ventricular transmural pressure in the failing heart, with beneficial effects on cardiac output [4–6]. These findings suggest that NCPAP may be beneficial in the treatment of congestive heart failure (CHF), and indeed several previous reports have documented benefits from various forms of positive airway pressure administered acutely in some patients with acute pulmonary oedema [7–10], or prior to cardiac transplantation in patients with severe chronic CHF [11]. In addition, two short-term studies of domiciliary nocturnal NCPAP have demonstrated beneficial effects on cardiac function in patients with CHF and sleep-disordered breathing [12, 13], although another recent study has failed to demonstrate benefit from this therapy [14].

The above reports raise the possibility that domiciliary nocturnal NCPAP may be a useful adjunctive therapy in patients with chronic severe CHF. The mechanism of such benefit could be either direct, through a beneficial effect of NCPAP on cardiac function, or indirect, through a beneficial cardiac effect of the relief of hypoxaemia and/or sleep-disordered breathing, particularly among patients with sleep apnoea or Cheyne-Stokes res-

piration. Support for a direct beneficial effect of NCPAP on cardiac function comes from the findings of BRADLEY *et al.* [15]. They found that the application of NCPAP for 10 min in awake patients with stable CHF and in sinus rhythm, was associated with a significant increase in cardiac index (CI), but only in a subgroup of patients with high pulmonary capillary wedge pressures. However, if NCPAP is to be used overnight in the clinical setting among patients with severe CHF, the haemodynamic effects of NCPAP need to be assessed over a longer time period than 10 min. In addition, haemodynamic effects may vary at different pressure levels, and may differ among patients with CHF who are not in sinus rhythm.

We therefore studied the time course of effects of NCPAP on haemodynamic variables, both during and after its application over a longer time period (3 h) in patients with severe but stable CHF. These patients were on maximum medical therapy, but still demonstrated severe exercise impairment.

### Patients and methods

#### Patients

Consecutive patients admitted to the cardiology department for assessment of CHF were considered for

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enrolment. Entry criteria included a clinical diagnosis of stable CHF, class 3 or 4 cardiac dyspnoea by the New York Heart Association Classification [16], and a left ventricular ejection fraction (LVEF) of 30% or less by echocardiography. Exclusion criteria included significant primary lung disease or unstable cardiac status, in addition to CHF secondary to valvular heart disease, or specific nasal problems that prevented the comfortable use of NCPAP. All patients gave written informed consent, and the study was approved by the Hospital Ethics Committee.

Eight patients were enrolled, and all were current non-smokers. Cardioactive medication was unaltered in the 3 day period prior to haemodynamic studies, and none had evidence of acute cardiac ischaemia or respiratory failure. Seven patients were in atrial fibrillation (AF), and one was in sinus rhythm (SR). All had full spirometry using a computerized system (TT Autolink, PK Morgan, Gillingham, UK). Six of the seven patients had full overnight sleep studies performed, using standard polysomnographic techniques [17, 18] to assess the presence or absence of any associated respiratory sleep disorder, such as sleep apnoea or Cheyne-Stokes respiration. Patients were familiarized with the NCPAP apparatus on the day prior to the study, and arterial blood gases were taken in the recumbent position immediately prior to insertion of the cardiac catheter.

#### Haemodynamic studies

The haemodynamic studies were performed in a quiet private room in the Coronary Care Unit with the patient awake and supine, and the last dose of diuretic given at least 4 h previously. A 7 Fr flow-directed thermodilution catheter (Multiflex TD thermodilution catheter; Abbott Critical Care Systems, Nth Chicago, IL, USA) was inserted *via* the left subclavian venous route. Before administration of NCPAP, baseline readings (time zero) were taken a minimum of 15 min after insertion of the catheter and after heart rate (HR) and blood pressure (BP) had returned to baseline levels. These readings included right atrial pressure (RAP), pulmonary artery pressures (PAPs), and pulmonary capillary wedge pressure (PCWP) recorded at end-expiration, in addition to HR and BP. Cardiac output (CO), cardiac index (CI), stroke volume (SV) and stroke volume index (SVI) were measured by the thermodilution technique [19], using normal saline cooled to 0°C, and taking the mean of five readings. Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were then calculated using standard formulae [20]. Nasal CPAP (RESMstar™; Respiration Inc., Murrayville, PA, USA) was then applied, using a comfortably fitting nasal mask at an initial pressure of 5 cmH<sub>2</sub>O [10, 15]. Patients were encouraged to keep their mouth closed, in order to ensure full transmission of mask pressure to the lungs [21], and to remain awake.

The above measurements were repeated after 0.25, 1, 1.5 and 2 h of NCPAP. At this point, the protocol dictated an increase in the NCPAP pressure level to 10 cmH<sub>2</sub>O among patients who showed either no change or

an increase in CI during 5 cmH<sub>2</sub>O NCPAP, and readings were repeated at the same time intervals as for the 5 cmH<sub>2</sub>O pressure level. Patients who demonstrated a decrease in CI during 5 cmH<sub>2</sub>O NCPAP were to be continued at this pressure level for a further 1 h. The NCPAP was then discontinued, patients remained supine and readings were taken after a further 0.25 and 0.75 h.

Arterial oxygen saturation (% Sao<sub>2</sub>) was monitored throughout the study period by pulse oximetry (Biox 3700; Ohmeda, Louisville, CO, USA).

#### Statistical analysis

The differences between the means of haemodynamic variables at each recording point during the study period were analysed using analysis of variance (ANOVA) for repeated measures. *Post hoc* analysis was performed using the Student Newman-Keuls (SNK) test for multiple comparisons to detect significant differences between baseline and each time-point. In order to determine which independent variables measured at baseline were correlated with the percentage fall in cardiac index (CI) whilst on NCPAP, stepwise multiple linear regression analysis was performed for CI at 0.25 and 2 h, and at the end of NCPAP application. Independent variables entered into the regression included age, LVEF, forced expiratory volume in one second/forced vital capacity (FEV<sub>1</sub>/FVC) (% predicted), baseline arterial oxygen tension (Pao<sub>2</sub>), RAP, PCWP, CI, SVI, SVR and PVR. These analyses were performed using the software package Statistica for Windows Release 4 (Statsoft, Inc. 1993). A significant value was taken as  $p < 0.05$ . Data are expressed as mean  $\pm$  SEM.

#### Results

Seven patients completed the study protocol, and their anthropometric and baseline pulmonary function data are outlined in table 1. The eighth subject (in AF) withdrew during the course of haemodynamic studies due to discomfort. There had been considerable technical difficulties with the insertion of the right heart catheter in this patient, which had significantly delayed the application of NCPAP. The patient found the prolonged period of confinement in the one position uncomfortable, and asked to discontinue the protocol because of this discomfort. His data were excluded from the final analysis.

All of the remaining seven patients were male, and none was significantly hypoxaemic at rest. On spirometry, two patients had mild airflow obstruction, and a third had a restrictive deficit. None of these patients had evidence of a primary respiratory disorder or were on respiratory medication, and it was felt that the abnormal spirometry was a consequence of CHF. Table 2 summarizes the patients' cardiovascular status. All were judged by their attending cardiologist to be on maximum medical therapy at the time of study. Whilst three

Table 1. – Anthropometric, spirometric, arterial blood gas and sleep data

Subject No.	Age yrs	Sex	Weight kgs	Height m	BMI kg·m <sup>-2</sup>	FEV <sub>1</sub> % pred	FVC % pred	FEV <sub>1</sub> /FVC % pred	Pao <sub>2</sub> kPa	Paco <sub>2</sub> kPa	AHI
1	64	M	60	1.60	23.4	41	49	84	14.2	3.51	1*
2	69	M	98	1.82	29.6	101	96	105	12.0	4.34	16 <sup>†</sup>
3	51	M	63	1.73	21.0	59	91	65	11.4	5.53	3*
4	52	M	79	1.73	26.4	113	106	110	13.3	4.96	22 <sup>†</sup>
5	75	M	78	1.80	24.1	73	106	70	10.7	5.05	5*
6	57	M	70	1.66	25.4	89	93	99	12.6	4.99	26 <sup>†</sup>
7	57	M	65	1.65	23.8	56	65	91	12.5	4.56	–

M: male; FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity Pao<sub>2</sub>: arterial oxygen tension; Paco<sub>2</sub>: arterial carbon dioxide tension. BMI: body mass index (weight/height<sup>2</sup>); % pred: percentage predicted; AHI: apnoea/hypopnoea frequency per hour of sleep (\*: normal <15 events·h<sup>-1</sup>; †: mild sleep apnoea 15–30 events·h<sup>-1</sup>).

Table 2. – Baseline cardiac function and medications

Subject No.	Aetiology of CHF	LVEF	NYHA Grade	Medications
1	ICM	15%	4	LD, Ami
2	IHD	30%	3	LD, Dig, AI
3	ICM	18%	3	LD, Dig, AI
4	ICM	25%	3	LD, Dig, AI
5	ICM	28%	3	LD, Dig
6	ICM	25%	3	LD, Dig, AI
7	IHD	22%	3	LD, Dig, AI

CHF: congestive heart failure; ICM: idiopathic cardiomyopathy; IHD: ischaemic heart disease; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association Classification; LD: loop diuretic; Ami: amiodarone; Dig: digoxin; AI: angiotensin converting enzyme (ACE) inhibitor.

patients (table 1) had an apnoea and hypopnoea frequency within the range of mild sleep apnoea as conventionally defined [18], none had significant oxygen desaturation during sleep, and none had symptoms suggestive of a sleep apnoea syndrome. No patient had evidence of Cheyne-Stokes respiration.

### Haemodynamic data

The effects of NCPAP on haemodynamic variables are outlined in table 3. As CI fell in all patients during the initial 2 h period, NCPAP was not increased to 10 cmH<sub>2</sub>O in any patient, and further measurements were made at 2.5 and 3 hr on 5 cmH<sub>2</sub>O before discontinuing NCPAP. Cardiac index fell in all patients whilst on NCPAP (p=0.0007 by ANOVA), and returned towards baseline values after discontinuation. Individual patient data for CI during and after NCPAP are illustrated in figure 1. Multiple comparisons testing showed a significant decrease in CI at each recording point whilst on NCPAP, which was maximum at 2 h (p<0.01). Cardiac index at 3.75 h (45 min after cessation of NCPAP) showed no significant difference from baseline, indicating that it was the NCPAP that was responsible for the observed changes, and not the supine body position.

One patient, who was in SR, did show a small improvement at 3 h (CI=2.6 l·min<sup>-1</sup>·m<sup>-2</sup>) compared to baseline (2.4). However, he experienced a fall at 0.25 h to 2.0 l·min<sup>-1</sup>·m<sup>-2</sup>, and the subsequent gradual increase in CI over the next 2.75 h was due almost exclusively

Table 3. – Haemodynamic data before, during and after NCPAP, 5 cmH<sub>2</sub>O

		Baseline	15 min	1 h	2h	3 h	Off NCPAP	ANOVA
CI	l·min <sup>-1</sup> ·m <sup>-2</sup>	3.3 (0.3)	2.9 (0.3)*	2.8 (0.2)**	2.8 (0.2)**	2.9 (0.2)*	3.3 (0.3)	0.0007
SVI	ml·m <sup>-2</sup>	44 (4)	39 (4)	35 (3)*	35 (3)*	37 (4)	38 (4)	0.03
SBP	mmHg	131 (7)	137 (9)	141 (10)*	149 (10)**	149 (10)**	144 (10)*	0.0006
DBP	mmHg	88 (4)	89 (3)	91 (4)	91 (4)	91 (6)	90 (4)	NS
HR	beats·min <sup>-1</sup>	84 (6)	80 (7)	82 (6)	85 (6)	86 (8)	84 (6)	NS
SVR	dyn·s <sup>-1</sup> ·cm <sup>5</sup>	1268 (108)	1480 (160) <sup>†</sup>	1538 (155)**	1560 (82)**	1501 (119)*	1368 (142)	0.003
PVR	dyn·s <sup>-1</sup> ·cm <sup>5</sup>	135 (32)	197 (79)	150 (49)	156 (49)	177 (59)	148 (31)	NS
PCWP	mmHg	21 (2.8)	22 (3)	25 (4)	24 (4)	23 (3)	24 (3)	NS
PASP	mmHg	45 (6)	46 (8)	47 (7)	47 (7)	47 (7)	47 (6)	NS
PADP	mmHg	21 (4)	24 (5)	24 (5)	24 (5)	25 (4)	25 (3)	NS
RAP	mmHg	8.9 (1.2)	9.7 (1.5) <sup>†</sup>	10.9 (1.4)	10.1 (1.7)	11.6 (1.5)	9.4 (1.4)	NS

Data is expressed as mean (SEM). Data for 1.5 and 2.5 h has been omitted for brevity. CI: cardiac index; SVI: stroke volume index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; SVR: systemic vascular resistance; PVR: pulmonary vascular resistance; PCWP: pulmonary capillary wedge pressure; PASP: pulmonary artery systolic pressure; PADP: pulmonary artery diastolic pressure; RAP: right atrial pressure; NCPAP: nasal continuous positive airway pressure; ANOVA: analysis of variance for repeated measures across all time periods; SNK: Student Newman-Keuls; NS: nonsignificant. \*: p<0.05; \*\*: p<0.01 for SNK test comparing each time period with baseline. †: data for six patients (baseline SVR = 1,272 (128) and RAP = 8.8 (1.5) for these patients).

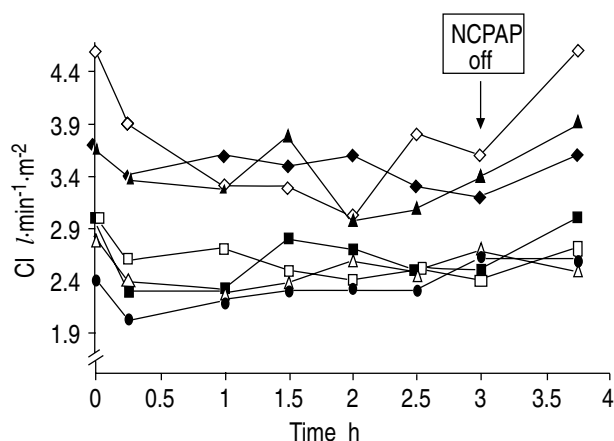


Fig. 1. — Cardiac index (CI) measurements for individual subjects from baseline (time 0) to 45 min after nasal continuous positive airway pressure (NCPAP) was stopped (3.75 h). NCPAP was discontinued immediately after recordings were taken at 3 h. Note that the vertical axis is cut off from zero.

to an increase in HR (from 90 to 111 beats·min<sup>-1</sup>) with a lower SV (41 ml) than at baseline (46 ml). His HR fell and SV increased after cessation of NCPAP.

The change in CI was closely matched by a significant fall in SVI ( $p=0.03$ ), which was maximal at 2 h, and no significant differences were found between readings at baseline and after withdrawal of NCPAP. Systolic BP ( $p=0.0006$ ) also rose during NCPAP, as did SVR ( $p=0.003$ ). Increases for both were maximal at 2 h. No significant changes were observed in PCWP, PASP, PADP, RAP or %  $S_{aO_2}$  during NCPAP.

On stepwise multiple linear regression analysis, the only significant correlation found was a negative one between baseline SVR and % fall in CI from baseline at 2 h (multiple  $r^2=0.8$ ;  $p=0.02$ ). The correlation between the two variables is shown in figure 2.

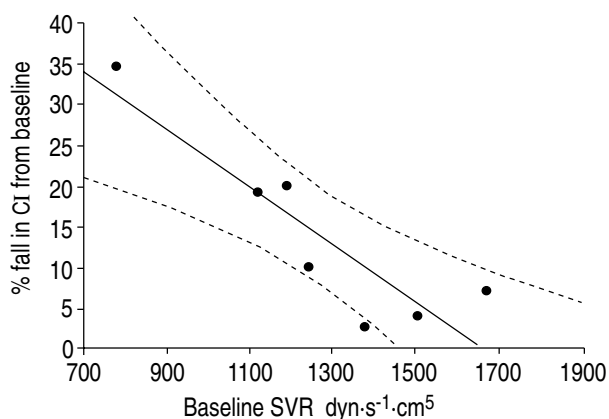


Fig. 2. — The relationship between baseline systemic vascular resistance (SVR) and cardiac index (CI) at 2 h (expressed as % fall from baseline). Data points are shown with 95% confidence limits;  $r=-0.89$  and  $p=0.007$  (Pearson product moment correlation coefficient).

## Discussion

The present study demonstrates a significant fall in cardiac output with NCPAP among awake patients with severe stable CHF. These findings differ from those of BRADLEY *et al.* [15], who studied the awake effects of NCPAP in stable CHF over a shorter time period (10 min). The present study used similar measurement techniques, and our patients resembled the responder group in the other study [15] in terms of PCWP, baseline CI, and ongoing cardiac therapy.

However, atrial fibrillation was seen in 6 out of the 7 patients in the present study, whereas all patients in the other study [15] were in SR, although the change in heart rate during NCPAP was similar in both studies. Our patients also had lower mean LVEFs (23 vs 30.8%) and lower mean SVRs (1,268 vs 1,717 dyn·s<sup>-1</sup>·cm<sup>5</sup>) than in the responder group in the other report [15].

The findings of the present study are supported by the observations of PINSKY *et al.* [22], who reported a fall in CI with positive airway pressure among patients after coronary artery bypass; and also DAVIES *et al.* [14], who found no improvement in cardiac function or patient performance after 2 weeks of domiciliary NCPAP treatment.

The present study recorded haemodynamic changes in patients with chronic stable CHF, and the findings do not necessarily disagree with reported benefits of positive pressure in patients with acute cardiac failure and pulmonary oedema [7–10]. End-points in these other studies included improvements in arterial blood gases, work of breathing, and requirement for assisted ventilation [8, 9]. Patients were on different medications, including intravenous inotropic support. Patients in the present study were stable, with no evidence of acute cardiac ischaemia or respiratory failure.

The methodology used in the present study, which is standard for assessing CI and cardiovascular pressures [7, 10, 11, 15], does not permit a precise definition of how NCPAP may lead to a reduction in CI. Positive airway pressure is known to reduce systemic venous return [23]. It also increases functional residual capacity (FRC), thus, elevating both pulmonary vascular resistance and right ventricular (RV) afterload. An increased RV afterload will reduce pulmonary venous return to the left heart [24, 25], and may also increase RV volume, which in turn can induce leftward shift of the interventricular septum and reduction in left ventricular (LV) volume [24]. Such changes in LV shape and size can adversely affect LV compliance [26].

All of the above mechanisms tend to reduce LV end-diastolic volume and, thus, preload. When contractility is normal, a reduction in preload decreases LV ejection by the Frank-Starling mechanism. As a result, the normal heart is considered to be preload-dependent [5, 6, 27], and normal subjects usually [15, 21], but not always [28], experience a consistent fall in CO with NCPAP. In contrast, CO in the failing heart is thought to be more responsive to changes in afterload, as LV contractility is reduced and is relatively unresponsive to changes in diastolic volume [5, 6]. It has been

hypothesized, therefore, that the negative effects of a NCPAP induced reduction in preload would be less marked than in the normal heart, and would tend to be outweighed by the beneficial effects of a reduction in LV afterload, and result in an increase in LV ejection [5, 6].

In the present study, patients with the lowest baseline SVRs had the greatest falls in CI (fig. 2), and were likely to have been significantly affected by the fall in preload. Their baseline SVR, which reflects afterload, was within the normal range, and any benefit derived from a reduction in afterload [4] is likely to have been minimal compared to the reduction in preload. The balance of effects would favour a fall in CI. Furthermore, these patients had the greatest increase in SVR at 2 h (34–64%), possibly as a vasomotor response to the fall in CI. In contrast, patients with high baseline SVRs, and thus high afterload, had much smaller reductions in CI. Their cardiac contractility may have been poorer, and, thus, less affected by the fall in preload. They may have gained some benefit from a fall in LV transmural pressure, and this could have counteracted the effect of reduced preload, minimizing the fall in CI. The increase in SVR at 2 h found in these patients was much lower (less than 20%).

The possibility that NCPAP reduces the work of breathing, and thus oxygen demand, is worthy of consideration, as a reduction in CI may, therefore, reflect reduced perfusion requirements. This is unlikely to have occurred in the present study, since none of the patients had significant pulmonary disease and all had good Pao<sub>2</sub> levels (>10.5 kPa) at rest (table 1). No significant change in % Sao<sub>2</sub> was seen in any patient. Furthermore, the findings of reduced CI and increased SVR are both considered to adversely affect survival in patients with CHF [29], and would probably have detrimental effects if maintained over a prolonged period of time in our patients.

We did not measure LV transmural pressure, and therefore, the values obtained for RAP, PAPs, and PCWP do not take into account any changes in transmural pressure with NCPAP. However, even if the full mask pressure was transmitted to the intrathoracic space and was subtracted from the observed readings, no significant changes in these pressures were found during NCPAP.

We chose to study patients while awake, since we felt that beneficial respiratory effects of NCPAP during sleep, related to the relief of sleep-disordered breathing and/or hypoxaemia, could have significantly modified the direct cardiac responses to NCPAP. Although three of our patients had sleep study evidence of mild sleep apnoea (table 1), this finding should not influence our awake measurements. None of our patients demonstrated any evidence of Cheyne-Stokes respiration or oxygen desaturation during the study period. Thus, the observed fall in cardiac output is most likely to have been a direct effect of NCPAP.

A number of possible confounding methodological factors in the present study, such as emotional distress, body position, and the effects of concurrent cardiac medication, can be discounted. Patient comfort was a

particular concern at all stages, and each subject was well acclimatized to the NCPAP device before haemodynamic studies. Haemodynamic studies were performed in a quiet room with investigators familiar to the subject present throughout the study.

The supine position is very unlikely to have influenced our results, since CI returned to baseline values when NCPAP was discontinued, without a change in posture (table 3). It has been proposed that NCPAP exerts a beneficial effect on CI through a reduction in LV afterload; and it could, therefore, be argued that any benefit would be masked by concurrent therapy with afterload reducing agents. This is unlikely, however, as patients in any of the studies that reported beneficial effects with NCPAP, have also been on such therapy [12, 13, 15]. Furthermore, any therapeutic role for NCPAP in patients with CHF would probably be in addition to existing medication, rather than as a replacement.

Data from the present study do not support the view that low levels of NCPAP can be applied with relative safety as a trial therapy in all patients with poorly controlled CHF [15], although we recognize from previous reports [7–15] that specific subgroups may benefit from NCPAP. Factors that influence an individual patient's response to NCPAP need to be defined before NCPAP can be used in the clinical setting. One possible factor predicting an adverse response to NCPAP is the finding of atrial fibrillation, in view of its presence among most of the patients in the present study.

However, the findings of the present study do not preclude a beneficial effect on cardiac output of NCPAP during sleep in patients with CHF and a coexisting respiratory sleep disorder, such as sleep apnoea or Cheyne-Stokes respiration, as has previously been reported by MALONE *et al.* [13]. However, our data suggest that such benefit is likely to be indirect, and related to relief by NCPAP of the adverse cardiac effects from the repetitive Müller manoeuvres and hypoxaemia associated with obstructive apnoeas [13, 30].

We conclude that domiciliary nocturnal NCPAP should not be prescribed as a form of therapy for CHF without first determining the individual patient's haemodynamic response. Further investigation is required to identify factors that might predict cardiac response to NCPAP in such patients.

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