The effect of continuous positive airway pressure (CPAP) on renal vascular resistance: the influence of renal denervation
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Objective: To non-invasively study the effects of continuous positive airway pressure breathing (CPAP) on renal vascular resistance in normal subjects and renal allograft recipients, in other words those with with denervated kidneys. We could then ascertain the influence of renal innervation on any resulting changes in renal haemodynamics.

Methods: Ten healthy volunteers and six renal transplant patients were studied. Using Doppler ultrasonography, the pulsatility index (PI), an index of renovascular resistance, was measured at incremental levels of CPAP (0, 2.5, 5.0 and 7.5 cmH2O).

Results: In both groups, the PI increased significantly between 0 and 5.0 cmH2O CPAP, with a further increase at 7.5 cmH2O CPAP.

Conclusions: We found that CPAP at 5.0 and 7.5 cmH2O caused a significant increase in renovascular resistance in both normal and renal transplant patients. There was no difference in the degree of rise in renovascular resistance between both groups, indicating that the renal nerves do not play a role in altering renal vascular resistance with the application of CPAP.

Introduction
Continuous positive airway pressure (CPAP) is used in the treatment of obstructive sleep apnoea, adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD) and acute cardiogenic pulmonary oedema [1]. Many patients on positive pressure ventilation, especially with the addition of positive end-expiratory pressure (PEEP), develop fluid retention and impaired renal function [2,3] and PEEP is known to reduce urinary output and sodium excretion [2,4]. Reduced renal blood flow has been implicated as a possible mechanism for the development of fluid retention [5]. This fall in renal blood flow may be secondary to a reduction in cardiac output, or increased renal venous pressure and redistribution of renal blood flow from cortical to medullary regions [6]. Sympathetic activation acting directly via renal nerve stimulation or indirectly via noradrenaline release may also play a role [7,8]. The fall in renal blood flow secondary to the application of PEEP in dogs is abolished by renal denervation, suggesting a major modulatory role for renal innervation. Fluid retention also occurs with CPAP, but the extent of changes in renal haemodynamics with CPAP are unknown.

We studied a group of normal volunteers to determine possible effects of CPAP on distal renovascular resistance. This is an indirect assessment of changes in renal blood flow. We then compared these findings to those from a group of patients post renal transplantation, in other words with renal denervation. By comparing these two groups, we could determine the influence of renal innervation on any resulting alterations in renal haemodynamics.

Methods
Subjects
Ten normal subjects and six renal transplant patients were studied. All participants were male. Each subject gave informed consent and the hospital ethics committee approved the study. The normal subjects were recruited from the medical staff with a mean ± SD age of 24 ± 1.56 years and none of them were on medication. Six male patients with renal allografts for treatment of chronic renal failure were randomly recruited from the nephrology outpatient department. They were at least 18 months post renal transplantation (mean 30 months) with an average age of 37.7 ± 4.27 years. Each patient had a stable renal function, with serum creatinine level < 200 mmol/l and no recent renal complications. All patients were on immunosuppressive therapy which included prednisolone, azathioprine and cyclosporin. Seven of the patients were on antihypertensive medication, consisting of a beta-blocker in five cases and nitrates in two. None of them had a history of cardiac or respiratory disease.
Each subject was studied at a similar time each day. CPAP was delivered via tight-fitting full-face mask by a continuous-flow system using a Downs flow generator (Vital Signs, Boston, Massachusetts, USA). CPAP was started at a level of 2.5 cmH2O and increased by increments of 2.5 cmH2O to a maximum of 7.5 cmH2O. CPAP was applied for 20 min at each of the three sequential pressure settings.

Ultrasonography
Doppler ultrasound examinations were performed using an Acuson 128 realtime ultrasound scanner (Acuson Corporation, Mountain View, California, USA) with pulsed Doppler and colour-flow facilities [9]. A 2 MHz probe was used. Each subject rested for 15 min before being scanned. In the normal subjects, the right kidney was scanned in the longitudinal plane via the translumbar route, with the subject in the seated position. The transplanted kidney was scanned via the transabdominal route, with the patient supine. A renal interlobar artery was identified both from its anatomical position and typical sonoimage showing the characteristic high diastolic blood velocity. The angle of the ultrasound beam was adjusted until the maximum Doppler frequency shift was obtained. The pulsatility index (PI) was calculated using the integrated computer software. The PI is obtained by calculating the difference between the peak systolic frequency shift of the Doppler spectrum (A) and the end-diastolic frequency shift (B), which is then divided by the mean frequency shift (mean), such that PI = A−B/mean [10]. PI is an index of distal resistance to flow in the vascular bed; the lower the PI, the less the resistance to flow and therefore the greater the rate of flow. The PI is independent of the vessel diameter and the angle between the Doppler beam and the vessel axis. There was little variation in the PI with each arterial pulsation, and the mean of a minimum of three PI measurements from the same interlobar artery was calculated at each time point. Heart rate and blood pressure were monitored throughout the study.

Validation
The PI has been validated in healthy volunteers [11]. Using dopamine and dobutamine to vary renovascular resistance, changes in renal vascular resistance (measured by classical methodology) correlated strongly with those in the PI [11]. A further study showed that the both the PI and resistive index (RI) correlated significantly with effective renal plasma flow, renal vascular resistance, filtration fraction and clearance of creatinine [12]. In a study of renal haemodynamics in COPD, PI and Tamx (mean of the maximum instantaneous flow) were used [13] and all the subjects increased their Tamx and had a simultaneous decrease in their PI in response to inhaled oxygen, suggesting that both parameters are equally sensitive to changes in renal haemodynamics in COPD. In our centre, the coefficient of variation of PI is 2.05% [9].

Statistics
The PI measurements during the different levels of CPAP were compared using the Friedman test for non-parametric data. The Dunn’s multiple comparison test was used, where appropriate, to determine at which levels the changes in PI were significant. Numerical variables were compared between the controls and renal transplant subjects by the Wilcoxon test for non-parametric data. The results are given as mean ± SD, and a P level less than 0.05 was considered significant.

Results
The mean age of the normal subjects was 24 ± 1.56 years and 37.7 ± 4.27 years in the renal transplant subjects (P < 0.01). There was a significant rise in the mean PI in the controls with the addition of CPAP (P < 0.001; Table 1, Fig 1). Using non-parametric testing, there was no significant change in PI between 0 and 2.5 cmH2O CPAP (Table 1). However, between 0 and 5.0 cmH2O CPAP, PI increased from 0.65 ± 0.06 to 0.7 ± 0.08 (P < 0.05), indicating that the application of CPAP caused an increase in renal vascular resistance and therefore a fall in renal blood flow. This increase in PI occurred in all except one subject. Between 0 and 7.5 cmH2O CPAP, there was a further rise in PI in all normal subjects to a mean of 0.82 ± 0.08 (P < 0.01). The increase in PI between 5.0 and 7.5 cmH2O CPAP was also significant (P < 0.05). The increase in PI was usually evident within 10 min of the application of CPAP. The renal transplant subjects had a higher baseline PI than the normal subjects (1.15 ± 0.18 compared to 0.65 ± 0.06, P < 0.05; Table 1). The PI increased significantly in all the transplant subjects with 5.0 and 7.5 cmH2O CPAP (Table 1, Fig 1).

We compared the rise in PI with the application of CPAP between the normal and transplant subjects (Table 1).

| CPAP (cmH2O) | PI in controls (n=10) | PI in transplant subjects (n=6) | P* |
|--------------|----------------------|-------------------------------|----|
| 0            | 0.65 ± 0.06          | 1.15 ± 0.18                  | <0.05 |
| 2.5          | 0.64 ± 0.08          |                               |     |
| 5.0          | 0.70 ± 0.08**        | 1.24 ± 0.2*                  | <0.05 |
| 7.5          | 0.82 ± 0.08**        | 1.37 ± 0.24**                | <0.05 |
| Change from 0–5.0 | 0.048 ± 0.03             | 0.096 ± 0.04               | NS  |
| Change from 0–7.5 | 0.17 ± 0.06             | 0.23 ± 0.09                | NS  |

*Differences between the two groups. Change from 0–5.0 refers to the change in PI between 0 and 5.0 cmH2O CPAP; while change from 0–7.5 refers to the change in PI between 0 and 7.5 cmH2O CPAP. *P < 0.05, **P < 0.01, versus 0 cmH2O CPAP; NS, not significant.
The increase in PI in response to 5.0 cmH\textsubscript{2}O CPAP was greater in the transplant subjects but this was not significant. Furthermore, there was no difference between the groups in the response to 7.5 cmH\textsubscript{2}O CPAP. However, when expressed in terms of percentage change in PI from baseline values, the increase in PI with 5.0 cmH\textsubscript{2}O was 7.7% in controls compared to 7.8% in the transplant subjects and, with 7.5 cmH\textsubscript{2}O CPAP, the increase was 26% in the controls compared to 20% in the transplant subjects.

Systolic blood pressure did not change in the controls between 0 and 5.0 cmH\textsubscript{2}O CPAP (115 ± 9.26 mmHg and 109 ± 8.63 mmHg, respectively; NS). However, the systolic blood pressure fell to 104 ± 11.0 mmHg on 7.5 cmH\textsubscript{2}O CPAP, which approached statistical significance (P = 0.06). Diastolic blood pressure fell significantly on 7.5 cmH\textsubscript{2}O CPAP, from 76.43 ± 8.84 mmHg at baseline to 72.9 ± 9.32 mmHg (P < 0.01). In the transplant subjects, there was no significant change in either systolic or diastolic blood pressure during the application of CPAP. Furthermore, there was no significant change in heart rate in all patients throughout the study.

**Discussion**

This study looked at the effect of a short period of CPAP on renal vascular resistance in both normal and renal transplant subjects. We found that increasing levels of CPAP to 7.5 cmH\textsubscript{2}O caused a significant increase in renovascular resistance, suggesting a fall in renal blood flow. This was found in both normal subjects and renal transplant patients, suggesting that the renal nerves do not play a role in altering renal haemodynamics secondary to the application of CPAP.

The primary aim of this study was to determine the changes in renal haemodynamics in response to varying levels of CPAP. The secondary aim was to look at the possible role of the renal nerves in such changes. Thus, we studied patients with renal transplants to determine whether denervation abolished the renovascular responses. Previous studies have looked at renal nerve regeneration in both animals and humans post renal transplantation. Histological studies have shown evidence of partial regeneration in human renal transplant recipients [14]. However, a recent study has shown that, despite this regeneration, the human transplanted kidney remains functionally denervated [15].

Previous animal and human studies have shown conflicting results on the effect of both CPAP and PEEP on renal haemodynamics [8,16–20]. The majority of these studies found a decrease in renal blood flow with the application of positive pressure ventilation [8,16,18,19]. However, Berry et al [17] found no change in renal blood flow in dogs following the application of 10 cmH\textsubscript{2}O PEEP. More recently, Andrivet et al [20] also found no alteration in renal blood flow in a group of patients on applying 10 cmH\textsubscript{2}O PEEP [20]. There are several possible explanations for these inconsistent findings. The most likely explanation is the difference in the intravascular volume of the subjects in the studies. In the study by Berry et al [17], the dogs had developed significant fluid retention prior to the measurement of renal blood flow and the cardiac index actually increased with the application of PEEP and, subsequently, the renal blood flow remained constant. In the majority of the other studies, the subjects were normovolaemic and had a fall in stroke volume secondary to CPAP/PEEP with a subsequent fall in renal blood flow [8,18,19]. Another possible factor may be the redistribution of renal blood flow with the introduction of positive pressure ventilation. Hall et al [21] found a redistribution in renal blood flow from the outer to inner cortex secondary to PEEP. The degree of this intrarenal redistribution would have a significant effect on the total renal blood flow. Finally, both the level of CPAP and PEEP and the length of time they were applied varied significantly in the previous studies and these two factors would allow hormones such as antidiuretic hormone (ADH) and aldosterone to have an effect on the resultant renal haemodynamics [16].

It was thought that both PEEP and CPAP affect renal haemodynamics indirectly by reducing cardiac output. PEEP results in a higher mean intrathoracic pressure than CPAP [22], thus leading to a greater fall in cardiac output and ultimately affecting renal blood flow to a greater degree than CPAP. Several studies have shown that both PEEP [16] and CPAP [23] cause a decrease in cardiac output in controls, and this is thought to occur because of reduced venous return secondary to increased intrathoracic pressure.
pressure. However, this has not been confirmed in other studies. Leech and Ascah [24] found no effect on cardiac output in a group of normal subjects following the application of 15 cmH2O nasal CPAP. Furthermore, Bradley et al [25] found that in 22 patients with congestive heart failure, the cardiac output increased with CPAP in the group with raised pulmonary capillary wedge pressure, whilst it fell in those with normal wedge pressures. They attributed the improved cardiac output in those with high wedge pressure to a reduction in left ventricular afterload secondary to the increase in intrathoracic pressure with CPAP. There are several possible explanations for the differing results found in these studies. These include different modes of CPAP application (such as face-mask versus nasal CPAP) [23], different methods of measuring the resultant effect on cardiac function and the possibility that volume loading in some of the studies influenced the resultant effect on cardiac function [26].

The mechanism for the change in renal haemodynamics in our subjects is unclear. Renal blood flow is dependent on both perfusion pressure and renal vascular resistance, both of which may be altered by CPAP. An increase in intrathoracic pressure results in a fall in venous return which causes an increase in renal venous pressure, leading to a rise in the renal vascular resistance and a subsequent fall in renal blood flow. Also, a fall in venous return secondary to increased intrathoracic pressure leads to a fall in cardiac output which results in an increase in renal vascular resistance and therefore a decrease in renal blood flow. We recorded the cardiac output in three normal subjects and five transplant subjects and found a significant fall in cardiac output with both 5.0 and 7.5 cmH2O CPAP. However, since we did not record the renal venous pressure, we cannot state whether the increase in renal vascular resistance was secondary to a change in renal venous pressure or to a change in cardiac output.

Renal denervation has been found to abolish the fall in renal blood flow secondary to the application of PEEP in dogs, suggesting that the renal nerves play a significant role in determining the renal haemodynamic response to positive pressure breathing in dogs [27]. Jacob et al [28] have looked at the effect of PEEP on renal haemodynamics in a group of patients immediately post renal transplantation. They found no significant difference in renal blood flow between zero end-expiratory pressure (ZEEP) and 15 cmH2O PEEP [28]. These findings contradict our findings. A number of differences between the two studies may explain the different findings. Firstly, we studied a group of subjects who were at least 18 months post renal transplantation, with stable renal function. Jacob et al carried out their study on subjects immediately post-transplantation. There is a higher level of circulating hormones and neuropeptides, especially noradrenaline, immediately post-surgery and these could have an effect on the response of the renal blood flow to PEEP [29]. Secondly, their results may have been affected by anaesthetic agents and by the continuous infusion of dopamine given during the transplant surgery [30]. Thirdly, ischaemic reperfusion injury may have affected the response to PEEP. Finally, and most importantly, their subjects were studied 1 h post-operatively and were volume loaded during the procedure (subjects received 5 l saline, albumin and 5 units of packed red blood cells) and this could have prevented the fall in renal blood flow secondary to PEEP. This contrasts with our subjects who were euvolemic.

In summary, the application of CPAP at 5.0 and 7.5 cmH2O caused a significant increase in renovascular resistance in both normal subjects and renal transplant subjects. The rise in renovascular resistance was greater with the higher level of CPAP. There was no difference in the extent of the increase in renovascular resistance in response to CPAP between both groups suggesting that the renal nerves do not play a role in altering renal vascular resistance with the application of CPAP.

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