Effect of Obstructive Respiratory Events on Blood Pressure and Renal Perfusion in a Pig Model for Sleep Apnea

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BACKGROUND
Obstructive sleep apnea (OSA) is associated with hypertension and the progression of chronic kidney disease (CKD). Renal sympathetic innervation contributes to either condition.

METHODS
We investigated the effect of renal sympathetic denervation (RDN) on blood pressure (BP), renal perfusion, and neurohumoral responses during and after repetitive obstructive apneas in a pig model for OSA. BP, femoral artery, and renal artery flow were measured in 29 spontaneously breathing urethane-chloralose–anesthetized pigs. The effect of RDN (n = 14) and irbesartan (n = 3) was investigated. Repetitive tracheal occlusions for 2 minutes with applied negative tracheal pressure at −80 mbar were performed over 4 hours.

RESULTS
Spontaneous breathing attempts during tracheal occlusion caused an intra-apneic breathing synchronous oscillating pattern of renal flow. Renal flow oscillations were >2-fold higher compared with femoral flow that almost showed changes proportional to the BP alterations (2.9%/mm Hg vs. 1.3%/mm Hg; P < 0.0001). A marked postapneic BP rise from 102 ± 3 to 172 ± 8 mm Hg (P < 0.00001) was associated with renal hypoperfusion (from 190 ± 24 to 70 ± 20 ml/min; P < 0.00001) occurring after application of obstructive respiratory events. RDN, but not irbesartan, inhibited postapneic BP rises and renal hypoperfusion and attenuated increased plasma renin activity and aldosterone concentration induced by repetitive tracheal occlusions. Additionally, increased urinary protein/creatinine ratio was significantly reduced by RDN, whereas intra-apneic hemodynamic changes or blood gases were not modified by RDN.

CONCLUSIONS
Repetitive obstructive respiratory events result in postapneic BP rises and renal hypoperfusion, as well as neurohumoral responses and increased protein/creatinine ratio. These changes are mainly sympathetically driven because they could be attenuated by RDN.

Keywords: blood pressure; blood pressure rise; hypertension; renal denervation; renal perfusion; sleep apnea.

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Obstructive sleep apnea (OSA) has an overall prevalence of 2%–4% but is much more prevalent in conditions with increased sympathetic activity such as hypertension, type 2 diabetes, heart failure, and chronic kidney disease (CKD).1–4 In turn, recent reports indicate that CKD is highly prevalent in severe OSA patients without hypertension or diabetes.5,6 Additionally, OSA is considered an etiological factor in the development of hypertension7 and in the evolution of drug-resistant hypertension.8 OSA is associated with sympathetic overactivity9 and, together with changes in renal perfusion, is involved in the development and progression of CKD and hypertension.10–13 Afferent signaling derived from the native failing kidneys plays a major role in renal efferent sympathoexcitation and potentiates the adverse effects of chronically increased total body sympathetic activity.14 Renal sympathetic denervation (RDN) decreases blood pressure (BP), renal norepinephrine spillover, and muscle sympathetic nerve activity.15–17 Additionally RDN improved OSA severity in resistant hypertension.18 Interestingly, RDN reduced doppler sonographic renal resistive indices shown to be markers of progressive renal impairment and increased cardiovascular morbidity and mortality in hypertensive patients.19

The role of increased sympathetic drive on renal perfusion, BP, and the development of kidney damage in OSA are not well known. This study aimed to investigate the role of sympathetic innervation for renal perfusion, BP, and neurohumoral responses by performing RDN in a pig model for OSA.

METHODS
All animal studies were conducted in accordance to the German law for protection of animals. Experiments were performed in 29 chloralose-urethane–anesthetized spontaneously breathing male castrated pigs of the German Landrace weighing 22–30 kg (20% urethane, 0.8 ml/kg intravenous

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load, 0.4 ml/kg/hour maintenance) and 4% alpha-chloralose (0.4 ml/kg intravenous load, 0.1 ml/kg/hour maintenance). For more details, see Linz et al.\textsuperscript{20,21} No mechanical ventilation was used in these pigs. All 29 pigs were submitted to the following surgery: Pigs were tracheotomized and an endotracheal tube was inserted. BP was measured using a Tip catheter (Millar PC 350; Millar Instruments, Houston, TX) that was inserted into the aorta close to the origin of the renal artery through a port in the right femoral artery. Left femoral artery and left renal flow were measured with Doppler flow probes (transit time flowmeter module system from Transonic Systems; Hugo Sachs Elektronik-Harvard Apparatus GmbH, March-Hugstetten, Germany) positioned on the blood vessels. To gain access to the kidney, a laparotomy was performed in all pigs in a lateral position just below the ribcage in a line parallel to the last rib, and the retroperitoneal space was opened. The flow probe was positioned onto the renal artery directly after its origin from the aorta. To mimic an obstructive apnea, the tracheal tube was occluded and connected to a negative pressure device for application of defined negative tracheal pressure (NTP). The Mueller maneuver, forced inspiration against airway obstruction, is used in the clinical setting to simulate obstructive sleep apnea (NTP). The Mueller maneuver, forced inspiration against airway obstruction, is used in the clinical setting to simulate obstructive sleep apnea.\textsuperscript{22} As a modification of this maneuver, we applied NTPs at −80 mbar. The negative pressure device consisted of a negative pressure container (50 L) with a manometer, which was voided by a vacuum pump and activated by a solenoid valve. Tracheal pressure was continuously recorded. Blood gases were determined during normal breathing and at the end of each tracheal occlusion. Simple tracheal occlusion without and with applied NTP at −80 mbar was performed for 2 minutes. The procedures could be repeated with reproducible results, and all procedures were applied to the same pig at time intervals of approximately 15 minutes up to 4 hours.\textsuperscript{20,21}

In 7 of these 29 pigs, 1 hour of repetitive NTP maneuvers was performed. Afterward, the already exposed renal arteries were surgically denervated by cutting all visible nerves in the area of the renal hilus and by stripping approximately 1 cm of the adventitia from the renal artery.\textsuperscript{21} No further surgical procedure was performed in these pigs. The area was then moistened with a 20% phenol/ethanol solution for 10–15 minutes. After RDN, the pigs were allowed to re-equilibrate for 1.5 hours, and repetitive OSA maneuvers were performed for another hour.

In 3 of these 29 pigs, tracheal occlusions with applied NTP were performed in the presence of the angiotensin receptor blocker irbesartan (1 mg/kg bolus followed by 0.3 mg/kg/hour intravenously). Nineteen of these 29 pigs were used to investigate the effect of repetitive tracheal occlusion. Tracheotomy was performed, and both kidneys were approached through bilateral retroperitoneal flank incisions. Five pigs that underwent surgery served as controls with 4 hours of anesthesia without further interventions. In 7 pigs that underwent surgery, repetitive NTP maneuvers (4 NTP maneuvers/hour, each lasting 2 minutes) were performed over 4 hours starting at 1.5 hours after surgery including sham RDN procedure (SHAM). In 7 pigs, exposure of the kidney and the renal arteries was combined with surgical and chemical RDN, and a similar protocol with repetitive NTP maneuvers was conducted at 1.5 hours after surgery (RDN). Urine and plasma samples were taken at baseline and at 1, 2, 3, and 4 hours. Creatinine kinase activity, creatinine, albumin, and sodium (in serum and urine) were quantified with standard kits (Roche Diagnostics, Mannheim, Germany) using a Hitachi 912 E analyzer. Plasma renin activity and plasma aldosterone concentration were determined. Urinary protein/creatinine ratio and fractional sodium excretion \( \text{FeSodium} = 100 \times \left( \frac{\text{Sodium}_{\text{urinary}} \times \text{Creatinine}_{\text{plasma}}}{\text{Sodium}_{\text{plasma}} \times \text{Creatinine}_{\text{urinary}}} \right) \) and glomerular filtration rate \( \text{GFR} = \left( \frac{\text{Creatinine}_{\text{urinary}} \times \text{Volume}_{\text{Urine}}}{\text{Creatinine}_{\text{plasma}} \times \text{time} \times \text{body weight}} \right) \) were calculated. Blood gases were determined before and after NTP maneuvers (Radiometer ABL 715, Willich, Deutschland).

### Data analysis

Because the respiratory cycle length, BP, and heart rate differed among the pigs and changed during the obstructive apneas, we performed a beat-to-beat analysis and described the relative changes in renal or femoral flow during the obstructive synchronous changes in BP and calculated the percentage (systolic) flow change per millimeter of mercury change in (systolic) BP (%/mm Hg; referred to as the relative flow gain), as described elsewhere.\textsuperscript{23} This method was used to describe the rapid hemodynamic changes by the first heartbeat after the transition from inspiration to expiration. respective baseline is the last heartbeat before the transition from inspiration to expiration identified by the intratracheal pressure changes. These changes were calculated separately during the preapneic phase and during tracheal occlusion. BP, renal and femoral artery flow, and respective vascular resistances before and during the obstructive apnea and at the postapneic maximum of BP were calculated. The time to the BP maximum after release of the apnea and the time to 80% recovery of renal flow compared with baseline values before tracheal occlusion were determined.

### Statistics

Data are presented as mean ± SEM. For the comparison of preapneic to postapneic hemodynamic values, a Student t test for paired data was used. For the comparison of the percentage change in systolic pressure between groups, a Wilcoxon test was performed. For the comparison of the hemodynamic changes in a respiratory cycle during tracheal occlusion within 1 pig, 1-way analysis of variance for repeated measures was used followed by a Dunnett’s test for a post hoc analysis. For the comparison of the neurohumoral changes and proteinuria, a 2-way analysis of variance for repeated measures was used (3 groups; 4 time points). Statistical significance was set at \( P < 0.05. \)

### RESULTS

#### Effect of RDN on baseline BP, renal flow, femoral flow, and heart rate

RDN did not change baseline BP or femoral flow but tended to reduce renal flow (148 ± 78 ml/minute vs.}
197 ± 46 ml/minute at baseline; \( P = 0.24 \). RDN reduced heart rate by 18% from 86 beats per minute to 72 beats per minute \( (P = 0.003) \).

**Effect of RDN on changes in BP, renal flow, and femoral flow during obstructive apneas**

Intra-apneic renal flow changes were characterized by a reduction in renal flow during the inspiratory phase and an increase in renal flow with the beginning of the expiratory phase (Figure 1). This was caused by a combined effect of a sudden BP rise by 16% and a decrease in renal resistance by 19% with the first heartbeat during the expiratory phase, resulting in an intra-apneic percentage renal flow change of 2.88% per mm Hg. By contrast, femoral resistance was just reduced by 0.1%, resulting in a percent femoral flow change of 1.21% per mm Hg, which means an almost linear change of femoral flow with BP \( (P < 0.001 \) vs. respective percentage renal flow change). With opening of the tracheal occlusion, the intra-apneic breathing synchronous hemodynamic changes disappeared. RDN did not influence the intra-apneic hemodynamic changes significantly.

**Effect of RDN on postapneic hemodynamic changes**

Figures 2 and 3 show postapneic BP alterations and changes in renal and femoral flow before and 1.5 hours after RDN. Application of NTP during 2 minutes of tracheal occlusion resulted in a postapneic systolic BP increase by 52 mm Hg compared with systolic BP before tracheal occlusion, which was associated with a postapneic decrease in renal flow by 65% \( (P < 0.0001) \) and an increase in the calculated renal resistance from \( 0.75 \pm 0.1 \text{ mm Hg} \times \text{min/ml} \) to \( 2.4 \pm 0.45 \text{ mm Hg} \times \text{min/ml} \) \( (P = 0.01) \). Time until 80% recovery of renal flow compared with baseline before tracheal occlusion was long and variable at 290 ± 98 seconds. Postapneic hemodynamic changes remained stable during 4 hours of repetitive tracheal occlusions and did not differ significantly within 1 pig. Postapneic BP rises \( (P = 0.002) \), renal hypoperfusion \( (P = 0.0004) \), and increase in renal resistance \( (0.91 \pm 0.6 \text{ mm Hg} \times \text{min/ml} \) vs. \( 2.4 \pm 0.45 \text{ mm Hg} \times \text{min/ml} \) before RDN; \( P = 0.04 \) \) were significantly attenuated by RDN. Neither postapneic BP rises \( (\text{systolic BP: 110 mm Hg to 167 mm Hg before irbesartan vs. 107 mm Hg to 170 mm Hg after irbesartan; not significant; } n = 3) \) nor postapneic renal hypoperfusion were modulated by the angiotensin receptor blocker irbesartan.
Neurohumoral responses and changes in urinary protein/creatinine ratio, glomerular filtration rate, and blood gases

Figure 4 shows plasma renin activity, plasma aldosterone, changes in urinary protein/creatinine-ratio, and changes in glomerular filtration rate in pigs with repetitive obstructive apneas for 4 hours. Repetitive obstructive apneas resulted in an earlier increase in circulating aldosterone concentration compared with plasma renin activity. However, 1 single tracheal occlusion was not sufficient to modulate plasma renin activity and aldosterone concentration (pilot experiments; data not shown). Urinary protein/creatinine-ratio was significantly increased, mainly because of an increase in protein excretion, after 3 and 4 hours. RDN attenuated the increase in renin activity, plasma aldosterone, and urinary protein/creatinine ratio. There was a trend toward increased glomerular filtration rate in SHAM, which was significantly attenuated by RDN after 4 hours of repetitive tracheal occlusions. Sodium excretion did not differ significantly between the groups at 4 hours of repetitive tracheal occlusions (not shown). Importantly, changes in blood gases by obstructive respiratory events were not affected by RDN (Table 1). In control pigs, SHAM, and RDN, blood creatinine kinase activity at 1.5 hours after the instrumentation (779 ± 112 U/L, 892.6 ± 111 U/L, and 788.3 ± 145 U/L, respectively) and after 4 hours of repetitive obstructive events (924 ± 115 U/L, 897 ± 173 U/L, and 729 ± 145 U/L, respectively) did not differ significantly between the groups.

DISCUSSION

Repetitive tracheal occlusion mimicking obstructive apneas resulted in postapneic BP rises that were associated with transient but pronounced renal hypoperfusion due to an increase in renal resistance. Repetitive postapneic hemodynamic changes for 4 hours were accompanied by an increase in plasma renin activity, plasma aldosterone concentration, and urinary protein/creatinine ratio. All postapneic hemodynamic and neurohumoral changes were attenuated by RDN. By contrast, intra-apneic hemodynamic changes and changes in blood gases induced by obstructive apneas were not modified by RDN.

During obstructive apneas, which are caused by collapses of the upper airway during sleep in OSA patients, repetitive forced inspiration against the obstructed upper airway causes pronounced oscillating negative thoracic pressure episodes down to −80 mbar. Intermittent NTP has been shown to cause distension and leftward septal displacement in the heart during diastole, impairing left ventricle filling and hindering cardiac output during the inspiratory phase. Consequently, breathing synchronous intra-apneic changes in BP were associated with strong changes in renal flow, as shown herein. Renal flow oscillations were >2-fold stronger compared with the...
Figure 3. Effect of 2 minutes of obstructive respiratory events with applied negative tracheal pressure (NTP) on systolic and diastolic values of blood pressure, femoral flow, and renal flow (a) before and (b) 1.5 hours after renal sympathetic denervation (RDN). Values are means ± SEM. Abbreviation: NS, not significant.

Figure 4. Effect of renal sympathetic denervation (RDN) on changes in (a) plasma renin activity, (b) plasma aldosterone concentration, (c) urinary protein/creatinine ratio, and (d) glomerular filtration rate at 1, 2, 3, and 4 hours of repetitive obstructive apneas in control pigs, sham RDN procedure (SHAM), and RDN. Values are means ± SEM. Abbreviation: Ctr., control.
In hypertensive patients, plasma angiotensin II is related to increased plasma renin activity and plasma aldosterone levels. a pronounced transient renal hypoperfusion, and resulted in 4 hours were associated with postapneic BP rises, together with hemodynamic changes, particularly the finding of transient vasoconstriction resulting in renal hypoperfusion. We applied NTP at –80 mbar during repetitive tracheal occlusions. These observations suggest that repetitive obstructive apneas activate the renin-angiotensin-aldosterone system but exclude a relevant role of the renin-angiotensin0aldosterone system for the observed acute and transient postapneic hemodynamic changes. Increased plasma renin activity and aldosterone concentrations were inhibited by RDN, suggesting the involvement of sympathetic activation in the release of these hormones. The renal sympathetic efferent and afferent nerves regulating the renin-angiotensin-aldosterone system exert a powerful influence on the initiation, development, and maintenance of elevated systemic BP and increased cardiovascular risk commonly present in patients with OSA and CKD. Of note, postapneic hemodynamic changes were not inhibited by the angiotensin receptor blocker irbesartan. Additionally, 1 single tracheal occlusion resulted in postapneic BP rises but did not cause increases in renin activity and aldosterone concentration. Renin activity and aldosterone concentration remained increased after 1 NTP maneuver, whereas BP fell again within a few minutes. Increased renin activity and aldosterone concentrations did not modulate hemodynamic responses to repetitive tracheal occlusions. These observations suggest that repetitive obstructive apneas activate the renin-angiotensin-aldosterone system but exclude a relevant role of the renin-angiotensin0aldosterone system for the observed acute and transient postapneic hemodynamic changes.

Table 1. Blood gases in control pigs and in pigs with renal denervation sham procedure (SHAM) and renal denervation procedure (RDN) with repetitive obstructive apneas

<table>
<thead>
<tr>
<th>Time points</th>
<th>Control</th>
<th>SHAM</th>
<th>RDN</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH Baseline</td>
<td>7.427 ± 0.032</td>
<td>7.420 ± 0.055</td>
<td>7.442 ± 0.183</td>
</tr>
<tr>
<td>2-min NTP</td>
<td>7.426 ± 0.042</td>
<td>7.221 ± 0.215</td>
<td>7.29 ± 0.192</td>
</tr>
<tr>
<td>pO₂, mm Hg Baseline</td>
<td>170.9 ± 6.9</td>
<td>162.3 ± 10.2</td>
<td>152.2 ± 5.9</td>
</tr>
<tr>
<td>2-min NTP</td>
<td>185.5 ± 8.7</td>
<td>47.1 ± 8.1</td>
<td>48.4 ± 9.5</td>
</tr>
<tr>
<td>pCO₂, mm Hg Baseline</td>
<td>38.3 ± 1.6</td>
<td>39.8 ± 1.1</td>
<td>41.2 ± 1.2</td>
</tr>
<tr>
<td>2-min NTP</td>
<td>56.4 ± 4.9</td>
<td>71.6 ± 2.7</td>
<td>62.1 ± 5.2</td>
</tr>
<tr>
<td>SO₂, % Baseline</td>
<td>99.4 ± 0.7</td>
<td>99.0 ± 0.5</td>
<td>98.8 ± 1.5</td>
</tr>
<tr>
<td>2-min NTP</td>
<td>99.4 ± 0.3</td>
<td>51.2 ± 6.7</td>
<td>52.2 ± 4.9</td>
</tr>
</tbody>
</table>

This table includes some data that are part of a previous paper. n = 5 per group. Data are presented as mean ± SEM.

Repetitive tracheal occlusions with application of NTP over 4 hours were associated with postapneic BP rises, together with a pronounced transient renal hypoperfusion, and resulted in increased plasma renin activity and plasma aldosterone levels. In hypertensive patients, plasma angiotensin II is related to the severity of OSA. During repetitive tracheal occlusions, aldosterone plasma concentration increased before renin plasma activity, suggesting different regulatory mechanisms of renin and aldosterone release. Renin release is strongly regulated by efferent sympathetic renal nerves, whereas aldosterone is regulated by a variety of mechanisms, including hypoxia, ion homeostasis, and sympathetic activation.

Increased plasma renin activity and aldosterone concentrations were inhibited by RDN, suggesting the involvement of sympathetic activation in the release of these hormones. The renal sympathetic efferent and afferent nerves regulating the renin-angiotensin-aldosterone system exert a powerful influence on the initiation, development, and maintenance of elevated systemic BP and increased cardiovascular risk commonly present in patients with OSA and CKD. Of note, postapneic hemodynamic changes were not inhibited by the angiotensin receptor blocker irbesartan. Additionally, 1 single tracheal occlusion resulted in postapneic BP rises but did not cause increases in renin activity and aldosterone concentration. Renin activity and aldosterone concentration remained increased after 1 NTP maneuver, whereas BP fell again within a few minutes. Increased renin activity and aldosterone concentrations did not modulate hemodynamic responses to repetitive tracheal occlusions. These observations suggest that repetitive obstructive apneas activate the renin-angiotensin-aldosterone system but exclude a relevant role of the renin-angiotensin0aldosterone system for the observed acute and transient postapneic hemodynamic changes.

Urinary albumin excretion is increased in patients with OSA and is an accepted marker of the severity of glomerular injury. Increased urinary protein/creatinine ratio in pigs with repetitive obstructive apneas might represent an early marker of end-organ damage (e.g., endothelial cardiovascular dysfunction and early renal damage). Increased glomerular filtration rate after repetitive obstructive apneas may indicate glomerular hyperfiltration, which is also clinically observed in OSA patients. RDN attenuated increased urinary protein/creatinine ratio and glomerular filtration rate induced by repetitive obstructive apneas, supporting the notion that heightened renal sympathetic activation underlie both observed alterations. Sympathetic activity is already elevated in early phases of chronic renal failure, and the magnitude of sympathetic overdrive increases with disease progression. Therefore, RDN may provide beneficial effects in OSA patients with hypertension and renal dysfunction. Renal protective effects of RDN have been described in both animal studies and clinical trials. In rats with aortic regurgitation, a model for cardiac volume overload, RDN decreased albuminuria and glomerular podocyte injury. Results of bilateral RDN in 15 patients with resistant
hypertension and stage 3–4 CKD showed a favorable short-term safety profile and beneficial BP-lowering effects.\(^{33}\)

Importantly, modulation of the sympathetic nervous system by RDN attenuated postapneic hemodynamic changes but did not influence apnea-induced changes in blood gases, characterized by hypoxia and hypercapnia. This suggests that postapneic hemodynamic changes, together with neurohumoral response and increased protein/creatinine ratio, are mainly mediated by increased sympathetic drive and not by changes in blood gases alone.

In this pig model for OSA, RDN did not significantly change renal flow during normal breathing at baseline but tended to reduce it. Previous work on this issue has been contradictory.\(^{34–40}\) In normal healthy dogs and rats, surgical removal of basal renal sympathetic nerve did not alter renal flow,\(^{34–37}\) whereas studies in healthy rabbits revealed that RDN resulted in augmentation of renal flow.\(^{38,39}\) In pigs, acute RDN increased renal flow, and the use of dopamine revealed that renal flow reserve was blunted.\(^{40}\) These discrepancies might be due to differences among animal species, as well as the method of RDN. Our study is unique in addressing the effect of RDN on renal hemodynamics not only under basal conditions but also during and after obstructive respiratory events in a large animal model.

In this study, we performed obstructive respiratory events with application of defined negative tracheal pressure as observed in OSA patients. Changes in sleep status or arousal in patients with OSA might have an additional effect on hemodynamics and endocrine activation, which is not captured by these experiments in anesthetized pigs. Moreover, only effects of RDN within 4 hours could be investigated in our study setting. The long-term effects of RDN on development of CKD in OSA are still to be explored in further studies. For acute renal denervation, we performed combined surgical and chemical renal nerve ablation, which might be more complete compared with the catheter-based approach. Baroreflexes and chemoreflexes were not specifically tested in this study.

Postapneic hemodynamic changes, a postapneic rise in BP accompanied by renal vasoconstriction, and neurohumoral activation in a pig model for OSA were mainly mediated by increased sympathetic activation because they were inhibited by RDN. Increased protein/creatinine ratio induced by repetitive obstructive apneas could be prevented by RDN.

REFERENCES


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DISCLOSURE

The authors declared no conflict of interest.


