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Authors
Bhandari, Simran K
Shi, Jiaxiao
Molnar, Miklos Z
et al.

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Comparisons of sleep apnoea rate and outcomes among patients with resistant and non-resistant hypertension

Simran K. Bhandari,1 Jiexiao Shi,2 Miklos Z. Molnar,3 Scott A. Ragsom,1 Stephen F. Derose,2 Csaba P. Kovesdy,3 David A. Calhoun,4 Kamyar Kalantar-Zadeh,5 Steven J. Jacobsen2 and John J. Sim1

1Division of Nephrology and Hypertension, Kaiser Permanente Los Angeles Medical Center, Los Angeles, 2Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, 3Division of Nephrology and Hypertension, University of California Irvine Medical Center, Irvine, California, 4Division of Nephrology, University of Tennessee Health Science Center, Memphis, Tennessee and 5Department of Cardiovascular Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA

ABSTRACT

Background and objective: We directly compared sleep apnoea (SA) rates and risk of cardiovascular and mortality outcomes among SA patients with resistant hypertension (RH) and non-RH within a large diverse hypertension population.

Methods: A retrospective cohort study between 1 January 2006 and 31 December 2010 among hypertensive adults (age ≥18 years) was performed within an integrated health system. Rates of SA in RH and non-RH were determined. Multivariable logistic regression analyses were used to calculate OR for SA. Cox proportional hazard modelling was used to estimate hazard ratios (HRs) for cardiovascular and mortality outcomes between SA in RH versus SA in non-RH adjusting for age, gender, race, BMI, chronic kidney disease and other comorbidities.

Results: SA was identified in 33 682 (7.2%) from 470 386 hypertensive individuals. SA in RH accounted for 5806 (9.6%) compared to SA in non-RH 27 876 individuals (6.8%). Multivariable OR (95% CI) for SA was 1.16 (1.12, 1.19), 3.57 (3.47, 3.66) and 2.20 (2.15, 2.25) for RH versus non-RH, BMI ≥30, and males, respectively. Compared to SA in non-RH individuals, SA in RH had a multivariable adjusted HR (95% CI) of 1.24 (1.13, 1.36), 1.43 (1.28, 1.61), 0.98 (0.85, 1.12) and 1.04 (0.95, 1.14) for ischaemic heart event (IHE), congestive heart failure (CHF), stroke and mortality, respectively.

Conclusion: We observed a modest increase in likelihood for SA among RH compared to non-RH patients. Risks for IHE and CHF were higher for SA in RH compared to SA in non-RH patients; however, there were no differences in risk for stroke and mortality.

INTRODUCTION

Sleep apnoea (SA) has been identified as one of the most common comorbidities associated with the development of resistant hypertension (RH).1–4 While SA is believed to occur in up to 5–20% of the adult population, rates as high as 37–56% have been described in the hypertensive population.5–8 The severity of hypertension (HTN) has been shown to increase with the severity of SA.9–11 Furthermore, treatment of SA has been shown to improve blood pressure among hypertensive populations.12–14

The prevalence and prognosis of SA among RH compared to non-RH has not been well described. Prior estimates on the prevalence of SA among RH have
been derived from smaller specialized populations and from tertiary referral centres which are likely to have higher rates of both RH and SA than the general hypertensive population. Direct comparison of outcomes in individuals with SA and RH to those with SA and non-RH is lacking.

We previously characterized and described an RH cohort within a large, ethnically diverse HTN population using an electronic health record (EHR) approach. Using this RH and non-RH cohort, we sought to compare the rates and characteristics of SA in RH versus SA in non-RH and study their comparative risk of cardiovascular and mortality outcomes.

METHODS

Study population
A retrospective cohort study of Kaiser Permanente Southern California (KPSC) members was performed between 1 January 2006 and 31 December 2010. This study was approved by the KPSC institutional review board (Approval #5932) and exempted from informed consent. The KPSC healthcare system is a prepaid integrated health plan currently providing comprehensive care to over 4.0 million members throughout Southern California. The patient population is racially/ethnically and socioeconomically diverse, reflecting the general population of Southern California. All KPSC members have similar benefits and access to healthcare services, clinic visits, procedures and copays for medications.

Details of the study population have been previously described. Individuals 18 years and older with HTN and a documented blood pressure measurement were identified in the time period between 1 January 2006 and 31 December 2010. Individuals were followed up until they experienced any outcome or until the end of the observation period (31 December 2010).

Data collection and laboratory measurements
All laboratory data, vital sign assessments (including blood pressure measurements) and diagnostic and procedure codes are collected in the EHR as part of routine clinical care encounters. Comorbidities, including diabetes mellitus (DM), coronary artery disease, congestive heart failure (CHF) and cerebrovascular disease, were assessed based on inpatient and outpatient International statistical classification of diseases (ICD)-9 diagnoses coding. Chronic kidney disease (CKD) was identified and defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m² estimated from serum creatinine levels using the Chronic Kidney Disease Epidemiology Collaboration Equation. End stage renal disease was defined as requiring haemodialysis, peritoneal dialysis or renal transplantation. Data on hospitalizations and diagnoses that occurred outside the healthcare system were available through administrative claims records. Antihypertensive medication use was retrieved from KPSC internal pharmacy dispensing records.

Definitions of RH
HTN was identified by inpatient and outpatient ICD-9 diagnoses codes specific to HTN (codes 401.xx, 402.xx, 403.xx, 404.xx and 405.xx). To be included in this study, all individuals were required to have a minimum of two outpatient separately dated ICD-9 codes for HTN. The date of the second ICD-9 HTN code was used as the index date. Outpatient blood pressure values closest in date to the index date were used. Individuals who did not have a blood pressure measurement or those who were diagnosed with secondary HTN, specifically individuals with ICD-9 codes for renovascular disease, adrenal disorders, Cushing’s syndrome, aortic coarctation and secondary HTN not specified, were excluded from the study cohort. Hyperaldosteronism was not an exclusion criteria. Although hyperaldosteronism is a form of secondary HTN, there is a known overlap with obesity and inappropriate aldosterone secretion with clinicians often coding for hyperaldosteronism based on serum studies alone.

Individuals were classified as having RH if their systolic blood pressure was ≥140 mm Hg and/or their diastolic blood pressure was ≥90 mm Hg while prescribed three or more different antihypertensive medications concomitantly, or when they were prescribed four or more medications concomitantly regardless of blood pressure. All other hypertensive individuals were categorized as having non-RH.

Identification of SA
SA was identified using inpatient and outpatient ICD-9 diagnoses codes for SA (327.20, 327.21, 327.23, 780.51, 780.53 and 780.57) and/or by current procedural terminology (CPT) coding for dispensation of continuous positive airway pressure (CPAP) or bi-level PAP (BiPAP) devices (94660, E0470, E0471 and E0601) (Table S1, Supplementary information). SA patients were identified during the period 1 January 2006 to 31 December 2010 and thus they may be identified before or after the RH diagnosis. We were unable to distinguish obstructive from central SA.

Outcomes
The primary outcomes evaluated were ischaemic heart event (IHE), CHF, cerebrovascular accident (CVA) and all-cause mortality as separate competing outcomes. Any hospitalization with the primary or secondary diagnoses of IHE, CHF and CVA were used to identify these outcomes (Table S2, Supplementary information). Mortality information for the cohort was obtained from internal health systems databases. 31 December 2010 was used to censor follow-up. Each event was followed up separately without competing outcomes. Individuals were followed up until the occurrence of that particular event, disenrollment from the health plan, end of the study period (31 December 2010) or death. Follow-up was not censored when another event occurred, with the exception of death.
Statistical analysis

The prevalence of SA among the non-RH and RH populations was determined in the study cohort. The demographic characteristics and comorbidities of individuals who met the criteria for SA and RH were compared with those with SA and non-RH. Chi-square test was used for comparison of ordinal variables and the nonparametric Kruskal–Wallis test was used for continuous variables. Multivariable logistic regression analyses were used to calculate OR and 95% CI for SA, with adjustment for age, sex, race, BMI, systolic blood pressure ≥140 and the presence of comorbidities, including DM, CKD, ischaemic heart disease, CHF and cerebrovascular disease.

The primary analysis was to compare the risk of IHE, CHF, CVA and all-cause mortality among SA in RH and SA in non-RH. Cox proportional hazards regression modelling was used to estimate hazard ratios (HRs) for each outcome separately for SA in RH and SA in non-RH. HRs were also calculated for each outcome separately among SA subjects with a positive airway pressure (PAP) device prescription versus no PAP device prescription. Multivariable HRs were calculated with adjustment for potential confounders including age, sex, race, BMI, systolic blood pressure ≥140, whether or not they were prescribed PAP (either CPAP or BiPAP), and pre-existing comorbidities including DM, CKD, ischaemic heart disease, CHF and cerebrovascular disease.

All statistical analyses were generated using the SAS statistical software (version 9.2; SAS Institute, Cary, NC, USA). Results with $P < 0.05$ were considered statistically significant.

RESULTS

Cohort characteristics

A total of 470,386 individuals were identified for the study cohort (Fig. 1), as described previously.16,17 SA was identified in 33,682 patients (7.2%) of the HTN population (Table 1). The SA cohort was comprised of 63% males, 54% whites, 14% blacks, 19% Hispanics and had a mean age of 62 years. Average blood pressure of the SA population was 132/75 mm Hg and 32% of the SA population was noted to have CPAP/BiPAP prescribed. RH was identified in 60,327 (12.8%) of hypertensive individuals of whom 5,806 (9.6%) were found to have SA. Of the non-RH population, 27,876 (6.8%) were noted to have SA ($P < 0.001$ when compared to SA in RH).

SA in RH patients had an average blood pressure of 139/75 mm Hg compared to 130/75 mm Hg in SA in non-RH. SA in RH compared to SA in non-RH was more frequent in males (67% vs 63%), were those older in age (65 years vs 62 years), were more likely obese (80% vs 71%) and were more likely to be on anticoagulation medications (10.1% vs 5.1%) and antithrombotic medications (8.5% vs 3.9%) (Table S3, Supplementary information). SA in RH were also more likely to have CPAP/BiPAP prescribed (65.1% vs 62.4%) compared to the SA in non-RH. Classes of antihypertensive medications were similar between both SA in RH and SA in non-RH. Diuretics were the most frequently prescribed class of medications for both the groups. Average number of antihypertensive medications was 4.1 for individuals with SA in RH compared to 1.5 medicines for those with SA in non-RH.

Compared with the SA in non-RH population, the SA in RH population had a greater prevalence of comorbid conditions including DM (59% vs 38%), CKD (41% vs 22%), ischaemic heart disease (50% vs 31%), atrial tachycardia (4.0% vs 1.1%), CHF (33% vs 14%) and cerebrovascular disease (17% vs 10%; $P < 0.001$ for all) (Table 1).

Regression analyses: SA risk

In multivariable logistic regression analyses adjusting for age, sex, race, BMI and the presence of comorbidities, the OR (95% CI) for SA in RH compared to non-RH was 1.16 (1.12–1.19) (Table 2). In crude and adjusted analyses, both BMI of ≥30 and male gender had increased risk of SA. Every 5-year age decrease had
an OR of 1.15 (95% CI: 1.14–1.15) for SA. White race compared to blacks, Asians and Hispanics was associated with greater likelihood of SA.

Regression analyses: Outcomes

Overall, 7245 events occurred among the SA and HTN cohort with 21.5% experiencing at least one event (Table 3). The overall mortality rate was 8.3% (2801 individuals). The total number of outcomes was 5218 in the SA in non-RH population and 2027 in the SA in RH. SA in RH had a greater proportion of individuals who reached any outcome (34.9% vs 18.7%) compared to SA in non-RH (P < 0.001). When compared to SA in non-RH, SA in RH had higher rates of IHE (13.5% vs 7.1%), CHF (10.4% vs 3.3%), CVA (5.4% vs 3.4%) and mortality (13.5% vs 7.2%; P < 0.001 for all).

In crude models, SA in RH was at greater risk for all outcomes compared with SA in non-RH. In adjusted models, compared with SA in non-RH, SA in RH individuals was at greater risk for IHE and CHF. Risks for CVA and all-cause mortality were similar between those with SA in non-RH and SA in RH. Overall, SA individuals prescribed CPAP/BiPAP compared to those not prescribed CPAP/BiPAP had lower risk for mortality in adjusted models (HR, 0.70 (0.65–0.76)) but higher...
risk for IHE (HR, 1.18 (1.09–1.28)) and CHF (HR, 1.20 (1.08–1.34)). Compared to SA in non-RH, SA in RH HRs was 1.24 (1.13–1.36), 1.43 (1.28–1.61), 0.98 (0.85–1.12) and 1.04 (0.95–1.14) for IHE, CHF, CVA, and all-cause mortality, respectively (Table 4).

DISCUSSION

SA and HTN have been closely linked conditions based on pooled information from various observations. In this study, we found that the risk for cardiovascular outcomes was increased in SA subjects with RH compared with those with non-RH. The SA in RH individuals had a 24% increased risk for IHE and 43% increased risk for CHF. Our study within a single population of over 450,000 hypertensive individuals is one of the first studies to directly compare the cardiovascular risk associated with SA in RH population to the risk of SA in non-RH population. While the risk for IHE and CHF remained higher in SA in RH subjects compared to the SA in non-RH subjects, mortality and CVA risk were not greater in SA in RH. Furthermore, in evaluating SA versus no SA, we found that among the RH population, SA was associated with an HR (95% CI) of 1.08 (1.03–1.14) for all events compared to no SA. Among the non-RH population, SA was associated with HR (95% CI) of 1.05 (1.02–1.08) for all events compared to no SA (results not shown).

We found a higher rate of SA among RH compared to SA among non-RH (9.6% vs 6.8%). RH has been previously described to have a strong association with SA with prevalence rates ranging from 70% to 85%.2,4,15,20 However, the majority of prior studies on the RA and SA populations included RH patients from specialty HTN clinics and thus less generalizable to the routine HTN environment. Conversely, our study identified SA in 7.2% of our HTN population. We believe that our lower rate drawn from a real-world practice environment is representative of the under-screening and over-diagnosis of SA in the community and prescribes the need for screening. While the public health benefit of CPAP use is well founded,5,15,16 its use is limited by adherence and persistence.21,22 The high use of BiPAP, non-invasive PAP (BiPAP, Bi-level PAP) in our study was consistent with previous observations2,15 and could be due to the high prevalence of obstructive sleep apnoea and high load cardiovascular disease.

Table 3  Event rates among the study population and by RH status

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All SA subjects</th>
<th>SA and non-RH</th>
<th>SA and RH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person years n (%)</td>
<td>Rate per 1000 person years (95% CI)</td>
<td>Person years n (%)</td>
</tr>
<tr>
<td>Ischaemic heart event</td>
<td>131,093 (8.19)</td>
<td>1972 (7.07)</td>
<td>22,399 (13.54)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>134,538 (4.51)</td>
<td>919 (3.30)</td>
<td>22,952 (10.35)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>135,201 (3.73)</td>
<td>945 (3.39)</td>
<td>23,685 (5.37)</td>
</tr>
<tr>
<td>Death</td>
<td>137,901 (8.32)</td>
<td>1,042 (3.39)</td>
<td>24,318 (13.54)</td>
</tr>
<tr>
<td>Individuals with any event</td>
<td>123,108 (21.51)</td>
<td>103,193 (18.72)</td>
<td>19,914 (34.91)</td>
</tr>
</tbody>
</table>

Table 4  Hazard ratio for ischaemic heart event, congestive heart failure, cerebrovascular event or death in RH versus non-RH individuals with SA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>P-value</th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHE</td>
<td>1.93 (1.77, 2.09)</td>
<td>1.24 (1.13, 1.36)</td>
<td>&lt;0.001</td>
<td>1.08 (1.00, 1.17)</td>
<td>1.18 (1.09, 1.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHF</td>
<td>3.19 (2.88, 3.55)</td>
<td>1.43 (1.28, 1.61)</td>
<td>&lt;0.001</td>
<td>1.07 (0.96, 1.19)</td>
<td>1.20 (1.08, 1.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>1.55 (1.36, 1.77)</td>
<td>0.98 (0.85, 1.12)</td>
<td>0.74</td>
<td>0.94 (0.84, 1.05)</td>
<td>1.04 (0.93, 1.17)</td>
<td>0.47</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.78 (1.64, 1.93)</td>
<td>1.04 (0.95, 1.14)</td>
<td>0.40</td>
<td>0.61 (0.57, 0.66)</td>
<td>0.70 (0.65, 0.76)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Multivariable HRs were calculated with adjustment for potential confounders including age, sex, race/ethnicity, BMI, systolic blood pressure ≥140, Charlson’s comorbidity index and pre-existing comorbidities including diabetes mellitus, chronic kidney disease, ischaemic heart disease, CHF, cerebrovascular disease and the use of PAP device (CPAP and BiPAP usage).

BiPAP, bi-level PAP; CHF, congestive heart failure; CI, confidence interval; CPAP, continuous PAP; HR, hazard ratio; IHE, ischaemic heart event; PAP, positive airway pressure; RH, resistant hypertension; SA, sleep apnoea.
under-detection of SA that routinely occurs. Despite the growing prevalence of SA, it is well known that SA in the majority of patients remains undiagnosed. We feel that SA may have been under-reported in our analysis. Thus, the true prevalence of SA in HTN likely falls somewhere between our observation and rates described from specialized populations.

The RH population remains an important subset of the hypertensive population with described rates that are continually increasing. People with RH have increased cardiovascular and mortality risks compared to those with non-RH. Given the increased risk, identification and treatment of secondary causes of RH may help to better control blood pressure and ultimately improve outcomes. SA has been identified as a common secondary cause associated with the development of RH.

The treatment of SA has been shown to suppress sympathetic activation and also improve blood pressure particularly in the RH population. Long-term adherence to PAP therapy has been shown to suppress sympathetic activity and improve blood pressure in patients with RH. In our study, we found an 18% increased risk for IHE and a 20% increased risk for CHF among SA subjects with CPAP/BiPAP prescription versus SA subjects without CPAP/BiPAP prescription. A confounder on progression to IHE and CHF is the competing risk of death in the SA population. The increased risk for IHE and CHF may speak to the fact that the SA population with CPAP/BiPAP prescription was less likely to die and thus more likely to reach another outcome. We found a 43% reduction in mortality among SA patients who were prescribed CPAP/BiPAP, underscoring the importance of SA identification and treatment.

There are several potential limitations that may confound our study findings and interpretations. We identified SA using ICD-9 and CPT codes only. Polysomnography results for each SA patient were not available including apnoea–hypopnoea indexes. To validate the accuracy of the coding, a random chart review of those coded with SA revealed that 88% of patients who had coded for SA had a documented polysomnography or were being treated for SA with CPAP or BiPAP. Although we defined RH based on the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and American Heart Association guidelines, our definition remains imperfect. We did not require the use of a diuretic; however, 97% of the RH population were on a diuretic. We used two blood pressure measurements to determine RH versus non-RH status without being able to take into consideration blood pressure variation with time. In contrast to the real-world phenomenon where blood pressures vary over time, we somewhat arbitrarily identified a cohort as RH. The assumption was that once subjects were identified as RH or non-RH, they would remain so during the observation period.

In conclusion, in a large ethnically diverse and gender-balanced HTN population, there was a modest increase in risk for SA in the RH population compared to non-RH. Risk for IHEs and CHF were increased in those with SA in RH compared to SA in non-RH. Our EHR-based study and cohort has the potential to provide valuable insights into management strategies for both the SA and the RH populations in addition to studying the natural history of these co-existing conditions.

Acknowledgements

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REFERENCES


Supplementary Information

Additional supplementary information can be accessed via the html version of this article at the publisher’s website:

Table S1 ICD-9 codes used to capture sleep apnoea.

Table S2 ICD-9 codes used to capture outcomes/events during hospitalizations.

Table S3 Anticoagulation and antithrombotic medications evaluated.