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Ambulatory Blood Pressure Patterns in Patients with Retinal Vein Occlusion

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Abstract

Purpose—Failure of blood pressure (BP) to dip during sleep (non-dipper pattern) is associated with cardiovascular disease (CVD) and stroke. The prevalence and degree of non-dipping and masked hypertension in patients with retinal vein occlusion (RVO), which is associated with stroke, has not been previously examined.

Methods—We measured clinic and 24-hour ambulatory BPs in 22 patients with RVO and 20 control participants without known eye disease matched by age and sex. Mean BP dipping, defined as the ratio of difference in mean awake and sleep systolic BPs to mean awake systolic BP, and masked and nocturnal hypertension were compared between groups.

Results—Mean 24-hour ambulatory BP was 144/79 mmHg among those with RVO and 136/77 mmHg among controls. Patients with RVO had an almost two-fold higher prevalence of non-dipping pattern (80.8% (95% CI 52.8, 94.1) vs. 50.4% (95% CI 26.1, 74.5);p=0.008). Average sleep systolic BP dip in RVO patients was 6.1% vs. 11.9% in controls (p=0.004). More RVO patients had masked hypertension by ambulatory BPs than controls (71% vs. 50%), but this difference was not statistically significant.

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Conclusion—Our data suggest an association between RVO and non-dipper BP pattern. Ambulatory BP monitoring may be useful in the evaluation of patients with RVO by identifying those who may benefit from more aggressive BP control.

Keywords

Retinal Vein Occlusion; Ambulatory Blood Pressure Monitoring; Non-Dipper; Cardiovascular Disease Risk; Epidemiology; Diagnostic Tests

Introduction

Hypertension is a well-known risk factor for patients with retinal vein occlusion (RVO),[1–4] but diagnosing hypertension in RVO patients based on office blood pressure (BP) measurements alone can miss patients with uncontrolled hypertension. Uncontrolled hypertension may manifest as masked hypertension, defined as normal BP in the office setting but elevated BP based on out-of-office BP measurements. Masked hypertension is associated with increased target-organ damage and poor cardiovascular prognosis.[5,6] Out-of-office measurements of BP can be obtained by 24-hour ambulatory BP monitoring, whereby the patient wears a portable device (Figure 1) that automatically records BP at pre-specified intervals. Masked hypertension may manifest as elevated BP during sleep, which has been shown to be a better predictor of cardiovascular outcomes than daytime BP alone, and is currently detectable only by 24-hour ambulatory BP monitoring.[7,8]

Ambulatory BP monitoring demonstrates that BP typically exhibits a circadian rhythm with a decrease during sleep (dipper pattern). Studies have shown the absence of a nocturnal decrease (non-dipper) or presence of a nocturnal rise in BP (riser pattern) to be independently associated with increased risk of cardiovascular events and strokes.[910]

Ambulatory BP monitoring may be valuable in RVO patients because it can identify those with masked hypertension or those with non-dipping, which is a risk factor for cardiovascular mortality even if overall BP average is not elevated.[7] In a Brazilian study, which used ABPM to evaluate for masked hypertension in RVO patients, 92% (76) of patients with branch RVO had hypertension. Further examination of nocturnal BP measurements revealed that half of those with hypertension exhibited non-dipper patterns.[11] Improved identification and treatment of hypertension among patients with RVO has the potential benefit in the management of RVO via concurrent management with primary care to reduce recurrent or subsequent stroke and CVD events. We therefore performed a cross-sectional study assessing 24-hour BP control and non-dipper pattern as well as secondary characteristics, such as the presence of masked hypertension and nocturnal hypertension, in patients with RVO compared to age and sex-matched controls.

Methods

Overall Design

We conducted a cross-sectional study using convenience sampling and chart review. This study was approved by the University of North Carolina Institutional Review Board (IRB), and informed consent was obtained from each participant. The study complied with all

aspects of the Health Insurance Portability and Accountability Act (HIPAA) and adhered to the tenets of the Declaration of Helsinki.

Study Participants

Inclusion criteria were patients seen at University of North Carolina Ophthalmology between January 2011 and May 2014 with a diagnosis of RVO. Seventy-six patients with RVO were identified by ICD-9 code (362.36 (branch RVO), 362.35 (central RVO-complete), 362.37(central RVO-partial), 362.30 (retinal vascular occlusion, unspecified), 362.37 (venous engorgement)) through UNC's electronic medical record. Patients with RVO diagnosed greater than 12 months previously were initially excluded but later included to broaden participant enrollment. Patients younger than 45 years of age at the time of RVO and patients with known or suspected hypercoagulable states were excluded from the study.

A study recruiter contacted the patients via telephone. Eighteen of those contacted were interested in participating of which 7 were finally recruited. Of the 33 patients who declined, 2 were deceased, 3 cited time limitations, 3 cited transportation limitations, 8 were not interested and 19 did not return the recruiter's phone call. An additional 15 patients were recruited as they presented or referred to clinic during this time frame, resulting in a total of 22 patients who agreed to participate in this study.

Controls were selected from a prior University of North Carolina study database of participants without known eye disease who underwent ambulatory BP monitoring to assess the reproducibility of masked hypertension among borderline hypertensives.[14] The controls were matched by age and sex, masked to their BP level and dipping status. These controls were recruited after measuring clinic blood pressures to evaluate the identification of masked hypertension using ABPM.

Clinic Blood Pressure Measurements

Clinic BP measurements were obtained prior to fitting participants with the ambulatory BP monitor. Three seated, non-dominant arm BP measurements were recorded at one-minute intervals using an appropriate cuff size after an initial 5 minutes of rest.

Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring (ABPM) was performed over a 24-hour period using an Oscar 2 ambulatory BP monitoring device (Suntech Medical, Morrisville, NC). The Oscar 2 ABPM has been previously validated.[12] The same ambulatory blood pressure instrumentation, methods, and analysis for RVO patients and controls. The BP cuff was worn on the non-dominant arm with the cuff size determined by upper arm circumference, and an in-office test measurement was performed to assess adequate fit and comfort. The device was programmed to take measurements at 30 minute intervals from 6am to 10pm and at 60 minute intervals from 10pm to 6am. BP readings were set at slightly variable time intervals to prevent anticipation effect. Any values that were outside preset limits (systolic ≥220 or ≤80 mmHg; diastolic ≥130 or ≤40 mmHg) were rejected, and a repeat measurement was recorded.

We used a participant diary to define sleep and awake periods and to note activities that may influence the fluctuation in daytime and nighttime BP. If a diary was not available, participants were asked the times they went to sleep and awoke at the time of follow-up the next day. If participants did not provide this information, we defined awake as 10am to 10pm and sleep as midnight to 6am. The ambulatory BP monitoring measurements were downloaded from the portable unit to a computer for summary and analysis. We minimized confounding factors that may influence ABPM results by asking participants about any events at night and sleep quality. If there was concern about poor sleep, such as using the restroom at night or leaving the bedroom to eat or read, we removed any isolated measurements that corresponded with those events and any outlier readings (diastolic BP <30 mm Hg, pulse pressure < 20 mm Hg, or isolated diastolic BP > 120 mm Hg with no other diastolic readings > 110 mm Hg) that could influence the averaged nocturnal and awake BP measurements. Following this procedure, we required a minimum of 14 awake and 6 sleep measurements to deem a session adequate, following protocol previously performed in other studies assessing nighttime dipping.[13]

Definitions

Following prior ABPM protocols, masked hypertension was defined as normal clinic BPs (BPs <140/90) with elevated awake ambulatory BPs (systolic BP ≥ 135 mmHg or diastolic BP ≥ 85 mmHg) or elevated sleep ambulatory BPs (systolic BP ≥ 120 mmHg or diastolic BP ≥ 70 mmHg).[10,14] Nocturnal hypertension was defined as sleep ambulatory systolic BP ≥ 120 mmHg or diastolic BP ≥ 70 mmHg.[14] Non-dipping was defined as dipping ≤10%.[13]

Statistical Analysis

BP dipping was calculated as the ratio of difference in mean awake and sleep systolic BPs to mean awake systolic BP. For example, if the participant had a mean awake systolic BP of 150 mmHg and a mean sleep systolic BP of 130 mmHg, the average systolic $\mathrm{BP\ \ dipping}=\frac{150\mathrm{mmHg}-130\mathrm{mmHg}}{150\mathrm{mmHg}}\times 100\%=13.3\%$. Patients with RVO were compared to the non-RVO participants using the two-sample Student's t-test for continuous variables and Chi-square or Fisher's Exact test for categorical variables. Analysis of covariance (ANCOVA) with a regression model was used to assess the relationship of diagnosis of RVO on the outcome of prevalence of non-dipping versus dipping status. Covariates that had a relatively equal distribution were omitted, and the final adjusted variables included race, smoking status, and diabetes. A second model was performed to include hypertension with the other covariates. All statistical analyses were performed using Stata 13 (StataCorp LP, College Station, Texas).

Results

Characteristics of Sample

Of 76 patients identified with RVO, 22 elected to participate and underwent ABPM. Two participants were later excluded due to inadequate number of sleep measurements. The mean age of participants with RVO was 68.9 years (Table 1). Five out of 20 (25%) were male. The

mean clinic BP was 151/85 mmHg among those with RVO and 129/78 mmHg among the comparison group.

BP Dipping

The ambulatory BP averages are shown in Figure 2. Seven RVO participants and 6 control participants did not provide an activity and sleep diary. These participants provided times of sleep and awakenings upon follow-up the next day. The mean (±SD) 24-hour ambulatory BP was 144/79 mmHg (±17/9 mmHg) among those with RVO and 136/77 mmHg (±12/9 mmHg) for the comparison group. The average systolic BP dipping ratio was 6.1% among those with RVO compared to 11.9% among those without RVO (p=0.004). Seventeen out of the 20 participants with RVO were non-dippers (85%) compared to 9 out of 20 controls (45%; p=0.008; Table 2). After adjusting for race, smoking status, and diabetes, the difference in non-dipper prevalence was 83.5% vs. 44.3% (p=0.021). When hypertension was also included in a second model, the difference remained statistically significant (84.4 vs. 45.2%; p=0.026).

Three participants with RVO exhibited a riser pattern, defined as average nighttime BPs exceeded average daytime BPs. Two of the 3 participants with RVO who exhibited nocturnal systolic BP dipping had elevated daytime systolic BPs. Six of the 8 participants with RVO who were not on antihypertensive treatment were non-dippers (75%). In addition, of the 7 participants with RVO who had normotensive office visit BP measurements, defined as clinic BP measurements <140/90 mmHg, 4 (57%) exhibited non-dipper patterns. Twelve of 13 participants with RVO who also had hypertension identified by office measurements were non-dippers (92%).

Masked Hypertension and Nocturnal Hypertension

Ambulatory measurements revealed elevated BPs among patients with RVO who had normotensive office visit BP measurements, as shown in Table 3. Five of 7 with RVO (71%) had masked hypertension by ambulatory measurements. Seventeen of 20 patients with RVO and 13 of 20 control participants had nocturnal hypertension (85 vs. 65%). Interestingly, among those who had nocturnal hypertension, 1 of 17 RVO patients (5%) and 5 of 13 control patients (38%) exhibited a dipper pattern.

Discussion

RVO is often associated with systemic diseases such as hypertension, hyperlipidemia, diabetes, coronary artery disease, and smoking.[3,15–17] Hypertension is a known risk factor for CVD morbidity and mortality.[18] While RVO is not an independent risk factor for cardiovascular or stroke-related mortality, patients with RVO have a high risk of hypertension (48%-85%) and an increasing trend in incident strokes.[17,19–22, 24, 27] A recent longitudinal study showed an increased risk of stroke in individuals with RVO versus the comparison group (16.8% vs 10.7%). [23] Central RVO has been associated with increased mortality that is likely attributable to systemic cardiovascular disorders.[21, 24, 27]

RVO is considered end-organ damage in hypertensive disease. Currently, most diagnoses of hypertension are based solely on office readings, but office BP measurements alone may

failed to identify patients with nocturnal or masked hypertension, which is diagnosed with ambulatory BP monitoring. This subset of patients would be susceptible to CVD and stroke-related mortality secondary to unidentified hypertension. Studies have demonstrated that ambulatory nighttime (sleep) BP non-dipper patterns are strong predictors of CVD and stroke risk.[9,10] Better nocturnal BP control could improve mortality in patients with non-dipper patterns.[10] Antihypertensive chronotherapy, the administration of antihypertensive regimens based on the circadian diurnal pattern, has been shown to significantly lower the incidence of CVD death, myocardial infarction, and strokes.[25]

In this cross-sectional study, patients with RVO had a nearly two-fold higher prevalence of non-dipping nocturnal BP pattern than participants from a non-RVO comparison group. This held true after adjusting for race, smoking, diabetes, and hypertension. When also accounting for differences in participants with hypertension between both groups, the difference in non-dipper rates persisted. This increased rate of non-dipping status in RVO patients likely reflects unidentified hypertension in this population.

Our control group was selected because they had the identical ABPM instrumentation and methods performed, and had no known eye disease. Of note, our comparison group had a 45% rate of non-dippers, which is higher than the 20% rate reported in the general population.[10] We identified more patients with normotensive clinic BPs who exhibited non-dipping, and thus elevated nocturnal blood pressures, which would have otherwise gone undetected by clinic BPs alone (57%). We also identified more patients who exhibited masked hypertension based on overall ABPM measurements (71%). Interestingly, we also found that 92% of patients with RVO who had a known diagnosis of hypertension also had a non-dipping status, which is higher than the previously reported prevalence of non-dippers among hypertensive patients (54%).[25] Even though the vast majority of these patients were already on antihypertensive medications, the high prevalence of non-dipping is surprising because it is a risk factor for cardiovascular mortality and stroke independent of office BP measurements.[7,25] ABPM is increasingly being recognized as an important component of modern hypertension diagnosis and management.[27] If ABPM proves to be useful in CVD risk stratification of RVO patients, it would expand the evidence-base for uses of this technology.

To our knowledge, this is the first study designed to examine the prevalence of non-dipping, degree of dipping, in addition to masked hypertension among patients with RVO compared to those without eye disease. Given that some study participants had normal clinic BP while exhibiting a non-dipping BP pattern and/or masked hypertension further suggests that ABPM may be an important component of the evaluation of a patient with RVO. The importance of nocturnal non-dipping status in addition to daytime hypertension in relation to CVD and associated morbidity[7,10] including RVO warrants further investigation. Additional studies are warranted to fully characterize dipping patterns among RVO patients and it's associated clinical relevance to both ocular and systemic morbidity.

We present the hypothesis that ABPM for RVO patients could be used to identify and risk stratify patients who do not have adequate BP control and who might benefit from additional or alternate timing of antihypertensive treatment to reduce morbidity and mortality from

CVD. Better 24-hour BP control may help reduce mortality from CVD and stroke in RVO patients.[25] Our study is limited by its small sample size. Although we were only able to successfully recruit 18% (7/40) of those patients identified by CPT code and contacted by a recruiter in addition to patients presenting to clinic, our results could be biased by an unidentified inherent difference in those agreeing to participate versus those declining. However, we believe such difference would be unlikely to affect the results away from the null. Also, the use of convenience sampling may limit the generalizability of our results to a broader population due to differences in sample characteristics and the general population. The use of diaries in some participants may introduce measurement bias in defining rest and activity periods during 24-hour ABPM; however, we attempted to reduce such bias by asking the remaining participants their awake and sleep times. We recognize that part of the RVO group receiving antihypertensive treatment may influence the results, although this would likely bias the difference in sleep blood pressure patterns towards the null. We also acknowledge that there are no definitive recommendations on the frequency of awake and sleep measurements in assessing nighttime dipping. We used the 14 awake and 6 sleep measurements as a balance of feasibility while providing a reasonable depiction of average BPs during sleep, as has been done in studies using CARDIA data.[13]

Our small pilot study identified a statistically significant higher prevalence of non-dippers in the RVO group compared to the controls. We believe additional large studies are warranted to further examine the relationship between RVO and 24-hour BP. The identification of a relationship between masked hypertension or nocturnal non-dipping status and RVO occurrence can serve as a mode for ophthalmologists to assist primary care in the reduction of systemic morbidity and mortality in a shared patient population. In addition, ABPM may also be beneficial in patients with other ocular stigmata of hypertensive retinopathy without RVO, such as retinal macroaneurysm and ischemic optic neuropathy, but additional studies are needed.[28]

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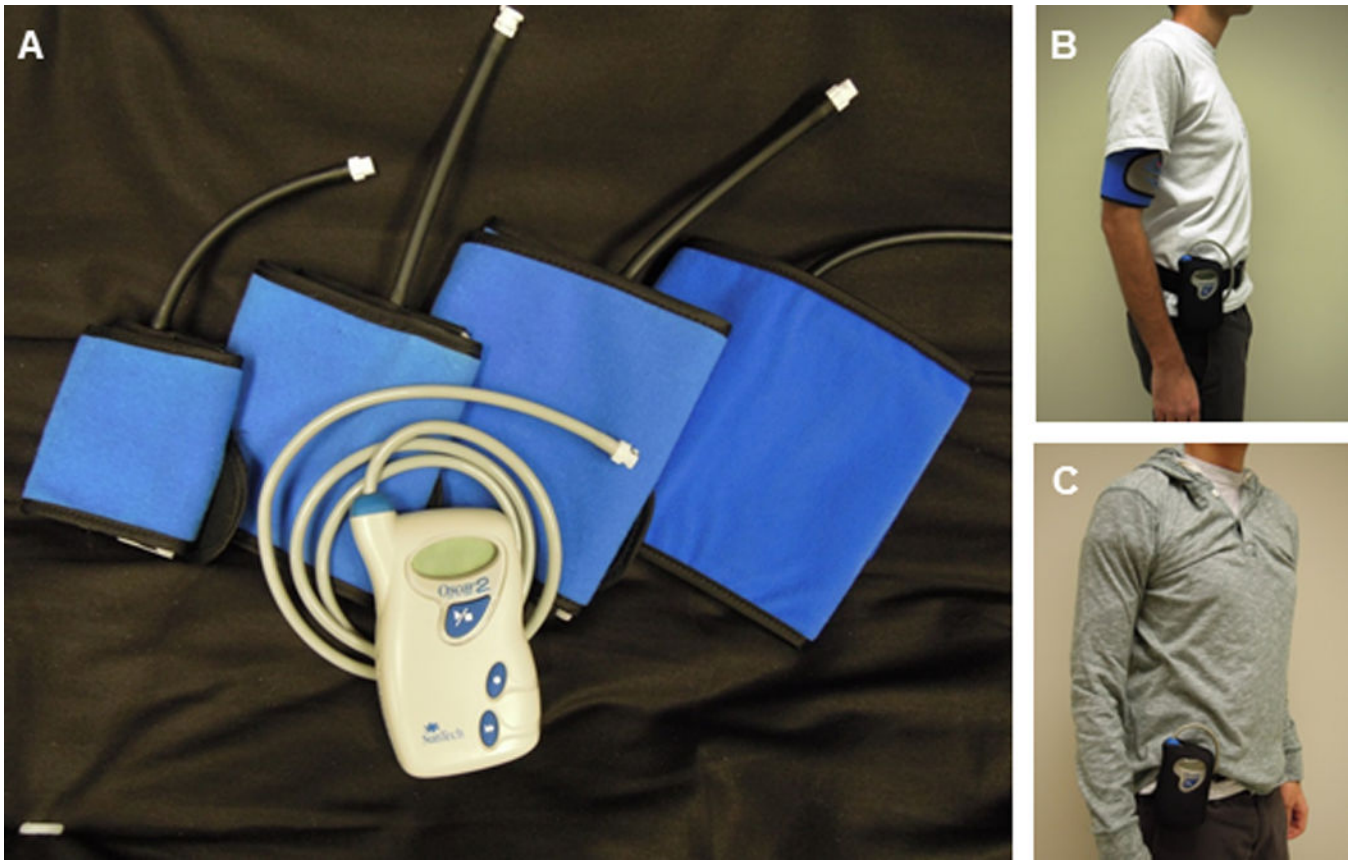

Figure 1. Ambulatory Blood Pressure Monitor

Legend: An ambulatory blood pressure monitor is a standard portable digital blood pressure (BP) device that records BP measurements over a 24-hour period. The various blood pressure cuff sizes can match individual arm circumference for accuracy of BP readings and patient comfort (Fig 1A). The device is portable and fits securely in a pouch either on a belt or waist strap, and the connecting cord slips under the patient's garment (Fig 1B). The blood pressure cuff can rest under clothing without restricting the patient's daily activities (Fig 1C).

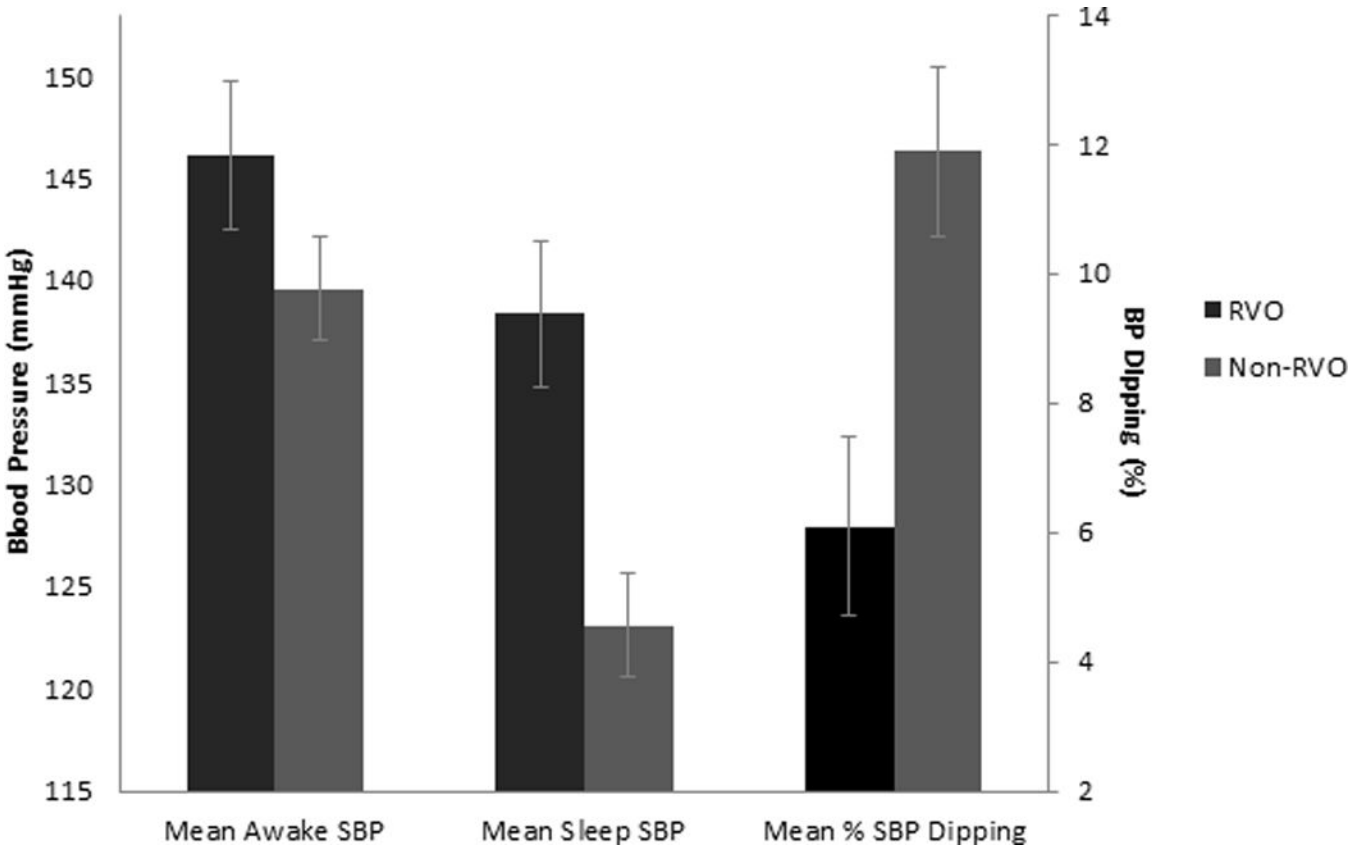

Figure 2. Ambulatory Systolic Blood Pressure Measurements by Presence of Retinal Vein Occlusion

Legend: BP, blood pressure; SBP, systolic blood pressure.

Table 1

Demographic and Clinical Characteristics of Participants Stratified by Presence of Retinal Vein Occlusion

	RVO* (n = 20)	Non-RVO (n = 20)	Difference (95% Confidence Interval)	P-value‡
Age, mean yrs (± SD)	68.9 (8.4)	67.7 (7.6)	1.2 (−4.0, 6.4)	0.6
Male, n (%)	5 (25.0)	5 (25.0)	n/a	1.0
Current Smoker, n (%)	6 (30.0)	1 (5.0)	n/a	0.091**
Caucasian, n (%)	17 (85.0)	17 (85.0)	n/a	1.0**
Diabetes Mellitus, n (%)	3 (15.0)	0 (0)	n/a	0.23**
Glaucoma, n (%)	5 (25.0)	0 (0)	n/a	0.047**
Baseline Clinic SBP, mean mmHg (± SD)	151.4 (21.1)	129.0 (17.4)	22.4 (10.0, 34.8)	0.0008
Baseline Clinic DBP, mean mmHg (± SD)	85.4(10.6)	78.3(12.6)	7.2 (−0.2, 14.6)	0.058
Clinic Pulse Pressure, mean mmHg (± SD)	65.9 (17.2)	50.7 (11.0)	15.2 (−6.0, 24.5)	0.002
Hypertension, n (%)†	13 (65.0)	6 (30.0)	n/a	0.027
Antihypertensive treatment	12 (60.0)	0 (0)	n/a	<0.001**

*Total, n = 40; RVO, n = 20; Control, n = 20. BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; Pulse Pressure, as defined as systolic pressure minus diastolic pressure

†Based on clinic SBP ≥ 140 mmHg or DBP ≥ 90 mmHg

‡Based on two-sample Student's T-test for continuous variables, Pearson's Chi-square test for categorical variables

**Based on Fisher's Exact test since at least one cell has expected count less than five

Table 2

Mean Ambulatory Blood Pressures by Presence of Retinal Vein Occlusion

	RVO* (n = 20)	Non-RVO (n = 20)	Difference (95% CI)	P-value†
24-h Ambulatory SBP, mean mmHg (± SD)	144.3 (16.6)	135.9 (12.0)	8.4 (−0.8, 17.6)	0.074
24-h Ambulatory DBP, mean mmHg (± SD)	79.4 (8.6)	76.8 (9.3)	2.6 (−3.1, 8.3)	0.37
Awake SBP average, mean mmHg (± SD)	146.2 (16.1)	139.6 (11.3)	6.65 (−2.3, 15.6)	0.14
Sleep SBP average, mean mmHg (± SD)	138.4 (19.8)	123.1 (15.2)	15.3 (3.9, 26.6)	0.010
Awake DBP average, mean mmHg (± SD)	81.0 (7.9)	79.6 (9.8)	1.4 (−4.3, 7.1)	0.63
Sleep DBP average, mean mmHg (± SD)	74.4 (11.9)	67.8 (8.6)	6.7 (0.1, 13.3)	0.047
Average Systolic BP Dip, % (mean ± SD)	6.1 (6.2)	11.9 (5.8)	−5.8 (−9.7, −2.0)	0.004
Proportion of Non-dippers, % (n)	85.0 (17)	45.0 (9)	n/a	0.008‡
Adjusted proportion of Non-dippers, % (95% Confidence Interval)	83.5 (57.9, 94.9)	44.3 (23.3, 67.5)	n/a	0.021**
Adjusted proportion of Non-dippers, % (95% Confidence Interval)	84.4 (57.9, 95.5)	45.2 (23.0, 69.5)	n/a	0.026††
Adjusted proportion of Non-dippers, % (95% Confidence Interval)	80.8 (52.8, 94.1)	50.4 (26.1, 74.5)	n/a	0.102‡‡

*Total, n = 40; RVO, n = 20; Control, n = 20. BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP Dip, nocturnal blood pressure dipping ratio as we defined as the ratio of change in mean daytime and nighttime systolic blood pressures to mean daytime systolic blood pressure

†Based on two-sample Student's T-test by presence of RVO

‡Based on Pearson's Chi-square test

**Adjusted for race, diabetes, and smoking status

††Adjusted for race, diabetes, smoking status, and hypertension

‡‡Adjusted for race, diabetes, smoking status, and continuous clinic SBP variable

Table 3

Masked Hypertension and Nocturnal Hypertension by Presence of Retinal Vein Occlusion

	RVO (n = 7)	Non-RVO (n = 14)	P-value**
Masked Hypertension by awake and sleep BPs, n (%)†	5 (71)	7 (50)	0.64
Nocturnal Hypertension, n (%)*,‡	17 (85)	13 (65)	0.27

*Total, n = 40; RVO, n = 20; Control, n = 20. BP, blood pressure.

†Based on awake ambulatory systolic BP ≥ 135 mmHg or diastolic BP ≥ 85 mmHg or sleep ambulatory systolic BP ≥ 120 mmHg or diastolic BP ≥ 70 mmHg

‡Based on sleep ambulatory systolic BP ≥ 120 mmHg or diastolic BP ≥ 70 mmHg

**Based on Fischer's Exact test