Received: 15 October 2020 | Revised: 10 November 2020 | Accepted: 11 November 2020

DOI: 10.1111/jch.14114

ORIGINAL PAPER

WILEY

Supine blood pressure—A clinically relevant determinant of vascular target organ damage in hypertensive patients

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Funding information
Medical Research Foundation; Western

Abstract

Night-time blood pressure (BP) is an important predictor of cardiovascular outcomes. Its assessment, however, remains challenging due to limited accessibility to ambulatory BP devices in many settings, costs, and other factors. We hypothesized that BP measured in a supine position during daytime may perform similarly to night-time BP when modeling their association with vascular hypertension-mediated organ damage (HMOD). Data from 165 hypertensive patients were used who as part of their routine clinic workup had a series of standardized BP measurements including seated attended office, seated and supine unattended office, and ambulatory BP monitoring. HMOD was determined by assessment of kidney function and pulse wave velocity. Correlation analysis was carried out, and univariate and multivariate models were fitted to assess the extent of shared variance between the BP modalities and their individual and shared contribution to HMOD variables. Of all standard non-24-hour systolic BP assessments, supine systolic BP shared the highest degree of variance with systolic night-time BP. In univariate analysis, both systolic supine and night-time BP were strong determinants of HMOD variables. In multivariate models, supine BP outperformed night-time BP as the most significant determinant of HMOD. These findings indicate that supine BP may not only be a clinically useful surrogate for night-time BP when ambulatory BP monitoring is not available, but also highlights the possibility that unattended supine BP may be more closely related to HMOD than other BP measurement modalities, a proposition that requires further investigations in prospective studies.

1 | INTRODUCTION

Night-time blood pressure (BP) is closely associated with hypertension-mediated organ damage (HMOD), cardiovascular (CV) events, and mortality.[1-6] In patients with elevated night-time BP and missing night-time BP dipping, decreased kidney function has commonly been observed.[7,8] These pathological night-time BP alterations were confirmed to be predictors of decline in eGFR in longitudinal

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retrospective association studies.[9,10] Similar results were shown for proteinuria. Associations between elevated night-time BP and urinary protein excretion are evident in both hypertensive and non-hypertensive patients.[11-13]

The macrocirculation is another target of HMOD. Arterial stiffness can be quantified by pulse wave velocity (PWV) measurement, which has been shown to be associated with CV morbidity and mortality.[14] Similar to markers of HMOD in the kidney, night-time BP elevations and reduced dipping patterns have been associated with increased PWV.[15,16]

Despite showing excellent predictive potential for HMOD, CV morbidity, and mortality, night-time BP is only obtained in a relatively small number of hypertensive patients, usually by ambulatory BP monitoring (ABPM) or home BP monitoring, with BP management predominantly being based on seated office BP measurements. The use of ambulatory BP monitoring to obtain night-time BP is further restricted by the limited availability of ABPM, the need for trained personnel, associated costs, and others.[17,18] Evidence of advantages of the methodology and the data collected with ABPM on the other hand is overwhelming.[19]

A partial resolution of this problem may be the identification of markers and alternatives that closely share a high degree of variance with night-time BP measurements if night-time BP measurements via ambulatory BP monitoring are unavailable. Such approaches include the use of home BP devices.[20]

Here, we propose a potential additional approach, namely the use of supine office BP measurement. Based on physiological considerations and the fact that night-time BP is usually recorded in a lying position, we hypothesized that standardized supine office BP measurement may closely correlate with night-time BP. Naturally, night-time BP is not only determined by a supine position but also by an altered state of consciousness, that is, sleep, which is impossible to mimic with any office BP assessment. Nevertheless, we hypothesized that supine BP may serve as a useful predictor of vascular HMOD, in particular if ABPM and night-time BP is not available.

2 | METHODS

We hypothesized that explanatory potential provided by night-time BP measurements as a predictor for HMOD is shared to some degree with supine BP. To test for this, we analyzed how much variance different modes of measuring BP share in a cohort of treated hypertensive patients and if correlation estimates is particularly prominent for night-time BP and supine BP. We then investigated whether both night-time BP and supine BP showed associations with hypertension-mediated organ damage related to the kidney and vascular system. It was further investigated if the variance in supine BP measurements was able to partially substitute the associative power between night-time BP and the HMOD variables by reducing its contribution to the overall bivariate model fitted with both independent variables.

2.1 | Study cohort

We analyzed study data of 165 patients who were referred to our tertiary hospital-based hypertension clinic at Royal Perth Hospital, Perth, Australia between January 2015 and December 2019. Patients referred to the outpatient clinic were offered to participate in this study and undergo extended testing. Patients who had one additional visit at which PWV, eGFR, and ACR were measured and an ABPM was performed were included in this analysis. The aim of this study was to prospectively collect relevant and standardized BP measures and HMOD estimates and investigate their association in this real-world setting. No power analysis was carried out as we continuously recruited from the outpatient clinic and analyzed the data after a set period of 5 years. The study was approved by the local Ethics Committee, the clinical audit of the data was approved as GEKO Quality Activity number 34 724, and informed, written consent was signed by all patients. The study complies with the Declaration of Helsinki.

Patients underwent testing of kidney function and urinary parameters, PWV measurement as well as collection of general medical history, medication history, and assessment of anthropometric data. Patients were included in the analysis if they had at least an ABPM and supine BP measurement performed for baseline assessment.

2.2 | Blood pressure measurements

BP measurements were standardized and obtained by a single trained research nurse for all patients assessed. The following data were collected in chronological order in a standardized clinical setting:

1. Attended seated office BP was measured simultaneously on both upper arms using the Microlife WatchBP device (Microlife AG Swiss Corporation, Widnau, Switzerland). A resting period of 1-2 minutes was allowed prior to starting BP measurements. The WatchBP device was predominantly used to exclude a significant BP difference between both arms and as a potential indicator for vascular abnormalities. It was also intended to provide some indication of the magnitude of any white coat component through comparison with unattended automated office BP (AOBP) measurements, which were carried out following the WatchBP assessment.

2. Unattended sitting AOBP was measured shortly after Watch BP assessment using the Omron HEM 907 Automatic Blood Pressure Monitor (Omron Healthcare Co., Kyoto, Japan). Patients were left alone in a room with dimmed lights to rest for five minutes in an upright, seated position with uncrossed legs. The arm with the higher Watch BP was used for AOBP measurements. Participants were instructed not to make use of their phones during this period or engage in any other physically or mentally stimulating activities. The BP device was programmed to allow for a five minute rest period prior to the first BP measurement. A total of three BP measurements were obtained with one minute intervals in between each measurement. The average of the three measurements was used for all further analyses.

3. Standing BP was assessed after the last of the three AOBP measurements. The examiner returned to the room and asked the patient to stand up. After 60 seconds, one further BP measurement was performed using the same device.

4. In an additional testing session, usually scheduled within 1-2 weeks following the clinic appointment, patients were instructed to undergo a 24-hour ABPM usually on the same day. The ABPM was carried out with clinically validated devices (Spacelabs, Snoqualmie, WA, USA; Mobil-O-Graph IEM GmbH, Stolberg, Germany; OSCAR SunTech, Morrisville, NC, USA) which were set up to measure the BP every 15 minutes during daytime and every 30 minutes during nighttime. Daytime and nighttime were defined in all patents as 6:00 to 22:00 h and 22:00 h to 6:00 h, respectively. Patients were asked to attend to their usual daily activities.[21] The patients also received standardized ABPM diaries and were instructed to record general activities including bedtime. Analysis of the data was carried out on a computer with the appropriate software by the manufactures abiding by the given instructions including adjustment to asleep and awake periods according to the ABPM diaries if required.[22] This initial analysis included a quality control of the ABPMs requiring at least 7 readings during nighttime and 20 readings during daytime (refs as sent) including checking the amount of valid readings for daytime and nighttime.[23,24]

5. In the same additional testing session, patients underwent measurements of PWV as detailed below. As part of the PWA measurements, standardized unattended supine BP measurements were obtained after five minutes of rest and the average of three readings calculated and used for analysis.

2.3 | Markers of kidney function and proteinuria

Blood and spot urine samples were collected from patients instructed to stay fasted overnight beforehand to assess estimated glomerular filtration rate (eGFR) and albumin-creatinine ratio (ACR). The eGFR was calculated according to the CKD-EPI formula[25] based on plasma creatinine.

2.4 | Supine BP

Patients were instructed to lie flat on a bed for five minutes before the BP was measured three times with each a minute in between on the left arm. The average of these three measurements was used for all further analysis. The blood pressure was measured with a SphygmoCor® XCEL system (AtCor Medical Pty Ltd, Australia).

2.5 | PWV

For assessment of PWV, the pulse of patients was recorded with a specialized cuff on the upper right thigh and a mechanical sensor held against the carotid artery on two locations by trained research nurses and doctors at the same time. With the temporal difference between pulse in thigh and neck together with the measured spatial distance between the two points of measurement, the PWV velocity was calculated from 10-second recordings of clean signals from both sites. We used the subtraction method in the standard software supplied by the manufacturer for this. The PWV was assessed twice, and the average of both measurements was used for all further analysis. The device used for PWV measurements was a SphygmoCor® XCEL system (AtCor Medical Pty Ltd, Australia) following the standard procedure outlined by the manufacturer.

2.6 | Statistical analysis

Baseline data are described as mean and standard deviation for continuous variables and as absolute quantity and relative quantity in percent for categorical variables. A correlation matrix was calculated between all systolic BP entities and visualized as a color map with squared Pearson coefficients (R^2), focussing on shared variance of the entities with night-time ambulatory BP. Two univariate models for each of the HMOD variables (eGFR, ACR, PWV) were created, one using night-time ambulatory BP as an independent variable and one using supine BP as independent variable. Separate bivariate models for each of the HMOD variable (eGFR, ACR, PWV) as dependent variables were fitted with both night-time ambulatory BP and supine BP as independent variables. Cases with missing data were removed for fitting of the individual models. R^2 values for all models were reported combined with standardized beta regression coefficients of the bivariate models to assess the influence of each variable on the overall model. For one exemplary HMOD variable, scatterplots were created to visualize the associations. Logistic regression models were fitted predicting systolic night-time hypertension (cutoff 120 mmHg) as a binary variable for each day-time blood pressure measure (supine, unattended sitting, attended sitting and standing, cutoff 140 mmHg).[26] The area under the curve (AUC) of the receiver operating curves (ROC) for these models was calculated and the curves visualized. Analyses were performed with Python 3[27,28] and R.

3 | RESULTS

3.1 | Baseline characteristics

Baseline characteristics of the 165 included participants are presented in Table 1. This table also shows data on individual prescribed antihypertensive agents. Forty-three patients (26%) were prescribed one antihypertensive agent, 65 (39%) two antihypertensive agents, 28 (17%) three antihypertensive agents and 29 (18%) were drug naive. Medication history was not available in 11 cases (4.6%).

3.2 | Correlation results between BP entities

For primary evaluation of shared variance between different BP entities, we calculated a correlation matrix for the available systolic BP

TABLE 1 Baseline Characteristics of study participants

	Overall
n	165
Sex, n (%)	
Female	67 (40.6)
Male	98 (59.4)
Sex, n (%)	
Age, mean (SD)	55.7 (16.6)
BMI, mean (SD)	30.8 (7.4)
Systolic ABPM, mean (SD)	135.6 (17.8)
Diastolic ABPM, mean (SD)	78.5 (12.1)
Type 2 Diabetes Mellitus, n (%)	
No	99 (63.5)
Yes	57 (36.5)
Calcium Channel Blocker, n (%)	
No	71 (44.9)
Yes	87 (55.1)
ACE Inhibitors, n (%)	
No	126 (79.7)
Yes	32 (20.3)
Angiotensin II Receptor Blockers, n (%)	
No	83 (52.5)
Yes	75 (47.5)
Beta-blocker, n (%)	
No	95 (60.1)
Yes	63 (39.9)

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACE, angiotensin-converting enzyme; BMI, body mass index; SD, standard deviation.

data. The methods of BP assessment that correlated most distinctly with night-time ambulatory BP were day-time ambulatory BP and supine BP, see heat map of correlation matrix in Figure 1. Among the non-ABPM BP measurement methods, supine blood pressure showed the highest correlation with night- and day-time ambulatory measurements.

3.3 | Regression analysis

All univariate regression models of systolic supine BP as an independent variable were significantly associated with the tested HMOD variables (eGFR, ACR,). The univariate models with night-time systolic ABPM as the independent variable were also highly significant for all HMOD variables. Other than the model with PWV as a dependent variable, none of the models with diastolic BP showed any significant associations.

In the multivariate models, both night-time ambulatory BP and supine BP were used as independent variables in the same bivariate model. In all systolic models, supine BP remained a significantly associated with the HMOD variables while night-time ABPM was not significantly associated with the dependent variables. All systolic regressions were overall significant models for the individual dependent HMOD variables. In the diastolic models, only the one with PWV as the dependent variable was overall significant, with supine BP being a significant independent variable while night-time ABPM was non-significant. Results and parameters of the univariate and multivariate models are summarized in Table 2. Scatterplots of the models for PWV are depicted in Figure 2.

The ROCs of the logistic regression models predicting night-time hypertension are shown in Figure 3. Supine BP had the highest ROC AUC of all assessed measurement methodologies.

4 | DISCUSSION

In this cross-sectional study, systolic supine BP of hypertensive patients showed highly significant associations with HMOD of the kidney and the large arteries. Similarly, significant associations were shown for ambulatory night-time BP. When both methods of BP measurements were combined in bivariate linear regression models with HMOD estimates as dependent variables, a consistent pattern emerged in all models: Supine BP alone explained the variance of the HMOD estimates on its own sufficiently and ambulatory night-time BP lost its significant contribution as an explanatory variable to the overall model. ROC AUC calculations of logistic regression models fitted to predict night-time hypertension as a binary variable confirmed the strong association of supine BP and night-time BP in this dataset. The ROC AUC of supine BP was 0.78, while all other assessed BP measures yielded AUCs well below 0.6 (see Figure 3).

These findings imply that the information contained in supine BP measurements during the day may explain much of the variance of detrimental health effects that has been attributed to night-time BP. Considering the adverse consequences of nocturnal hypertension and non-dipping patterns on cardiovascular outcomes, supine BP as a surrogate variable in this context might be clinically highly valuable, particularly if ABPM data are unavailable.

Indeed, supine blood pressure has been shown in the past to yield additional predictive power to detect patients with increased nocturnal BP in comparison with standard day-time procedures.[2] Krzesiñski et al suggested in their study mainly aimed to investigate the diagnostic performance parameters of the methodology that further research might be able to confirm supine BP as a potential surrogate for risk-relevant information contained in nocturnal BP measurements. We based our hypothesis for this analysis on this previous research and simple, physiological considerations: Night-time blood pressure has two specific characteristics which include an altered state of consciousness (which cannot be replicated) and the lying position, which can be simulated at any time of the day as done here with supine BP measurement, to explore whether it may offer a similar explanatory power as night-time BP does for HMOD.

To our knowledge, this is the first study to link supine BP with nocturnal ambulatory BP and to show a strong association of supine

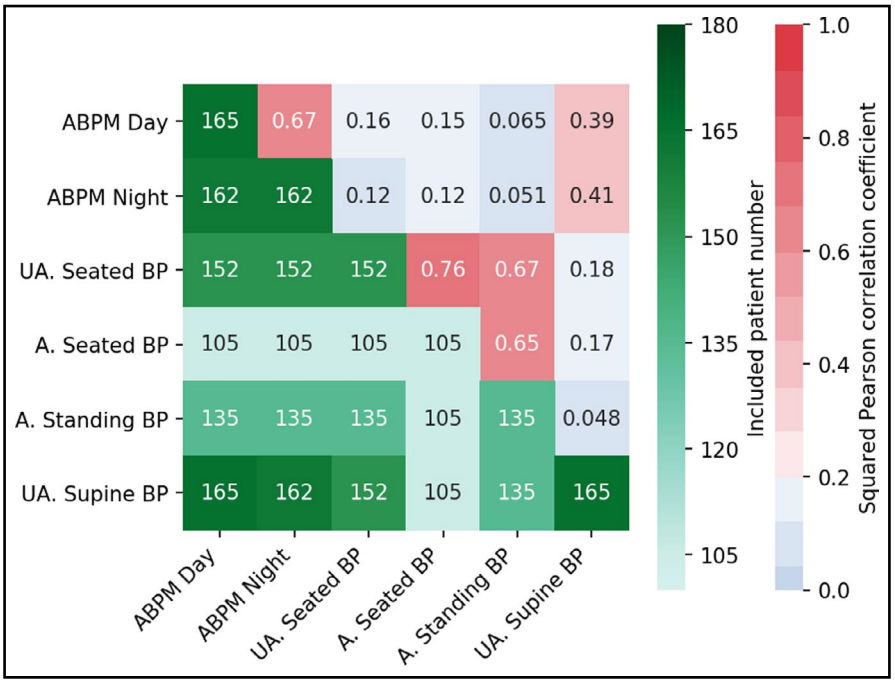

FIGURE 1 Color map of the Pearson correlation matrix between various systolic blood pressure entities. The R^2 values are reported representing the proportion of variance explained by the association between the variables. In the upper right part of the graph, red color in increasing intensity represents moderate to strong correlations. Blue colors in increasing intensity represent small to no shared variance. In the center diagonal and lower left part of the graph, green color and absolute numbers indicate the quantity of cases included in the corresponding correlation. ABPM, Ambulatory Blood Pressure Monitoring; A, Attended; BP, Blood Pressure; UA, Unattended

TABLE 2 Summary of uni- and bivariate Models. R^2 values are provided for both uni- and bivariate models. Standardized coefficients of the variable in the bivariate models are shown with their associated p-values

		Univariate	Bivariate Model		
Dependent Variable	**Independent Variable**	**R^2**	**Standardized beta coefficients**	***p*-value**	**R^2 bi**
eGFR	Supine SBP	15.4	-0.05162	**<0.001**	15.1
eGFR	Night-time systolic ABPM	6.1	0.000392	0.973	
eGFR	Supine DBP	<0.1	-0.00547	0.795	0.1
eGFR	Night-time diastolic ABPM	<0.1	0.006798	0.738	
Alb	Supine SBP	10.5	0.174287	**0.011**	11.5
Alb	Night-time systolic ABPM	7.8	0.073601	0.229	
Alb	Supine DBP	1.4	0.161302	0.143	1.5
Alb	Night-time diastolic ABPM	0.2	-0.05486	0.605	
PWV	Supine SBP	33.4	0.000406	**<0.001**	35.5
PWV	Night-time systolic ABPM	20.2	8.83E-05	0.142	
PWV	Supine DBP	3.7	0.000254	**0.043**	3.7
PWV	Night-time diastolic ABPM	1.2	-2.67E-05	0.825	

Abbreviations: ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure; SBP, systolic blood pressure.

BP with common forms of HMOD in patients with hypertension. Furthermore, the finding that in a direct competitive bivariate model the information contained in supine BP is able to substitute and even outperform the information contained in night-time BP in relation to the prediction of HMOD is novel.

It needs to be emphasized that the applied methodology in this analysis does not necessarily reflect any causal relationships between the measured BP entities and HMOD variables. Furthermore, while the lying position is common to both supine BP assessments during a clinical encounter and during nocturnal BP measurements,

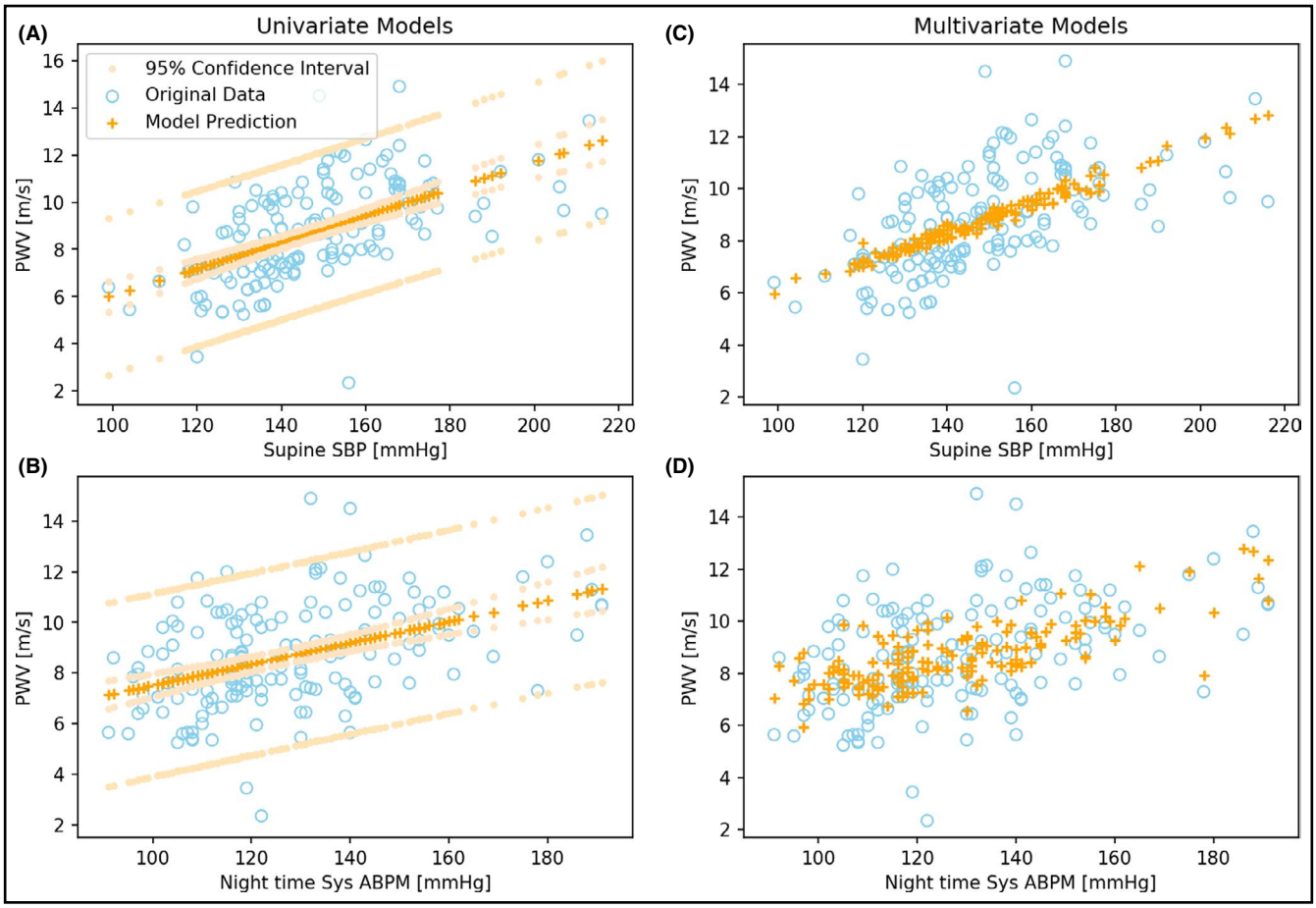

FIGURE 2 Scatterplots of the univariate linear regression models (fitted) of supine BP (A) and night-time systolic ABPM BP (B) as independent variables and PWV as a dependent variable. The orange crosses represent the predicted values of the linear model forming the line of best fit. Beige dots represent the mean (inner line) and observed (outer line) 95% confidence intervals of these predictions. The multivariate linear regression model is shown in panels C (supine BP on x-axis) and D. Models were fitted using ordinary least squares. PWV—Pulse Wave Velocity, Sys—Systolic, SBP—systolic blood pressure, ABPM—Ambulatory Blood Pressure Monitoring

the latter is further influenced by several factors related to sleep that cannot be accounted for in the current analysis. However, when measured in a standardized fashion as done in this study, it may more closely reflect nocturnal BP and therefore may have similar power to show associations with HMOD.

This lack of direct causality, however, does not diminish the utility of supine BP as a potential surrogate parameter. In cases of unavailability of ABPMs, cost or time restrictions or severe disturbance of the patients sleep, such a surrogate may prove to be helpful. The surprising results of this study are that supine BP had the best explanatory power in bivariate models, highlighting its potential as a surrogate not only for night-time BP but perhaps more importantly, for HMOD prediction in general. Of note, of all non-ABPM measurements, supine BP had had the strongest correlation with day-time and night-time ABPM measurements. This may also be a potential explanation for the strong performance of supine BP when associated with HMOD. It could not only better represent variance of night-time BP better due to the supine position, but also contain sufficient relevant information about day-time BP due to the diurnal time of measurement.

This study has several limitations. It needs to be pointed out that the timing of the measurements of the different BP entities in this study could have confounded correlations between them. Of all BP modalities, AOBP, Watch BP, and standing BP were carried out in the closest temporal proximity. Supine BP was carried out in a follow-up appointment together with PWV measurements usually within the following 1-2 weeks of the first appointment. Of note, no medication changes occurred between various BP measurements. Ambulatory BP monitoring was usually performed between the two appointments. Very high correlations in particular between AOBP, Watch BP, and standing BP might be partially driven by this. The main results of this analysis rely, however, on temporally not directly connected measurements (APBM and supine BP) or variables such as eGFR and PWV, which tend to be very stable within a time frame of a few weeks in the absence of acute illness. It is therefore unlikely that the main results are predominantly driven by temporal association between the measurements. For the association between PWV and supine BP, the fact that both were assessed in immediate succession and PWV is depending on current BP as a covariate

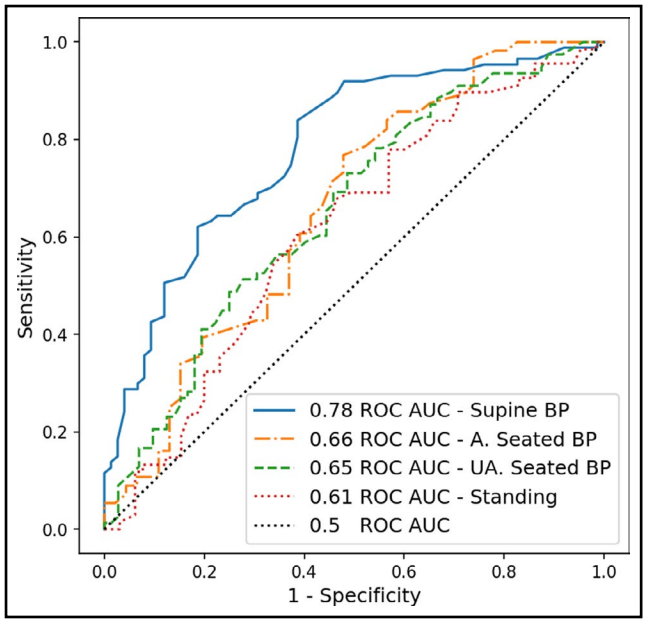

FIGURE 3 Receiver operating curves (ROC) for logistic regression models predicting systolic night-time hypertension (cutoff 120 mmHg) as a binary dependent variable with day-time blood pressure measurements (cutoff 140 mmHg) as independent, continuous variables. Fitting the model with supine blood pressure yielded the highest area under the curve (0.78), indicating a stronger association with night-time blood pressure

may result in a stronger bias of these factors in this particular case. This may also explain the excess over-performance of PWV as an independent model variable for HMOD in the models as opposed to other HMOD estimates. On the other hand, the finding of distinct associations in models using other estimates of HMOD (eGFR and ACR) ameliorates the risk that this bias has a diminishing effect on the general results of the presented analysis.

Another noteworthy limitation arises from conditions that only become evident at night such as obstructive sleep apnea (OSA) which can be a major driver of pathological nocturnal BP patterns.[30,31] The correlation between office supine and nocturnal BP may only be valid in patients who have no evidence of OSA. While the body position is the same, nocturnal BP would be influenced substantially by OSA, whereas this is unlikely to impact significantly on supine BP. Future research needs to address this by investigating the performance of supine BP in relevant subgroups of patients with and without OSA and analyzing its properties as an explanatory variable in these subgroups.

Advantages of the study include the wide range of standardized BP measurement methodologies that were employed and on the availability of relevant estimates of HMOD representing multiple organ systems. Furthermore, it needs to be emphasized that we obtained highly standardized, unattended supine BP measurements. This may explain why supine has not been found as a high-performing method of blood pressure in terms of risk estimation in the past, since supine BP measurements in previous research are often carried out in an attended and less standardized manner. This is supported by an elegant study by Fagard et al, who observed that repeated automated supine BP measurements increased in their correlation with left ventricular hypertrophy with increased numbers of measurements taken.[32] Additionally, this study found that the additional information provided by 24 h measurements had only a moderate effect in regards to increased explained variance of left ventricular mass, which was only significant for diastolic BP. This is in line with the analysis and results of this study, which extends the results from Fagard et al[32] to other variables which have been shown to be important estimates of HMOD more recently.

The statistical approach clearly points out the main results at hand, which is the strong association between HMOD and night-time BP and supine BP. Furthermore, we investigated this in a unique patient cohort of at-risk hypertensive patients followed up in a tertiary hospital hypertension specialist clinic.

Surprisingly, the evidence surrounding supine hypertension as a marker of HMOD or a surrogate for night-time BP is scarce. Most studies so far have concluded that supine BP tends to be slightly lower than sitting measurements[33] others, however, showed opposite results.[34,35] One study concluded that supine BP may have beneficial diagnostic properties representing night-time BP better than sitting measurements only.[29] If supine BP indeed proves to be a representative reflection of information usually only accessible through night-time BP that has been shown to be crucial for the prediction of HMOD and therefore CV risk, it might have substantial clinical implications, especially if ambulatory BP monitoring is unavailable. It needs to be pointed out, however, that this study gives by no means any indication that supine BP measurement may be a sufficient surrogate for ABPM measures overall.

In conclusion, our analysis provides novel insights into the potential of supine BP as a variable for CV-risk estimation based on HMOD. This is based on a high degree of shared variance with nocturnal BP measurements. Overall, supine BP contained sufficient shared variance with night-time BP and additional associative power to outperform night-time BP in regression models of HMOD in this analysis. In other words, the information derived from night-time blood pressure to explain CV risk in previous research might at least partially be reflected in supine BP measurements. Future research efforts are required to reproduce and confirm these results, extend their applicability in prospective studies looking into correlation, performance of supine BP as a predictor for HMOD, and ultimately hard clinical outcomes in comparison with night-time BP. Integration of supine BP in the data collection of applicable clinical studies would provide an excellent starting point to address these important questions.

ACKNOWLEDGEMENTS

The authors acknowledge Mrs Derrin Brockman and the Medical Research Foundation for their administrative and technical support. This work was supported by resources provided by the Pawsey Supercomputing Centre with funding from the Australian Government and the Government of Western Australia.

CONFLICT OF INTEREST

JMN and the other authors declare that they have no conflict of interest. LMLG has received a scholarship from the National Council on Science and Technology, Mexico (CONACYT). MPS is supported by an NHMRC Research Fellowship and has received consulting fees, and/or travel and research support from Medtronic, Abbott, Novartis, Servier, Pfizer, and Boehringer-Ingelheim.

AUTHOR CONTRIBUTIONS

Janis M. NOLDE involved in conceptualization, data curation, formal analysis, investigation, visualization, writing-original draft, and writing-review and editing. Márcio Galindo KIUCHI, Revathy CARNAGARIN, Vance B. MATTHEWS, and Lakshini Y. HERAT involved in conceptualization, and writing-review and editing. Shaun FROST involved in conceptualization, data curation, investigation, and writing-review and editing. Dennis KANNENKERIL involved in conceptualization, formal analysis, investigation, writing-review and editing, and supervision. Leslie Marisol LUGO-GAVIDIA, Justine CHAN, and Anu JOYSON involved in investigation, data curation, and writing-review and editing. Omar AZZAM involved in conceptualization, investigation, writing-review and editing, and supervision. Markus P. SCHLAICH involved in conceptualization, formal analysis, data curation, funding acquisition, project administration, supervision, writing-original draft, writing-review and editing, and supervision.

DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study.

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How to cite this article: Nolde JM, Kiuchi MG, Carnagarin R, et al. Supine blood pressure—A clinically relevant determinant of vascular target organ damage in hypertensive patients. *J Clin Hypertens*. 2021;23:44–52. https://doi.org/10.1111/jch.14114