



Low night-time heart rate is longitudinally associated with lower augmentation index and central systolic blood pressure in hypertension

Paolo Palatini¹ · Francesca Saladini¹ · Lucio Mos² · Claudio Fania¹ · Adriano Mazzer³ · Edoardo Casiglia¹

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Abstract

Purpose Several studies have shown that the augmentation index (AIx) is negatively correlated with heart rate (HR). This led some authors to claim that the use of HR-lowering drugs may be detrimental in hypertension. The aim of this study was to assess the longitudinal and cross-sectional relationships of HR with AIx and central blood pressure (BP) in 346 subjects from the HARVEST (mean age 30.7 ± 8.5 years).

Methods At baseline, HR was measured with 24-h ambulatory recording. Central hemodynamics were evaluated with Specaway DAT system after a median of 8.0 years from baseline. In multivariate linear regression analyses, AIx and central systolic BP were used as dependent variables and night-time HR or office HR as predictors adjusting for several risk factors and confounders.

Results In fully adjusted models, baseline night-time HR was a significant positive predictor of AIx ($p < 0.001$) and central BP ($p = 0.014$) measured 8 years later. Adjusted office HR measured at the time of arterial distensibility assessment was inversely correlated with AIx ($p = 0.001$) a relationship which was attenuated after physical activity ($p = 0.004$) and left ventricular ejection time ($p = 0.015$) were taken into account. In addition, office HR was inversely correlated with central BP ($p = 0.039$) a relationship which was no longer significant after physical activity and ejection time were accounted for.

Conclusions These data show that HR measured during sleep is longitudinally associated with AIx and central BP. Thus, low HR in the long term may have beneficial effects on central hemodynamics and the wall properties of the large arteries in hypertension.

Keywords Heart rate · Ambulatory · Aortic pressure · Augmentation index · Arterial stiffness · Hypertension

Abbreviations

AIx Augmentation index
BMI Body mass index

BP Blood pressure
HR Heart rate
LV Left ventricular
PWV Pulse wave velocity
SD Standard deviation
SEM Standard error mean

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✉ Paolo Palatini
palatini@unipd.it

¹ Department of Medicine, University of Padova, via Giustiniani, 2, 35128 Padua, Italy

² Emergency Area, Town Hospital, San Daniele del Friuli, Italy

³ Department of Internal Medicine, Town Hospital, Vittorio Veneto, Italy

Introduction

Arterial stiffness is traditionally assessed by means of pulse wave velocity (PWV) (Laurent et al. 2016). However, other measures of arterial stiffness can provide relevant clinical information such as the augmentation index (AIx), which gives an estimate of aortic wave reflection (McEniery et al. 2005; Wilkinson et al. 2002). This index has been found to be a predictor of mortality and cardiovascular events independently of peripheral pressures and is thus likely to

be clinically useful (Vlachopoulos et al. 2010; Janner et al. 2013). However, AIx has been shown to be influenced by several clinical variables including age, sex, height, blood pressure (BP), and small artery compliance (McEniery et al. 2005; Wilkinson et al. 2002). In addition, several studies have shown that AIx is negatively correlated with heart rate (HR), and thus, modulation of HR with drugs may have an important impact on this index and on patients' prognosis (McEniery et al. 2005; Wilkinson et al. 2000). This led some authors to affirm that the use of beta-blockers in hypertension can increase arterial stiffness through the reduction in HR and that these drugs should no longer be included among first-line antihypertensive agents (Williams et al. 2006; Messerli et al. 2016). However, the present information on the relationship between HR and central hemodynamics is based on cross-sectional (McEniery et al. 2005; Wilkinson et al. 2002) or short-term (Manisty and Hughes 2013) studies, whereas the long-term relationship between these clinical variables is largely unknown. High HR has been positively correlated with future arterial stiffness (Benetos et al. 2002; Tomiyama et al. 2010) and adverse cardiovascular outcomes (Palatini et al. 2002; Jouven et al. 2005; Kolloch et al. 2008) in a large number of longitudinal studies. It is, thus, possible that the apparent adverse effect of low HR on central hemodynamics observed in cross-sectional studies is outweighed by its long-term benefits on the arterial wall. Thus, the aim of this study was to assess the longitudinal and cross-sectional relationships of HR with AIx and other central hemodynamic variables in a sample of stage 1 hypertensive adults younger than 45 years. In particular, we tested the long-term prognostic value of HR recorded during sleep with ambulatory monitoring which proved to have better prognostic capacity than HR recorded during waking hours or measured in the office (Hozawa et al. 2008; Hansen et al. 2008; Palatini et al. 2013). Another aim of this investigation was to assess the relationship of baseline ambulatory HR with the development of hypertension needing pharmacological treatment.

Materials and methods

The study participants, took part in the HARVEST (Hypertension and Ambulatory Recording VEnetia SStudy), a long-term prospective observational study, initiated in April 1990 in Italy (Palatini et al. 1994b; Sartori et al. 2003; Saladini et al. 2017). Four HARVEST centers agreed to participate in the arterial elasticity study. Arterial elasticity assessment was performed in 346 subjects, a median of 8.0 years after enrolment (interquartile range 2.2–11.1 years). Their mean age at baseline was 30.7 ± 8.5 years and 74.6% were males. Patients' recruitment was obtained with the collaboration of the local general practitioners who were instructed during local meetings. Patients enrolled were 18–45-year-old

subjects, screened for stage 1 hypertension (office systolic BP, 140–159 mmHg, and/or clinic diastolic BP, 90–99 mmHg), who had never been treated for hypertension before. The presence of diabetes, renal impairment, cardiac diseases, and secondary forms of hypertension was excluded at the baseline on the basis of a complete history, physical examination, and by standard diagnostic procedures (Palatini et al. 1994b; Sartori et al. 2003; Saladini et al. 2017). These included serum potassium, urinalysis, plasma renin activity, plasma and urinary aldosterone, and urinary catecholamines. To further exclude the presence of renovascular disease, all patients underwent a doppler examination of the renal arteries or renal scintigraphy. A written informed consent was given by the participants. The study was approved by the HARVEST Ethics Committee and by the Ethics Committee of the University of Padova.

Procedures

Baseline data included medical and family history and a self-compiled questionnaire about current use of alcoholic beverages, smoking status, and physical activity habits (Palatini et al. 1994b; Sartori et al. 2003; Saladini et al. 2017). At the enrollment, all subjects underwent physical examination, anthropometry, office, and ambulatory BP and heart rate measurements. Subjects were categorized as nonexercisers if they did not regularly perform any sports activity and as exercisers if they had performed sports at least once a week during the previous 2 months. Subsequently, among the nonexercisers, the fully sedentary subjects were distinguished from those who performed light physical activities, such as walking, gardening, etc. Among the exercisers, the subjects performing competitive sports were separated from those not involved in competitions (Palatini et al. 1994b). Brachial office BP at entry was the mean of six measurements obtained with a mercury sphygmomanometer, during two visits, performed 2 weeks apart. 24-h BP and heart rate monitoring was performed using the A&D TM2420 model 7 (A&D, Tokyo, Japan) or ICR Spacelabs 90207 monitor (Spacelabs, Redmond, WA, USA) devices. Both these devices were previously validated (Palatini et al. 1991; O'Brien et al. 1991) and were shown to provide comparable results (Palatini et al. 1994a). All assessments including 24-h ambulatory monitoring were performed on a non-exercise day. In each patient, 24-h recording was started between 8:00 a.m. and 10:00 a.m., soon after office BP measurement.

Follow-up visits were scheduled after 1, 2, 3, and 6 months and thereafter at 6-month intervals. At the beginning, all subjects were given general information about non-pharmacological measures by the HARVEST investigators, following the suggestions of the current guidelines on the management of hypertensive patients. If after at least

6 months of implementation of non-pharmacological measures, the participant's BP was above the "operational threshold level", the patient was rescheduled for a visit within 2–4 weeks, and the average BP was calculated. If BP was still above the limit, the patient was given antihypertensive drug treatment, otherwise, he or she was checked at monthly intervals. The BP "operational threshold level" was established on the basis of the criteria adopted by international guidelines at the time of patients' evaluation. Hypertension needing pharmacological treatment was considered as one of the endpoints of the study. Details on follow-up procedures in the HARVEST study are reported in the supplementary material. The arterial distensibility assessment was always performed before giving antihypertensive treatment.

Arterial distensibility assessment

Central BP was assessed from brachial pressure waveform, recorded at the radial artery with applanation tonometry. We used the DAT System (SN1002-960604-12, Specaway, Sydney, Australia), connected to a Millar tonometer (SPC-301; Millar Instruments, Huston, TX, USA). After acquiring 30 sequential waveforms at the radial artery, a software system, which incorporated a validated transfer function, was used to generate an average peripheral and corresponding ascending aortic pressure waveform (Chen et al. 1997). From the radial pulse wave analysis, using a generalized transfer function, derived from the invasive measurements, we obtained central BP values (Chen et al. 1997; Gallagher et al. 2004). The device also returned the radial AIx as the ratio of the difference between the pressure at the second systolic shoulder and diastolic BP to that between diastolic BP and pressure at the first inflection point: $AIx = 100 \times (P_2 - DBP) / (P_1 - DBP)$ (Cameron et al. 1998). PWV ($D/\Delta T$) was determined by simultaneous applanation tonometry and electrocardiography recording, where D was the distance between two sampling sites (carotid and radial artery) and ΔT was the time of travel of pulse wave over this distance. Left ventricular (LV) ejection time was derived from the radial waveform by measuring the time interval from the foot of the pressure waveform to the beginning of the incisura caused by aortic valve closure (Weber et al. 2006; Sugawara et al. 2007).

Patients also underwent measurement of small artery compliance by means of arterial pulse waveform analysis using the HDI/Pulse Wave™ CR2000 (Hypertension Diagnostics, Inc., Eagan, NY, USA) (Cohn et al. 1995). This technique involves a 30-s non-invasive recording of radial artery waveforms by applanation tonometry. The tonometry unit contained an array of pressure transducers capable of measuring the relative intra-arterial pulse amplitude with high accuracy. The tonometer was centered

over the radial artery obtaining the optimal waveform by pneumatical stabilization. Brachial BP was oscillometrically measured on the opposite arm. A beat-marking algorithm determined the beginning of the systole, peak systole, onset of diastole, and end-diastole for each beat during the measurement period. To obtain arterial compliance, a model was used that divides the total systemic arterial compliance into large artery and small artery (or oscillatory) compliance (Cohn et al. 1995). The reproducibility of the arterial distensibility measures during the same session and after 4 months was assessed in 72 subjects, as previously described (Longo et al. 2006). Arterial distensibility assessment was always performed in the early afternoon.

Data analysis

Systolic BP amplification was calculated as the difference between peripheral brachial BP and central BP. In keeping with most studies on the prognostic significance of HR, participants were divided into quintiles of either night-time or office HR. To simplify the data presentation, subjects in quintiles 2–4 were grouped together. Thus, we finally obtained three groups with low HR, intermediate HR, and high HR (Tables 1, 2). The top HR quintile has been frequently used in the literature to define people with tachycardia (Palatini et al. 2016).

Statistical analysis

Data are presented as mean \pm standard deviation (SD) unless specified. The distributions of clinical variables at baseline were compared across groups by ANCOVA adjusting for age and sex. The significance of differences in categorical variables was assessed with the χ^2 test. One-way ANCOVA was used to compare central hemodynamic variables between the HR groups, adjusting for variables potentially influencing central hemodynamics (Table 2). A multivariable linear regression model was used to define the relationship between night-time HR or office HR (predictors) and hemodynamic variables (dependent variables) adjusting for other risk factors and confounders (see Tables 3, 4). A logistic regression model was used to test the predictive capacity of ambulatory and office HRs for development of hypertension needing treatment adjusting for the same variables included in the linear regression analyses. A two-tailed probability value < 0.05 was considered significant. All analyses were performed using Systat versions 12 (SPAA Inc., Evanston, IL, USA).

Table 1 Baseline characteristics in 346 study participants grouped according to night-time heart rate

Variables	Low heart rate (≤ 54.2 bpm), $N=69$	Intermediate heart rate (54.2–68.3 bpm), $N=208$	High heart rate (≥ 68.4 bpm), $N=69$	p value
Age, years	30.4 \pm 8.3	30.1 \pm 8.6	32.8 \pm 8.3	0.50
Sex, % males	89.8	78.8	46.4	<0.0001
BMI, kg/m ²	24.3 \pm 2.6	24.7 \pm 3.2	25.2 \pm 4.2	0.007
Cigarette smokers, %	26.7	18.8	26.9	0.24*
Alcohol drinkers, %	55.0	42.6	35.8	0.086*
Physically active, %	57.3	46.6	37.7	0.069*
Office SBP, mmHg	138.7 \pm 17.0	141.8 \pm 12.7	141.6 \pm 10.6	0.29
Office DBP, mmHg	85.6 \pm 10.7	89.9 \pm 7.7	92.6 \pm 6.7	0.20
Office heart rate, bpm	65.0 \pm 8.5	73.2 \pm 8.4	79.2 \pm 10.0	<0.0001
24 h SBP, mmHg	130.9 \pm 9.9	131.2 \pm 10.1	128.8 \pm 10.7	0.88
24 h DBP, mmHg	75.9 \pm 9.5	79.3 \pm 7.3	82.5 \pm 6.7	0.001
24 h heart rate, bpm	62.1 \pm 6.3	72.3 \pm 5.4	81.1 \pm 5.6	<0.0001

Data are mean values \pm standard deviation; all p values are adjusted for age and sex except age and sex
BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

*Data unadjusted; p value for ANCOVA

Table 2 Central hemodynamic variables in 346 study participants grouped according to baseline night-time heart rate

Variables	Low heart rate (≤ 54.2 bpm), $N=69$	Intermediate heart rate (54.2–68.3 bpm), $N=208$	High heart rate (≥ 68.4 bpm), $N=69$	p value
Central SBP, mmHg	119.0 \pm 1.7	121.8 \pm 1.0	126.0 \pm 1.8	0.031
Central DBP, mmHg	81.9 \pm 1.1	84.3 \pm 0.6	86. \pm 1.1	0.040
Pressure amplification, mmHg	15.0 \pm 1.1	13.0 \pm 0.6	9.8 \pm 1.1	0.002
Augmentation Index, %	5.5 \pm 2.6	15.1 \pm 1.5	18.8 \pm 2.8	0.001

Data are mean \pm SEM and are adjusted for age, sex, body height, body mass index, pulse wave velocity, and small artery compliance
SBP indicates systolic blood pressure, *DBP* diastolic blood pressure

Table 3 Multiple regression analysis showing the longitudinal relationship of baseline night-time heart rate with augmentation index (dependent variable) measured 8.0 years later

Predictors	Coefficient	Standard error	p value
Night-time heart rate	0.531	0.153	0.0006
Age	0.777	0.142	<0.0001
Sex	7.455	3.869	0.055
Office mean blood pressure	0.485	0.139	0.0006
Body height	– 0.579	0.194	0.003
Body mass index	– 0.290	0.339	0.39
Smoking	1.054	1.607	0.51
Alcohol consumption	– 5.844	2.009	0.004
Pulse wave velocity	1.515	0.406	0.0002
Small artery compliance	– 0.953	0.473	0.045
Physical activity	2.662	1.131	0.019
LV ejection time	0.187	0.063	0.003

The variance inflation factor was <2.5 for all variables
LV left ventricular

Table 4 Multiple regression analysis showing the cross-sectional relationship of office resting heart rate with augmentation index (dependent variable) measured in the same session

Predictors	Coefficient	Standard error	p value
Office heart rate	– 0.407	0.116	0.001
Age	0.538	0.124	<0.0001
Sex	11.32	3.644	0.002
Office mean blood pressure	0.545	0.137	<0.0001
Body Height	– 0.555	0.186	0.003
Body mass index	– 0.089	0.321	0.78
Smoking	– 0.308	1.471	0.83
Alcohol consumption	– 5.140	1.903	0.007
Pulse wave velocity	1.599	0.391	<0.0001
Small artery compliance	– 1.171	0.460	0.011

p value for office heart rate = 0.004 after inclusion of physical activity in the model and = 0.015 after inclusion of left ventricular ejection time. The variance inflation factor was <2.5 for all variables

Results

The baseline characteristics of the study participants, grouped according to night-time HR, are presented in Table 1. Participants with high night-time HR were heavier, were more frequently females, and had higher 24-h diastolic BP compared to the other two groups. In addition, they were less active in sports, though the difference did not attain the level of statistical significance.

Follow-up data

Baseline ambulatory HR as predictor of follow-up central hemodynamics and incident hypertension

Follow-up central BP and AIx progressively increased on going from the participants with low to those with high baseline night-time HR (Table 2). In a multivariable regression analysis, baseline night-time HR was an independent positive predictor of central systolic BP ($p=0.014$), pressure amplification ($p=0.004$), and AIx ($p<0.001$, Table 3) measured 8.0 years later. The relationships with AIx were weaker for 24-h HR ($p=0.014$) and daytime HR ($p=0.070$). Baseline office HR was unrelated to follow-up central hemodynamics ($p=n.s.$).

During the 8-year follow-up, 153 participants (44.2%) developed hypertension needing pharmacological treatment. In a fully adjusted logistic regression model (using the same variables, as shown in Table 3), baseline night-time HR was an independent positive predictor of incident hypertension with an odds ratio of 1.39 (95% CI 1.04–1.75) for each 10-bpm increment in HR ($p=0.027$). The association with future hypertension was weaker and non-significant for 24-h HR ($p=0.070$) and daytime HR ($p=0.065$). Baseline office HR was not associated with this outcome ($p=n.s.$).

Follow-up office HR as predictor of central hemodynamics

Office HR measured at the time of the arterial distensibility assessment was negatively associated with AIx ($p=0.001$, Table 4) and central systolic BP ($p=0.039$). After inclusion of physical activity habits ($p=0.004$) and LV ejection time ($p=0.015$) in the regression, the strength of the negative office HR relationship with AIx was attenuated, and the relationship with central BP was abolished ($p=0.14$ and $p=0.58$, respectively). Office HR was an independent positive predictor of PWV ($p=0.003$) measured in the same session. In all regression models, the variance inflation factor was <2.5 for all variables indicating the absence of multicollinearity.

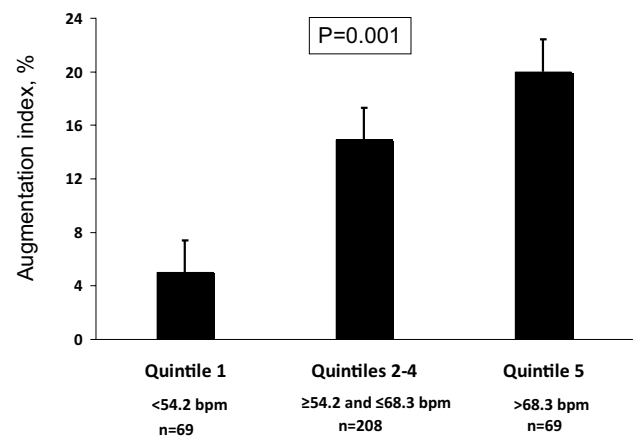


Fig. 1 Augmentation index measured 8 years after baseline examination in 346 HARVEST participants divided into quintiles of baseline night-time heart rate. Data are mean \pm SEM. p for ANCOVA after adjusting for age, sex, body height, body mass index, mean office blood pressure, pulse wave velocity, small artery compliance, and left ventricular ejection time

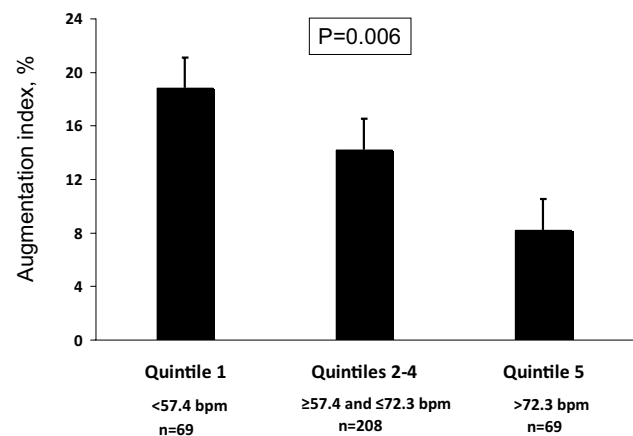


Fig. 2 Augmentation index in 346 HARVEST participants divided into quintiles of office resting heart rate measured in the same session. Data are mean \pm SEM. p for ANCOVA after adjusting for age, sex, body height, body mass index, mean office blood pressure, pulse wave velocity, and small artery compliance. After inclusion of left ventricular ejection time in the model the association was attenuated to a non-significant level ($p=0.093$)

In Figs. 1 and 2, the divergent relationships of baseline night-time HR and follow-up office HR with AIx are shown in the participants divided into HR groups. A positive independent relationship was found for baseline night-time HR (Fig. 1) and a negative relationship for follow-up office HR (Fig. 2). Adjusted mean \pm SEM AIx was $19.9 \pm 2.5\%$ in the top night-time HR quintile, $14.8 \pm 1.4\%$ in the intermediate quintiles, and $5.0 \pm 2.7\%$ in the bottom quintile. The corresponding values for adjusted

central systolic BP were 126.0 ± 1.8 , 121.8 ± 1.0 , and 119.0 ± 1.7 mmHg, respectively.

Discussion

The present data show that HR recorded with ambulatory monitoring is a positive longitudinal predictor of AIx, central BP, and pressure amplification indicating that low HR in the long term has a favorable impact on central hemodynamics in hypertension. The association of night-time HR with central hemodynamics remained significant also when variables such as physical activity, PWV, or small artery compliance, which have been implicated as possible modulators of AIx (Edwards and Lang 2005; Laurent et al. 2011; Courand and Lantelme 2014; Segers et al. 2001; Saladini et al. 2014) were taken into account. Another interesting finding was that baseline night-time HR was associated with future hypertension needing pharmacological treatment, whereas 24-h HR, daytime HR, and office HR were not significantly associated with this outcome. These results were obtained in a cohort of young-to-middle-age subjects screened for stage 1 hypertension and never treated for the disease.

The relationship between HR and arterial stiffness depends on the complex interplay of many different factors. Several cross-sectional studies have shown that a lower resting HR is associated with higher aortic systolic BP and greater AIx (Wilkinson et al. 2000, 2002; Courand and Lantelme 2014; Laurent et al. 2003). This observation has been attributed to a shift of the backward wave reflected from the periphery into late systole secondary to the prolongation of LV ejection time and to the increase in stroke volume at low HRs (McEniery et al. 2005; Wilkinson et al. 2000, 2002; Messerli et al. 2016). This finding led some authors to claim that HR reduction in hypertension is detrimental, because it may favor the risk of cardiovascular events (Williams et al. 2006; Messerli et al. 2016). However, other factors such as high PWV and low small artery compliance can cause earlier backward wave reflection, thereby increasing AIx and central BP (Courand and Lantelme 2014; Saladini et al. 2014). Studies in human beings have shown that there is a progressive increase in PWV by increasing HR with pacing which is independent from pressure changes (Lantelme et al. 2002; Tan et al. 2016), and in the present study, office HR was cross-sectionally associated with PWV. Thus, pharmacological HR lowering by reducing PWV might have a favorable effect on central hemodynamics. However, the present results showed that when PWV was accounted for in the multivariable regressions, AIx and central systolic BP still had a negative relationship with simultaneously measured office HR (Table 4).

A totally different picture was observed for long-term associations. Tomiyama et al. (2010) and Benetos et al.

(2002) have shown that high HR was a long-term predictor of accelerated arterial stiffness measured with PWV in either normotensive or hypertensive subjects. Our results show that a positive longitudinal relationship with HR is present also for central hemodynamics. Indeed, in the present study, night-time HR was an independent predictor of AIx and central BP measured 8 years after baseline HR assessment. This finding indicates that HR reduction in the long run can have a favorable effect and not a detrimental one on all parameters of arterial distensibility and contributes to explain why people with lower HR have a reduced risk of cardiovascular events and mortality in hypertension (Palatini et al. 2002; Jouven et al. 2005; Kolloch et al. 2008). The association of night-time HR with incident hypertension confirms the previous results from other investigators (Inoue et al. 2007; Wang et al. 2014). Elevated heart rate exposes the arteries to increased magnitude and frequency of mechanical load which may eventually increase the stiffness of the vascular wall (Giannoglou et al. 2008) as shown by the above-mentioned reports. It is thus possible that the increase in vascular stiffness favors the development of hypertension in people with tachycardia.

In the present study, among the ambulatory HRs, night-time HR emerged as the strongest predictor of future central hemodynamics and systemic hypertension. This finding is in keeping with the previous data which showed that high HR during the night-time but not during waking hours was associated with increased cardiovascular events (Palatini et al. 2013) or non-cardiovascular mortality (Hozawa et al. 2008; Hansen et al. 2008) indicating that night-time HR is more representative of the overall hemodynamic load on the arteries. HR during sleep is more stable and reproducible than HR measured during waking hours or in the office which may be influenced by random fluctuations related to emotional triggers or occasional physical activities (Palatini et al. 2013).

Study limitations

A possible limitation of the present study is that central systolic BP was estimated from non-invasive pressure waveforms and was not measured directly. With this technique, the values for central pressures depend on the validity and applicability of the generalized transfer function used to generate the central aortic waveforms. However, the transfer function used by the DAT system to derive central BP has been validated in several studies which showed a good correspondence between calculated and directly recorded central BP (Chen et al. 1997; Adji et al. 2007). In addition, it should be noted that the calibration of central aortic pressures heavily depends on the accuracy of the brachial BP measurements. Another potential weakness of this study is

that we did not control for dietary factors. Dietary components such as antioxidants might be important in determining differences in arterial distensibility parameters. However, our data were obtained from a homogeneous cohort of people with similar dietary habits. Finally, the present results were obtained in subjects younger than 45 years, and thus, they may not be extrapolated to older individuals. However, the previous data suggest that central AIx is a more sensitive marker of large artery stiffness in younger (<50 years) than older individuals (McEniery et al. 2005).

Conclusion

In contrast with data from cross-sectional studies, we found that HR recorded during sleep with ambulatory monitoring was directly and positively associated with central hemodynamics measured 8 years later. Thus, HR lowering in hypertension may have long-term favorable effects on the wall properties of the large arteries and improve patients' prognosis. However, whether lowering high ambulatory HR can actually improve cardiovascular outcomes in hypertensive patients remains to be seen.

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Compliance with ethical standards

Conflict of interest The authors declare no competing financial interest.

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