Associations of Daytime, Nighttime, and 24-Hour Heart Rate With Four Distinct Markers of Inflammation in Hypertensive Patients: The Styrian Hypertension Study

Bríain ó Hartaigh, PhD;[1,2] Martin Gaksch, MD;[3] Katharina Kienreich, MD;[3] Martin R. Grübler, BSc;[4] Nicolas Verheyen, MD;[4] Winfried März, MD;[5] Andreas Tomaschitz, MD;[4,6] Thomas M. Gill, MD;[2] Stefan Pilz, MD, PhD[3,7]

From the Department of Radiology, Dalio Institute of Cardiovascular Imaging, NewYork-Presbyterian Hospital and the Weill Cornell Medical College, New York, NY;[1] Department of Internal Medicine, Section of Geriatrics, Yale School of Medicine, Adler Geriatric Center, New Haven, CT;[2] Division of Endocrinology and Metabolism, Department of Internal Medicine, Medical University of Graz, Graz, Austria;[3] Department of Cardiology, Medical University of Graz, Graz, Austria;[4] Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria;[5] Specialist Clinic for Rehabilitation, PV Bad Aussee, Bad Aussee, Austria;[6] and Department of Epidemiology and Biostatistics, EMGO Institute for Health and Care Research, VU University Medical Centre, Amsterdam, The Netherlands[7]

The current study assessed which measure of heart rate (HR) is most associated with inflammatory activity. Among 368 hypertensive patients (mean age±standard deviation, 60.6±10.8; 52.9% women), mean daytime (from 6 AM to 10 PM), nighttime (from 10 PM to 6 AM), and 24-hour HR were recorded using a continuous 24-hour ambulatory blood pressure monitoring portable device. Associations of daytime, nighttime, and 24-hour HR with leukocytes, platelets, C-reactive protein (CRP), and 25-hydroxyvitamin D were calculated using multivariate linear regression, reporting unstandardized coefficients (*B*) with standard errors (SEs). Mean daytime, nighttime, and 24-hour HR were 73, 64, and 71 beats per minute, respectively. All HR measures were positively associated with leukocytes after adjustment. Nighttime HR was additionally related with higher CRP. When all HR measures were simultaneously added to a single multivariate model, only the positive associations of nighttime HR with leukocytes (*B* [SE]=0.06 [0.03], *P*=.04), as well as with CRP (*B* [SE]=0.20 [0.07], *P*=.005), persisted. Nighttime HR was more closely associated with inflammatory activity. These observations lend some insight toward the pathophysiological mechanisms that implicate HR in cardiovascular risk and provide valuable direction for forthcoming investigations. *J Clin Hypertens (Greenwich).* 2014;16:856–861. © 2014 Wiley Periodicals, Inc.

Prior epidemiological studies have documented a strong and independent relationship between high heart rate (HR) and adverse cardiovascular prognosis within a broad spectrum of populations.[1–5] Although the precise mechanisms have not been thoroughly clarified, convincing evidence indicates that this easy-to-measure and affordable parameter may heighten the inflammatory response, an essential component of the atherosclerotic process.[6,7] While the positive association between elevated HR and various markers of inflammation has been defined,[8–10] prior studies have evaluated only a single measure of daytime HR.

HR is a sensitive indicator of autonomic nervous system activity[11] and is influenced by numerous factors including (but not limited to) environmental conditions,[12] psychological circumstances,[13] physical fitness,[14] medication therapy,[15,16] and circadian rhythm.[17] To date, it remains uncertain whether the positive association between HR and inflammation can be more accurately predicted by other HR metrics determined over the course of 24 hours, as compared with HR measured during daytime only.

The aim of this study was to assess the associations of HR obtained from daytime, nighttime, and 24-hour recordings, with four distinct markers of inflammation (ie, leukocytes, platelets, C-reactive protein [CRP], and 25-hydroxyvitamin D [25[OH]D]) in a population of hypertensive patients.

METHODS

Study Patients and Setting

In this investigation, cross-sectional data from the Styrian Hypertension Study (SHS) were used.[18] Briefly, the SHS is an ongoing single-center cohort study designed to evaluate biomarkers in relation to arterial hypertension and cardiovascular risk in patients with a history of hypertension defined according to medical records or patient interview. Patients aged 18 years or older were recruited across 3 years (between August 2010 and July 2013) from the outpatient clinics at the Department of Cardiology and the Department of Internal Medicine, Division of Endocrinology and Metabolism, Medical University of Graz, Austria. The main exclusion criteria were stroke or myocardial infarction (MI) within the previous 4 weeks before study inclusion, pregnant and lactating women, and an estimated life expectancy of <1 year. Patients presenting

Address for correspondence: Bríain ó Hartaigh, PhD, Department of Radiology, Dalio Institute of Cardiovascular Imaging, New York-Presbyterian Hospital and the Weill Cornell Medical College, 413 East 69th Street, Suite 108, New York, NY
E-mail: briainohartaigh@gmail.com

Manuscript received: July 2, 2014; **revised:** July 25, 2014; **accepted:** July 27, 2014
DOI: 10.1111/jch.12420

with any clinically significant acute disease such as infectious diseases were additionally excluded. Based on these criteria, the study sample included 383 patients, all of whom provided written informed consent. The appropriate ethics committee at the Medical University of Graz, Austria, approved the study, which was also designed to comply with Good Clinical Practice guidelines and the Declaration of Helsinki.

Assessment of Ambulatory BP and Heart Rate

A continuous 24-hour ambulatory blood pressure monitoring (ABPM) portable device (Spacelabs 90207A; OSI Systems Inc, Issaquah, WA) was employed to determine patients' mean 24-hour systolic and diastolic blood pressure (BP). The circumference of the upper arm was measured in all patients to select the appropriate cuff for BP recordings. Mean daytime HR was acquired from 15-minute ABPM sequences during the day from 6 AM to 10 PM, and mean nighttime HR was determined from 30-minute ABPM sequences during the night from 10 PM to 6 AM. Mean 24-hour HR was also derived from 24-hour ABPM, similar to BP recordings as mentioned earlier. All measurements were recorded and analyzed by trained personnel at the Medical University of Graz, Austria.

Definition of Study Variables

Weight and height were measured with the patients wearing no shoes and light clothes, and body mass index (BMI) was subsequently calculated using the formula: weight (kg)/height (m^2). Smoking status, diabetes mellitus based on American Diabetes Association criteria, history of cardiovascular diseases (CVDs) including MI and stroke or transient ischemic attack (TIA), and self-reported use of cardiovascular medication (ie, β-blockers, angiotensin-converting enzyme [ACE] inhibitors, and calcium channel blockers) were recorded by questionnaire with patients answering "yes" or "no." These data were additionally validated by review of all available medical reports of the study patients.

Laboratory Assessment

Blood sampling was conducted during the morning between 7 AM and 11 AM, with patients resting in the seated position for 10 minutes. On the morning of blood collection, patients fasted for at least 12 hours and were instructed to refrain from tobacco consumption. Four distinct markers of inflammation were selected a priori for analyses. Total leukocyte count (expressed as the number of leukocytes$\times 10^3/\mu L$) was measured on a Sysmex XE-5000 automated hematology analyzer (Sysmex America, Inc, Mundelein, IL), with the absolute count quantified by fluorescent flow cytometry methods. Platelet (number of platelets$\times 10^3/\mu L$) measurement was also performed using the same automated hematology analyzer, with the total count later quantified using a DC voltage sheath flow detection method. Both hematological parameters were derived from blood samples anticoagulated with K_2EDTA. Plasma CRP in mg/L was measured by the commercially available COBAS C system (Roche Diagnostics Corp, Indianapolis, IN), and a CRP Gen 3 automated particle-enhanced turbidimetric assay. The lower and upper detection limits were 0.3 mg/L and 350 mg/L, and the maximum intra-assay and interassay coefficients of variation were 3.7% and 4.0%, respectively. 25[OH]D was also used as a marker of inflammation, as previous data strongly suggest a clinically significant inverse association between 25[OH]D and inflammation.[19] 25[OH]D (ng/mL) was measured by means of a chemiluminescence assay (IDS, iSYS 25-hydroxyvitamin D; Immunodiagnostic Systems Ltd, Boldon, UK) on an IDS-iSYS multidiscipline automated analyzer. Within-day coefficients of variation were 5.5% to 12.1%, and interday coefficients of variation were 8.9% to 16.9%, respectively. Standard analyses of fasting plasma glucose, total cholesterol, and triglyceride concentrations were performed according to routine laboratory procedures.

Statistical Methods

Of the 383 patients enrolled, 15 (3.9%) were excluded because of missing information on the HR measures, leaving 368 patients in the analytic sample. For normally distributed variables, mean±standard deviation was reported; otherwise, the median and interquartile range was presented. Categorical variables were summarized as counts with proportions. The mean differences in the inflammatory markers across quartiles of daytime, nighttime, and 24-hour HR were summarized using analysis of variance with a Bonferroni post hoc test. Multivariate linear regression reporting unstandardized coefficients (*B*) with standard errors (SE) was employed to evaluate the associations of daytime, nighttime, and 24-hour HR with the markers of inflammation. Three models were employed. The first model was unadjusted, the second model was adjusted for age and sex, and the third model was additionally adjusted for smoking status, BMI, BP, fasting glucose, total cholesterol and triglyceride concentrations, history of CVD, and cardiovascular medication (ie, β-blockers, ACE inhibitors, and calcium channel blockers). Subsequently, daytime, nighttime, and 24-hour HR were each added to a single multivariate model to determine which measure was most associated with each of the inflammatory markers. Because some patients may not have been asleep when the nighttime HR recording commenced, we tested the robustness and stability of this measure by substituting the current variable (ie, from 10 PM to 6 AM) with a stricter version of nocturnal HR (from 1 AM to 6 AM). Further, as a sensitivity check, we repeated the analyses after omitting patients who reported the use of cardiovascular medications or who

[Correction added after initial online publication on September 30, 2014: On the second page of the article, "10 AM" has been changed to "11 AM" and "Spacelabs 90207" has been changed to "Spacelabs 90207A".]

had a prior history of CVD, as these factors may have influenced the relationship between HR and inflammation. Results were considered statistically significant at a two-tailed *P* value of <.05. Statistical calculations were computed using STATA version 13.0 (StataCorp LP, College Station, TX).

RESULTS

Baseline characteristics of the study cohort are provided in Table I. The mean age was 61 years and more than half (52.9%) of the study patients were women. According to BMI, the population was, on average, overweight (BMI=29.5). The prevalence of smoking (15.0%) and type 2 diabetes mellitus (20.1%) were relatively low, as were prior history of MI (7.2%) and stroke or TIA (7.5%). Overall, more than half (51.3%) of the study patients reported using β-blockers, while more than one third (35.3%) and one quarter (26.2%) reported taking ACE inhibitors and calcium channel blockers, respectively. As expected, mean nighttime HR was lower compared with daytime and 24-hour HR.

TABLE I. Baseline Characteristics

Patients, No.	368
Variables	
Age, mean±SD, y	60.6±10.8
Women, No. (%)	198 (52.9)
Current smoker, No. (%)	56 (15.0)
Type 2 diabetes mellitus, No. (%)	75 (20.1)
Objective measures	
BMI, mean±SD, kg/m^2	29.5±5.1
24-h ambulatory DBP, mean±SD, mm Hg	77±9
24-h ambulatory SBP, mean±SD, mm Hg	128±13
Fasting glucose, mg/dL, median (Q1–Q3)	95 (88–107)
Total cholesterol, mg/dL, median (Q1–Q3)	200 (167–227)
Triglycerides, mg/dL, median (Q1–Q3)	111 (77–150)
Markers of inflammation, median (Q1–Q3)	
Leukocyte count×10^3/μL	5.7 (4.8–6.8)
Platelet count×10^3/μL	228 (196–275)
CRP, mg/L	1.7 (0.9–3.3)
25[OH]D, ng/mL	28.2 (21.5–36.2)
Prior history of CVD, No. (%)	
MI	27 (7.2)
Stroke or TIA	28 (7.5)
Atrial fibrillation	12 (3.2)
Medication use, No. (%)	
β-Blockers	192 (51.3)
ACE inhibitors	132 (35.3)
Calcium channel blockers	98 (26.2)
HR measures, mean±SD, beats per min	
Daytime HR	73±10
Nighttime HR	64±9
24-h HR	71±10

Abbreviations: 25[OH]D, 25-hydroxyvitamin D; ACE, angiotensin-converting enzyme; BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; HR, heart rate; MI, myocardial infarction; SBP, systolic blood pressure; SD, standard deviation; TIA, transient ischemic attack; WBC, white blood cell.

The HR variables demonstrated high collinearity with one another, as evidenced by Pearson correlation coefficients of 0.99 (between daytime and 24-hour HR), 0.87 (between nighttime and 24-hour HR), and 0.81 (between daytime and nighttime HR) (all *P*<.001).

Table II provides the mean differences of the inflammation markers according to quartiles of the HR variables. There was a significant increase in the number of leukocytes and platelets according to all of the HR measures. In addition, there was a significant increase in concentrations of CRP, as well as a decline in 25[OH]D levels according to elevated nighttime HR only. On closer inspection, these observed differences seemed mainly driven by the fourth and, in some cases, the third quartile of the HR variables.

Table III describes the relationship between the HR variables and inflammatory markers using multivariate linear regression. All three HR measures were associated with heightened inflammatory activity. In unadjusted analyses (model 1), nighttime and 24-hour HR were positively associated with all of the inflammatory markers, whereas daytime HR was associated with leukocytes and platelets only. Yet, following adjustment for age and sex (model 2), each HR variable was significantly associated with all of the individual markers of inflammation. Further adjustment for a number of conventional risk factors (model 3) attenuated the associations of daytime and 24-hour HR with platelets, CRP, and 25[OH]D. Likewise, the relationship of nighttime HR with platelets and 25[OH]D disappeared after full adjustment, although, in addition to leukocytes, nighttime HR remained significantly associated with CRP.

In a multivariate model that included all three HR variables, only nighttime HR was retained as an important predictor of inflammation (Table IV). That is, each beat-per-minute increment in nighttime HR increased leukocytes by 0.06 (SE=0.03, *P*=.04), as well as CRP by 0.20 (SE=0.07, *P*=.005) after adjustment.

When the analyses were repeated, substituting nighttime HR (ie, from 10 PM to 6 AM) with a more stringent measure of nocturnal HR (from 1 AM to 6 AM), the results were virtually identical for the association between strict nighttime HR with leukocytes (*B* [SE] =0.04 [0.01], *P*<.001), as well as with CRP (*B* [SE]=0.06 [0.02], *P*=.01). Reanalysis of the data omitting patients who reported using β-blockers, ACE inhibitors, and/or calcium channel blockers did not affect the results appreciably, nor did the findings differ after excluding patients with a history of MI, stroke and TIA, or atrial fibrillation (data not reported). The results remained materially unchanged when men and women were analyzed separately (data not shown).

DISCUSSION

The current investigation set out to determine the relationship of HR recorded during daytime and nighttime and during 24 hours with a set of inflam-

TABLE II. Mean Differences in the Inflammatory Markers According to Quartiles of Daytime, Nighttime, and 24-Hour HR

	HR Quartiles				
	First (n=96) Reference	Second (n=90)	Third (n=96)	Fourth (n=86)	*P* Value[#]
Daytime HR, beats per min	61±5	70±2	77±2	86±5	
Leukocyte count×10^3/μL	5.6±0.14	0.1±0.02	0.4±0.06	0.7±0.07[a]	.02
Platelet count×10^3/μL	223±5.8	7±−0.7	28±0.1[a]	23±0.1[a]	.003
CRP, mg/L	2.3±0.34	0.3±−0.02	1.4±0.17	0.6±0.03	.07
25[OH]D, ng/mL	31.1±1.23	−1.9±−0.11	−2.7±−0.09	−1.7±−0.05	.42
Nighttime HR, beats per min	53±4	61±2	67±2	76±5	
Leukocyte count×10^3/μL	5.5±0.14	0.3±0.02	0.3±0.01	1.2±0.07[a,b,c]	<.001
Platelet count×10^3/μL	226±5.6	7±0.1	15±0.1	25±1.8[a]	.03
CRP, mg/L	1.9±0.26	1.0±0.16	0.8±−0.01	1.9±0.29[a]	.005
25[OH]D, ng/mL	32.4±1.19	−3.9±−0.02	−2.6±−0.01	−4.8±−0.04[a]	.02
24-h HR, beats per min	60±4	68±2	74±2	84±5	
Leukocyte count×10^3/μL	5.5±0.13	0.3±0.03	0.5±0.03	0.8±0.08[a]	.01
Platelet count×10^3/μL	222±6.0	12±−0.7	27±−0.1[a]	24±1.3[a]	.007
CRP, mg/L	2.3±0.35	0.2±−0.04	1.2±0.08	0.6±0.04	.09
25[OH]D, ng/mL	31.8±1.15	−2.5±0.16	−3.4±−0.12	−2.8±0.07	.16

Abbreviations: 25[OH]D, 25-hydroxyvitamin D; CRP, C-reactive protein. Differences shown for inflammatory markers are vs the first quartile of heart rate measures (reference). Values are reported as mean±standard deviation for heart rate (HR) measures and mean±standard error for the inflammatory markers. [#]*P* values were determined using analysis of variance. [a]*P*<.05 vs the first quartile. [b]*P*<.05 vs the second quartile. [c]*P*<.05 vs the third quartile.

TABLE III. Crude, Partial, and Fully Adjusted Regression Coefficients for Each Marker of Inflammation According to Daytime, Nighttime, and 24-Hour HR

	Model 1		Model 2		Model 3	
	B	SE	*B*	SE	*B*	SE
Daytime HR						
Leukocytes	0.03[a]	0.01	0.03[a]	0.01	0.02[b]	0.01
Platelets	1.01[c]	0.30	0.70[b]	0.30	0.54	0.34
CRP	0.03	0.02	0.04[b]	0.02	0.03	0.02
25[OH]D	−0.10	0.06	−0.12[b]	0.06	−0.03	0.07
Nighttime HR						
Leukocytes	0.05[a]	0.01	0.05[a]	0.01	0.04[a]	0.01
Platelets	0.87[c]	0.34	0.71[b]	0.33	0.59	0.36
CRP	0.07[c]	0.02	0.08[c]	0.02	0.06[c]	0.02
25[OH]D	−0.18[c]	0.06	−0.20[c]	0.07	−0.09	0.07
24-h HR						
Leukocytes	0.04[a]	0.01	0.04[a]	0.01	0.03[c]	0.01
Platelets	1.04[c]	0.31	0.73[b]	0.32	0.57	0.36
CRP	0.04[b]	0.02	0.05[b]	0.02	0.03	0.02
25[OH]D	−0.12[b]	0.06	−0.14[b]	0.06	−0.04	0.07

Abbreviations: 25[OH]D, 25-hydroxyvitamin D; CRP, C-reactive protein; HR, heart rate. Values are unstandardized regression coefficients (*B*) with standard errors (SE). Model 1 was unadjusted, model 2 was adjusted for age and sex, and model 3 was also adjusted for smoking status, body mass index, 24-hour ambulatory blood pressure, fasting glucose, total cholesterol and triglyceride concentrations, history of cardiovascular disease, and cardiovascular medication.[a]*P*<.001. [b]*P*<.05. [c]*P*<.01.

matory markers in hypertensive patients. All three measures of HR were associated with inflammatory activity. Specifically, each HR measure was positively related with leukocytes, whereas nighttime HR was additionally associated with higher concentrations of CRP.

The findings from this investigation are consistent with those of prior studies that assessed the relationship between daytime HR and inflammation. In a 3-year follow-up of persons with known cardiovascular risk, Nanchen and colleagues[9] found that elevated resting HR was highly correlated with CRP and numerous other markers of systemic inflammation. Results from the Multi-Ethnic Study of Atherosclerosis (MESA)[20] found that a high resting HR was significantly associated with CRP, interleukin 6, and fibrinogen. In a healthy adult population, Inoue and coworkers[21] reported that for every 10 beat-per-minute increment in resting HR, the odds of having a high leukocyte count increased by approximately 30%, even in the absence of cigarette smoking.

To our knowledge, no prior study has evaluated the association between nighttime and 24-hour HR with inflammatory markers. It is possible that these other HR metrics could provide better predictive value for identifying persons at risk for subclinical inflammation and, consequently, for poor cardiovascular outcomes. A major finding of this study was that nighttime HR emerged as a robust predictor of inflammatory activity from among the three HR measures. Moreover, the

TABLE IV. Summary of Regression Coefficients for Each Marker of Inflammation According to HR Measures Included in the Same Model

	Leukocytes		Platelets		CRP		25[OH]D	
	B	SE	*B*	SE	*B*	SE	*B*	SE
Daytime HR	−0.01	0.10	3.28	3.70	0.39	0.24	0.08	0.73
Nighttime HR	0.06	0.03[a]	1.19	1.08	0.20	0.07[b]	−0.17	0.21
24-h HR	−0.01	0.12	−3.84	4.60	−0.53	0.30	0.03	0.90

Abbreviations: 25[OH]D, 25-hydroxyvitamin D; CRP, C-reactive protein; HR, heart rate. Values reported are unstandardized regression coefficients (*B*) with standard errors (SEs). Model included daytime, nighttime, and 24-hour heart rate. Model further included age and sex, smoking status, body mass index, 24-hour ambulatory blood pressure, fasting glucose, total cholesterol and triglyceride concentrations, history of cardiovascular disease, and cardiovascular medication. [a]$P<.05$. [b]$P<.01$.

association between nighttime HR and inflammation persisted even after adjusting for the other HR measures. In the same model, however, the association of either daytime or 24-hour HR with the inflammation markers disappeared, which is fitting with the findings of Johansen and colleagues,[22] where nighttime HR was the only HR measure associated with worse prognosis following multivariable adjustment. Seemingly, nighttime HR may provide a more superior indication of inflammatory activity as compared with other HR measures. This clearly deserves further investigation.

The actions of the autonomic nervous system follow a distinct circadian pattern, whereby sympathetic activity increases during the day and diminishes during the night.[17] HR tends to follow a similar circadian pattern, characterized by a morning surge, followed by progressively higher values during the day and a clear nocturnal dip,[17,22] demonstrating a relative vagal dominance in the regulation of nighttime HR.[23] Nevertheless, impairment of autonomic neural activity during the night may negatively influence cardiovascular risk. In light of this conjecture, prior studies have reported a link between a blunted nocturnal decline in BP and adverse cardiovascular outcomes,[24] presumably owing to an altered circadian rhythm in the absence of sympathetic withdrawal during nighttime. Although the precise intrinsic and extrinsic mechanisms affecting the circadian profile of the autonomic nervous system are yet to be fully elucidated, it is biologically plausible that an exaggerated nocturnal rise in sympathetic overdrive may have accounted for the interplay observed between nighttime HR and inflammation in the current study. Indeed, others have documented a relationship between resting HR and systemic inflammation via mechanisms driven by autonomic nervous system dysfunction.[10,25] However, further examination of this hypothesis was beyond the scope of the current investigation. Additional studies are warranted to test this notion.

Study Limitations

Our study has several limitations. The cross-sectional design precludes causal inference. The study was performed in a sample of Caucasians presenting with hypertension. Caution should be taken when extrapolating these findings to other populations. Patients enrolled in this study were not strictly and consecutively derived from our outpatient clinics, which may have introduced selection bias in the current investigation. The study sample was relatively small, and each marker of inflammation was determined only once. Likewise, HR measures were recorded over the course of only 1 day. To further advance our understanding of the relationship between HR and inflammation, larger epidemiological studies with time-dependent measures are needed. Although four distinct markers of inflammation were employed, we cannot discount the possibility that the associations would have differed according to other unmeasured inflammatory markers. Moreover, HR is a sensitive indicator of autonomic nervous system function, and it is possible that other unmeasured factors (ie, environmental conditions, psychological disturbances, and physical fitness) could have altered the association between HR and inflammation. The duration of time used for excluding persons who had a prior stroke or MI might not have been sufficient, and, as a consequence, could have impacted the markers of inflammation. It is likely that some individuals were awake during the early phases of nighttime recording (ie, from 10 PM to 12 AM), which could have influenced the current findings. Although, when nighttime HR was replaced with a more stringent nocturnal measure (from 1 AM to 6 AM), when patients were expected to be sleeping, the results remained unchanged. Because internal (ie, physiologic) and external (ie, environmental) influences are minimized, nighttime HR may be a more reliable and accurate measure of resting HR and a better predictor of inflammatory activity.

CONCLUSIONS

We examined the relationship between daytime, nighttime, and 24-hour HR with four distinct markers of inflammation in a sample of hypertensive patients. Nighttime HR proved to be the most accurate predictor of inflammatory activity. These results suggest that it

might be necessary to assess other measures of HR over the course of 24 hours (eg, nighttime HR), rather than just daytime alone, thereby permitting the opportunity to capture a better estimate of one's habitual HR, along with a more reliable and better predictor of inflammation.

Acknowledgments: We thank the Laboratory of the Division of Endocrinology and Metabolism for its work and support to the present research. Each author contributed substantially to the manuscript with regards to study conception and design; analysis and interpretation of data; the initial drafting and revision of the manuscript for intellectual content and quality; and final approval of the paper.

Financial Support: Katharina Kienreich and Martin Gaksch received funding support from the Austrian National Bank (Jubilaeumsfond: project # 13878 and 13905). Dr Gill is the recipient of an Academic Leadership Award (K07AG043587) from the National Institute on Aging and is supported by the Yale Claude D. Pepper Older Americans Independence Center (P30AG21342).

Disclosures: The authors report no conflicts of interest to disclose.

References

1. Okin PM, Kjeldsen SE, Julius S, et al. Effect of changing heart rate during treatment of hypertension on incidence of heart failure. *Am J Cardiol*. 2012;109:699–704.
2. O'Hartaigh B, Bosch JA, Pilz S, et al. Influence of resting heart rate on mortality in patients undergoing coronary angiography (from the Ludwigshafen Risk and Cardiovascular Health [LURIC] Study). *Am J Cardiol*. 2012;110:515–520.
3. Nauman J, Janszky I, Vatten LJ, et al. Temporal changes in resting heart rate and deaths from ischemic heart disease. *JAMA*. 2011;306:2579–2587.
4. Jensen MT, Marott JL, Jensen GB. Elevated resting heart rate is associated with greater risk of cardiovascular and all-cause mortality in current and former smokers. *Int J Cardiol*. 2011;151:148–154.
5. Cooney MT, Vartiainen E, Laatikainen T, et al. Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. *Am Heart J*. 2010;159:612–619 e3.
6. Giannoglou GD, Chatzizisis YS, Zamboulis C, et al. Elevated heart rate and atherosclerosis: an overview of the pathogenetic mechanisms. *Int J Cardiol*. 2008;126:302–312.
7. Zamorano JL. Heart rate management: a therapeutic goal throughout the cardiovascular continuum. *Eur Heart J Suppl*. 2008;10:F17–F21.
8. O'Hartaigh B, Bosch JA, Carroll D, et al. Evidence of a synergistic association between heart rate, inflammation, and cardiovascular mortality in patients undergoing coronary angiography. *Eur Heart J*. 2012;34:932–941.
9. Nanchen D, Stott DJ, Gussekloo J, et al. Resting heart rate and incident heart failure and cardiovascular mortality in older adults: role of inflammation and endothelial dysfunction: the PROSPER study. *Eur J Heart Fail*. 2013;15:581–588.
10. Rogowski O, Shapira I, Shirom A, et al. Heart rate and microinflammation in men: a relevant atherothrombotic link. *Heart*. 2007;93:940–944.
11. Lahiri MK, Kannankeril PJ, Goldberger JJ. Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications. *J Am Coll Cardiol*. 2008;51:1725–1733.
12. Eijgelsheim M, Newton-Cheh C, Sotoodehnia N, et al. Genome-wide association analysis identifies multiple loci related to resting heart rate. *Hum Mol Genet*. 2010;19:3885–3894.
13. Vogel CU, Wolpert C, Wehling M. How to measure heart rate? *Eur J Clin Pharmacol*. 2004;60:461–466.
14. Blair SN, Kannel WB, Kohl HW, et al. Surrogate measures of physical activity and physical fitness. Evidence for sedentary traits of resting tachycardia, obesity, and low vital capacity. *Am J Epidemiol*. 1989;129:1145–1156.
15. Castagno D, Petrie MC, Claggett B, et al. Should we SHIFT our thinking about digoxin? Observations on ivabradine and heart rate reduction in heart failure. *Eur Heart J*. 2012;33:1137–1141.
16. Cucherat M, Borer JS. Reduction of resting heart rate with antianginal drugs: review and meta-analysis. *Am J Ther*. 2011;19:269–280.
17. Koroboki E, Manios E, Psaltopoulou T, et al. Circadian variation of blood pressure and heart rate in normotensives, white-coat, masked, treated and untreated hypertensives. *Hellenic J Cardiol*. 2012;53:432–438.
18. Grubler MR, Kienreich K, Gaksch M, et al. Aldosterone to active renin ratio is associated with nocturnal blood pressure in obese and treated hypertensive patients: the Styrian Hypertension Study. *J Clin Hypertens (Greenwich)*. 2014;16:289–294.
19. Autier P, Boniol M, Pizot C, et al. Vitamin D status and ill health: a systematic review. *Lancet Diabetes Endocrinol*. 2014;2:76–89.
20. Whelton SP, Narla V, Blaha MJ, et al. Association between resting heart rate and inflammatory biomarkers (high-sensitivity C-reactive protein, interleukin-6, and fibrinogen) (from the multi-ethnic study of atherosclerosis). *Am J Cardiol*. 2014;113:644–649.
21. Inoue T, Iseki K, Iseki C, et al. Elevated resting heart rate is associated with white blood cell count in middle-aged and elderly individuals without apparent cardiovascular disease. *Angiology*. 2012;63:541–546.
22. Johansen CD, Olsen RH, Pedersen LR, et al. Resting, night-time, and 24 h heart rate as markers of cardiovascular risk in middle-aged and elderly men and women with no apparent heart disease. *Eur Heart J*. 2013;34:1732–1739.
23. Verrier RL, Tan A. Heart rate, autonomic markers, and cardiac mortality. *Heart Rhythm*. 2009;6:S68–S75.
24. Giles TD. Circadian rhythm of blood pressure and the relation to cardiovascular events. *J Hypertens Suppl*. 2006;24:S11–S16.
25. Lampert R, Bremner JD, Su S, et al. Decreased heart rate variability is associated with higher levels of inflammation in middle-aged men. *Am Heart J*. 2008;156:759 e1–759 e7.