Circadian Variation of Arterial Pressure Wave Reflections

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Background: Various factors are implicated in the circadian pattern of cardiovascular vulnerability. The exact mechanisms involved in the peak incidence of cardiovascular events occurring during the early morning hours after awaking are not completely known. The purpose of our study was to investigate the circadian variation of timing and intensity of wave reflections in healthy individuals and to test the hypothesis that significant changes occur during the day.

Methods: Thirteen healthy non-smokers (seven women and six men, mean age 40.7 ± 16.5 years) were examined. Aortic pulse wave analysis was performed to estimate surrogates of wave reflections intensity (augmentation index [Alx]) and timing. Twelve measurements separated by 1-h intervals were performed from 8 AM to 7 PM each study day.

Results: Analysis of variance for repeated measures indicated significant changes during the 12-h period for heart rate corrected Alx (P = .033) and heart rate (P = .035). The Alx was maximal at 8 AM within 1-h after awaking (17% ± 3.6%); it was gradually diminished until 3 PM (9% ± 4.1%) and again increased to a second (albeit lower) peak value during the late afternoon (7 PM).

Conclusions: It is possible that the increased intensity of reflected waves occurring during the early morning in combination with the rising trend of blood pressure and heart rate at the same time results in an aggravated left ventricular afterload and an increase in myocardial oxygen demand. The morning-related enhancement of wave reflections may have potential implications for the increased risk for cardiovascular events during the early morning, which remains to be clarified. Am J Hypertens 2006;19:259–263 © 2006 American Journal of Hypertension, Ltd.

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pulses; heart rate; augmentation index; and arrival time of reflected waves at central aorta. For each subject, 12 measurements separated by 1-h intervals were performed beginning at 8 AM and ending at 7 PM. All subjects were examined on Sundays, without engaging in any intensive physical or mental activity or stress. The first examination was made within 1 h after the subjects awakened and before they had breakfast. Subjects consumed a standard breakfast immediately after their first measurement and a standard meal after their sixth measurement.

**Sample Size Estimation**

The sample size was estimated based on the expected minimal change of unadjusted augmentation index (AIx). Given the variability and reproducibility of repeated AIx measurements, as well as previously reported AIx differences with clinical implications, a minimum statistically significant change in AIx greater than 5% to 6% was used for estimating the sample size. A sample of approximately 13 subjects was estimated as efficient (80% power) to detect a change by 7% in AIx (α = 0.05 and β = 0.20; two-tailed test).

**Study Population**

A total of 13 healthy volunteers (seven women and six men, mean age 40.7 ± 16.5 years and body mass index 23.9 ± 4.3 kg/m²) were examined. Only nonsmokers were enrolled in the study. No subject had a history or evidence of any cardiovascular or other disease, and none were taking any medication, vitamins, or nutritional supplements. No subject reported any symptoms of sleep disorders such as insomnia, obstructive sleep apnea, narcolepsy, or restless legs syndrome. Subjects were advised to consume specific quantities and types of food the last day before the study and also to abstain from consuming alcohol and caffeine as well as all products containing these substances at least 12-h before the first measurement. To ensure dietary compliance, 24-h recalls were reviewed.

**Measurement of BP**

Measurement of BP was done in accordance with the recommendations of the American Heart Association. In the present study brachial BP was measured by using an automated digital oscillometric BP monitor (Omron HEM 705-CP, Kyoto, Japan). Three measurements were made and the average peripheral systolic and diastolic pressures were used. The device has been validated, and it has been used in large research studies such as the Anglo-Scandinavian Cardiac Outcome Trial as well as in study designs with repeated BP measurements, instead of the traditional mercury ("gold standard") manometer.

**Estimation of Wave Reflections and Arterial Stiffness**

Surrogates of wave reflections and arterial stiffness were estimated by aortic pulse wave analysis. First, peripheral pressure waveforms were recorded by placing the radial artery with a hand-held tonometer (Millar Instruments, Houston, TX); pressure waveforms obtained by this method have previously been validated by comparing them with intra-arterial pressure waveforms. Central waveforms were then derived from the radial waveforms by using generalized transfer functions. For this purpose we used the Sphygmocor System (AtCor Medical Pty. Ltd., Sydney, Australia), which is a Food and Drug Administration–approved, widely used device for noninvasive estimation and analysis of aortic pressure waveforms. Augmentation index, both unadjusted (AIx) and adjusted at heart rate 75 beats/min (AIx@75), was used to express the intensity of wave reflections. The AIx(%) was calculated as the ratio of augmented pressure (pressure at the second inflection point minus pressure at the first inflection point of the systolic part of pressure waveform) to pulse pressure. In addition, timing of the reflected wave (tr), which is a surrogate of pulse wave velocity, was determined as the time between the first foot of the pressure wave and the inflection point indicating the arrival of the reflected wave at central aorta. Adjustment of tr for heart rate was made by using the reflection time index (RTI: %), which is the arrival time of the reflected wave at central aorta expressed as a percentage of the cardiac period.

**Statistical Analysis**

Values are presented as mean value ± standard error (SE). Variables were tested for normal distribution by nonparametric Kolmogorov-Smirnov test. Analysis of variance for repeated measures was used to test the null hypothesis that the standard parameters (BP, heart rate, augmentation index, and timing of wave reflections) did not change significantly during the 12-h monitoring period. $P < 0.05$ were considered statistically significant.

**Results**

Variation of the measured variables from 8 AM to 7 PM is illustrated in Fig. 1. Analysis of variance indicated statistically significant changes during the 12-h period for AIx@75 ($P = 0.033, F = 2.01$), AIx ($P = 0.011, F = 2.37$), and heart rate ($P = 0.035, F = 2.66$). The variation of peripheral and aortic BP was not statistically significant. The maximal value of augmentation index adjusted for heart rate was observed at 8 AM within 1 h after awakening (17% ± 3.6%). At the same time (8 AM), maximal values were also observed for brachial systolic (120 ± 6.9 mm Hg), diastolic (74 ± 3.5 mm Hg), and pulse pressures (46 ± 4.2 mm Hg) and also for heart rate (75 ± 4 beats/min). The minimal values of AIx@75, brachial
systolic BP, and diastolic BP were observed at 3 PM; 9% ± 4.1%, 114 ± 6.6 mm Hg and 71 ± 3.2 mm Hg, respectively. Heart rate and pulse pressure reached their minimal values at 12 PM; 64 ± 2.9 beats/min and 41 ± 3.2 mm Hg, respectively. The difference between the maximal and the minimal values was statistically significant for AI@75 (P = .033), AIx (P = .011), and heart rate (P = .025), but not for timing of reflected waves or for systolic, diastolic, and pulse pressure.

**Discussion**

The major finding of the present study was the significant variation of wave reflections intensity during the day (from 8 AM to 7 PM), as shown by analysis of aortic pulse wave patterns, which were also altered depending on the time of the day (Fig. 2).

A maximal augmentation of aortic systolic BP, which resulted by the reflected waves, occurred at morning within 1 h after awaking (8 AM), which accords with previous findings in young healthy men, whereas the lower one occurred at 3 PM. In addition, a second peak value of wave reflections intensity, although lower than that in the morning, was observed at 7 PM. On the other hand, the arrival time of the reflected waves at central aorta, a surrogate of pulse wave velocity, showed a slight variation during the 12-h monitoring period.

**Circadian Pattern of Cardiovascular Events**

A diurnal variation in the onset of cardiovascular disorders has been well documented. It is known that cardiac events present a peak incidence from 6 AM to 11 AM, and that their onset is stimulated by various physiologic phenomena that occur upon awaking, although the exact mechanisms for this are unknown. The peak increase in the intensity of the reflected waves at the central aorta may be an additional burdensome factor occurring upon awaking. In the present study a second peak increase in AIx was observed at 7 PM. Whether this AIx increase participates in the second peak incidence of cardiac events that have been also observed at approximately 5 to 7 PM remains to be investigated.

**Physiologic Bases of Wave Reflections**

Left ventricular ejection generates a pressure wave that propagates from the aorta to peripheral arterial sites throughout the human body. Forward traveling pressure waves are reflected at points of structural or functional discontinuity (eg, change in vessel diameter or in arterial wall elasticity). Consequently, forward and backward traveling pressure waves are summated, modulating the characteristic pressure waveform, which varies along the vascular tree. Timing and amplitude of the pressure waves are the key factors for an optimal and effective ventricular–vascular coupling. Early return of the reflected waves at the central aorta induces an augmentation in aortic systolic pressure with a parallel decrease in diastolic pressures. Accordingly an increase in AIx leads to a rise in
cardiac load with direct adverse effects on coronary perfusion, myocardial oxygen demand, left ventricular mass, and vascular remodeling.23

Physiologic Factors Responsible for Changes in Wave Reflections

Various cardiovascular parameters participate in the modification of timing and amplitude of reflected waves, expressed by AIx. The inverse strong relation between heart rate and AIx has led to the development of an adjusted index for heart rate changes, namely AI@75.16 Thus the observed 12-h variation of wave reflections is independent of heart rate alterations. It should be highlighted that despite the morning peak values of heart rate, the AIx still remained maximal, thus adding an additional burden to left ventricular function while disturbing the myocardial oxygen demand–supply balance.

Blood pressure influences arterial stiffness and wave reflections and vice versa. The higher the BP the higher the arterial stiffness and the AIx. However, wave reflections also contribute to aortic pressure modification. That is, a higher AIx (ie, wave reflections of a higher magnitude or earlier arrival in the ascending aorta, or both) leads to a higher aortic systolic pressure and pulse pressure and therefore to a greater left ventricular load. A slight increase in BP during the early morning was observed in our study, explaining in part the peak AIx values noted at this time.

The observed variation in wave reflections could also be attributed to modifications in endothelial vasoreactivity, alterations in vascular tone, and peripheral resistance.24,25 Local differential effects of nitric oxide and vasoconstrictive compounds, changing balance between vasodilators such as nitric oxide, prostacyclin, and vasoconstrictors such as norepinephrine, angiotensin II, and endothelin-126 may participate in the underlying mechanisms that lead to the peak morning values of AIx; this, however, remains to be clarified by further research.

The minimal values of augmentation index were observed at 3 PM. A possible explanation is the postprandial changes in peripheral resistance,27 but another explanation is the well-known reduction in wave reflections from the splanchnic bed,28 which may be caused by insulin release.29 To clarify which is the major component of the significant 12-h variation of AIx (the peak morning increase or the postprandial fall), we reanalyzed the data set excluding the two postprandial AIx values (3 and 4 PM). The AIx, both corrected and not corrected for heart rate, still varied significantly (P = .014 and P = .028, respectively; data not shown).

Study Limitations

A few limitations of this study should be acknowledged. Measurements were obtained during the period from 8 AM to 7 PM, and therefore no data are available for the nighttime variation of wave reflections and arterial stiffness indices. However, because no automated technique exists for the estimation of wave reflections and arterial stiffness indices, the repeated use of applanation tonometry during the night-time would probably interrupt sleep. Increased catecholamine levels and sleep disorders would be major confounders for night-time monitoring of wave reflections by this technique, which nonetheless would add considerably to the current understanding of the 24-h variation of wave reflections and arterial stiffness. Measurements were made on Sundays (despite the fact that Sunday is not a “peak day” for cardiovascular events) to avoid any occupational or other environmental stress–related factors. Accordingly it could be hypothesized that morning values of AIx might be higher if measured during a working day. In addition caffeine consumption, which mostly occurs in the early morning hours, may further increase wave reflections.30 It should be also emphasized that our study population consisted of healthy individuals, and thus the reported results and observations should be extrapolated to other groups with cardiovascular risk factors only with caution.

Perspectives

It is possible that the increased intensity of reflected waves during the early morning, in combination with the rise in BP and heart rate, results in an aggravated left ventricular afterload and also in increased myocardial oxygen demand. Concerning study designs, the morning increase in wave reflections and changes in aortic pressure wave patterns should be carefully recognized in clinical studies of wave reflections so that the measurements are performed at approximately the same time of day. The circadian variation in wave reflections and arterial mechanical properties should be further investigated at populations with risk factors (especially hypertension or overt cardiovascular disease), as it could be hypothesized that the variation of wave reflections would be even more pronounced in those patients.

References


