Effects of Aging and Cardiac Denervation on Heart Rate Variability During Sleep

Vincent Crasset, MD; Silvia Mezzetti, MD; Martine Antoine, MD; Paul Linkowski, MD, PhD; Jean Paul Degaute, MD, PhD; Philippe van de Borne, MD, PhD

Background—Cardiac vagal predominance increases the RR interval and RR high-frequency (HF) variability during non–rapid eye movement (non-REM) sleep (stages I through IV) in young subjects. Aging suppresses deep sleep, but effects of age-related changes in sleep architecture on RR are unknown. Whether mechanical effects of changes in the breathing pattern on the sinus node during sleep affect RR variability is unclear.

Methods and Results—Polygraphic sleep recordings and RR and RR spectral profiles were determined in 8 young (22.5±3.3 years) and 8 older (55.0±7.3 years) healthy volunteers. HF oscillations in RR of 8 cardiac-denervated heart transplant recipients determined mechanical effects of respiration on the sinoatrial node during sleep. Transition from wakefulness to non-REM sleep increased the RR interval in young and older subjects and increased the HF variability of RR in the young (P<0.05) but not in the older subjects. Older subjects disclosed a faster RR (P<0.01) and a lower HF variability (P<0.05) during non-REM sleep than the young subjects. Aging did not affect light and REM sleep but decreased deep sleep (stage IV) from 39±23 to 6±6 minutes (P<0.001). Reduction in sleep stage IV with aging blunted the increase in RR and in RR HF variability during non-REM sleep (r>0.55, P<0.05). Transition from wakefulness to non-REM sleep doubled the markedly reduced HF variability of RR in the heart transplant recipients (P<0.05).

Conclusions—Disappearance of deep sleep with aging impairs nocturnal increase in cardiac vagal activity. Mechanical effects of changes in breathing pattern during sleep favor increases in HF oscillations of the RR interval during non-REM sleep. (Circulation. 2001;103:84-88.)

Key Words: aging ■ sleep ■ heart rate ■ transplantation

Mechanisms controlling cardiac autonomic function during sleep are not well known. What is known is (1) that the RR interval (RR) displays low-frequency (LF) oscillations of ≈0.10 Hz and faster oscillations at the respiratory frequency (high frequency, HF) during wakefulness and (2) that reduced cardiac sympatovagal balance increases RR and induces a relative predominance of the HF oscillatory profiles of RR during deep sleep (stages III and IV) in young healthy humans. Aging markedly suppresses deep sleep, but the effects of age-related changes in sleep architecture on RR and on RR variability are unknown. This is of clinical importance, because post–myocardial infarction patients have a blunted increase in cardiac vagal activity during non–rapid eye movement (non-REM) sleep (stages I through IV). Nocturnal RR variability during sleep has also been proposed as a marker of obstructive sleep apnea syndrome. Thus, assessment of RR variability may be useful in focusing resources on those patients with the highest risk, but better knowledge of the age-related changes in sleep architecture on RR variability is needed before this can be done.

The mechanisms controlling the HF variability of RR during sleep are unclear. The HF variability of RR is mediated not only by direct modulation of vagal efferent activity resulting from baroreceptor responses to respiratory blood pressure fluctuations but also by mechanical effects of sinus node stretch from respiration-related changes in venous return. Rib cage movements contribute more to tidal volume than diaphragmatic movements during non-REM sleep. Moreover, both tidal volume and breathing frequency decrease during non-REM sleep; however, whether the mechanical effects of these changes in the breathing pattern on the sinus node affect the HF variability of RR during sleep is unknown.

Our study tested 2 hypotheses: that the disappearance of deep sleep with aging impairs the nocturnal increase in cardiac vagal activity and that mechanical effects of changes in the breathing pattern affect HF oscillatory profiles of RR during sleep. We therefore determined RR, RR variability, and respiration during polygraphic sleep recordings in healthy young and elderly volunteers. Recording of HF oscillations in the RR of cardiac-denervated heart transplant recipients determined the mechanical effects of respiration on the sinoatrial node during sleep.

© 2001 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org
Methods

We studied 2 groups of normal subjects 22.5±3.3 years of age (mean±SD; range, 18 to 28 years; n=8; all men) and 55.0±7.3 years (range, 41 to 66 years; n=8; 6 men, 2 women). None was taking any medication. We also studied a group of 8 heart transplant recipients 56.5±6.4 years of age (range, 39 to 63 years; n=8; 4 men, 4 women). Heart transplant patients were studied 48±17 months after transplantation. Immunosuppression in these patients was achieved by combination therapy with cyclosporine (n=8), azathioprine (n=7), and prednisolone (n=6). All heart transplant patients were free of heart failure, and the left ventricular ejection fraction determined by radionuclide ventriculogram was 60±8%. All patients were also free of diabetes, renal failure, and moderate or severe rejection as shown by histologic evaluation. Six of the heart transplant patients were receiving antihypertensive medication at the time of the study, specifically a calcium antagonist (amlodipine, n=5), a β-blocker (atenolol, n=1), and an ACE inhibitor (enalapril, n=1).

The Erasme Hospital Human Subjects Review Committee approved the study, and informed written consent was obtained from all subjects.

Measurements

The subjects were studied in the supine position. ECG (Siemens) and thoracic and abdominal movements (Respitrace) were recorded online on a personal computer (Compaq 4/66I) for subsequent analysis. All patients underwent complete polysomnographic recordings with EEG, electrooculogram, submental electromyogram, leg movement (Sleepmate), oxygen saturation (Ohmeda), and nasal air flow (Sleepmate) determinations. For the EEG, occipital, central, and frontal leads were used.

Protocol

All participants were studied in the Sleep Laboratory of the Department of Psychiatry, Erasme Hospital, Brussels, Belgium, and were habituated for 1 night to the sleep laboratory environment. Subjects went to sleep and woke up at their usual times. Mean sleep onset occurred at 10:09 PM, 113±79 minutes (mean±SD) after the beginning of the ECG and respiration recordings. The subjects woke up at 7:45 AM.

Data Analysis

Sleep analysis was performed by an experienced rater following the Rechtschaffen and Kales criteria.4,14 None of the subjects included in the study disclosed >4 apneas per hour. Analog-to-digital conversion was performed at 1000 samples per second for the ECG and 200 samples per second for the respiratory signal. The data were then analyzed offline with a personal computer (Compaq). The principles of the software for data acquisition and spectral analysis have been described elsewhere.3,11,15 The signal of respiratory activity was sampled once every cardiac cycle. These procedures produced 2 time series (tachogram and respirogram). Stationary segments devoid of arrhythmias and artifacts were obtained during awake periods (n=565), non-REM sleep (stages I through IV, n=1026), and REM sleep (n=265) in the 16 control subjects. Non-REM sleep was divided into light sleep (stages I and II, n=928) and deep sleep (stages III and IV, n=98). These sequences were analyzed with discrete Fourier algorithms and then averaged for each individual subject. The normalized LF and HF units (nu) provided a marker of the cardiac sympathovagal balance in the control subjects.16,17 These values were obtained by calculating the absolute variability of the LF (0.04 to 0.15 Hz) and HF (0.16 to 0.50 Hz) components as a percentage of total power (0.02 to 0.50 Hz), after subtracting the power of the very LF component (frequencies below nominal 0.03 Hz).16,17 The markedly depressed variability of RR of the cardiomagnetically denervated patients was assessed in absolute units (ms2).11

Statistical Analysis

Results are expressed as mean±SD. Statistical analysis consisted of paired and unpaired Student’s t tests when appropriate. The absolute variability and the LF/HF ratio of RR were not normally distributed and were analyzed with Mann-Whitney and Wilcoxon tests corrected for ties. Correlation was estimated with the Pearson coefficient. Significance was assumed at P<0.05.

Results

Effects of Age-Related Changes in Sleep Architecture on RR and RR Variability

Aging did not affect light and REM sleep but decreased the duration of sleep stage IV from 39±23 to 6±6 minutes (P<0.001; the Table).

The transition from wake to non-REM sleep increased RR in the young and older subjects (from 1026±186 to 1220±192 ms and from 891±109 to 975±99 ms, respectively; P<0.001 for both groups). RR decreased when shifting from non-REM to REM sleep only in the young subjects (P<0.05) and remained larger during REM sleep than during awake periods only in the elderly subjects (P<0.01; Figure 1).

RR did not differ between young and older subjects during awake periods but was larger in the young subjects than in the older subjects during both non-REM (1220±192 versus 975±99 ms) and REM (1134±156 versus 959±118 ms) sleep (both P<0.05).

The total RR variability was higher in the young subjects than in the older volunteers during awake periods (6802±4193 versus 1712±895 ms2; P<0.05), non-REM

Figure 1. RR during awake periods, non-REM, and REM sleep in normal young (open bars) and older (solid bars) subjects. Reduction in RR with aging is particularly evident during non-REM and REM sleep. *P<0.05, **P<0.01 vs young; ***P<0.01, XXP<0.001 vs awake.
sleep (5757±2568 versus 2748±2759 ms², \(P<0.05\)), and REM sleep (11414±7505 versus 2009±1387 ms², \(P<0.01\)).

The normalized HF variability of RR increased when the young subjects shifted from wakefulness to non-REM sleep (from 42±11 to 54±9 nu, \(P<0.05\); Figure 2) and decreased again during the shift from non-REM sleep to REM sleep to 45±10 nu, \(P<0.05\) versus non-REM sleep). Opposite changes occurred in the normalized LF variability of RR, which decreased during the shift from wakefulness to non-REM sleep and increased again during the shift from non-REM sleep to REM sleep in the young subjects (all \(P<0.05\)). These changes were lost with aging (Figure 2).

As a result, older subjects disclosed a higher normalized LF component and a lower normalized HF component than the young subjects during non-REM sleep (LF, 62±12 versus 46±9 nu; and HF, 38±12 versus 54±9 nu; \(P<0.05\), respectively, in old and young subjects). The normalized LF and HF powers did not differ between the young and older subjects during wakefulness or REM sleep.

The LF/HF ratio of RR decreased from 1.7±0.7 to 1.0±0.4 during the shift from wakefulness to non-REM sleep (\(P<0.05\)) and increased again to 1.5±0.7 during REM sleep (\(P<0.05\) versus non-REM sleep in the young subjects). These changes were lost with aging as the older subjects disclosed an LF/HF ratio of RR of 2.9±1.2 during wakefulness, 2.6±1.6 during non-REM sleep, and 2.9±2.2 during REM sleep (\(P>0.17\)). The LF/HF ratio of RR was lower in the young subjects than the older subjects during awake periods (1.7±0.7 versus 2.9±1.2, respectively; \(P<0.05\)) and during non-REM sleep (1.0±0.4 versus 2.6±1.6, respectively; \(P<0.01\)). The LF/HF ratios of RR did not differ during REM sleep.

Reduction in sleep stage IV with aging blunted the increase in RR and in the normalized HF variability of RR during the transition from wakefulness to non-REM sleep (\(r=0.58\) and \(r=0.55\), \(P<0.05\), respectively).

**Figure 2.** Effects of aging on RR variability during non-REM and REM sleep. HF oscillations in RR became more predominant than LF oscillations in RR during non-REM sleep in normal young subjects (open bars). These changes were lost with aging (solid bars). +P<0.05 vs old; + +P<0.05 vs awake.

**Effects of Sleep-Related Changes in the Breathing Pattern on RR Variability**

The heart transplant recipients disclosed 330±48 minutes of non-REM sleep and 72±14 minutes of REM sleep. Breathing frequency decreased in these patients from 0.28±0.04 Hz during waking periods to 0.25±0.02 Hz during non-REM sleep (\(P<0.05\)). Respiratory variance also decreased to 65±33% of awake values during non-REM sleep (\(P<0.05\)).

These changes were similar to those recorded in the age-matched control subjects in whom breathing frequency was 0.30±0.04 Hz during wakefulness and decreased to 0.25±0.02 Hz during non-REM sleep (\(P=0.61\) versus changes in patients). The respiratory variance of the age-matched control subjects also decreased to 70±33% of awake values during non-REM sleep (\(P=0.75\) versus changes in patients).

RR of 759±94 ms did not increase during non-REM sleep in the heart transplant recipients but tended to increase during REM sleep (823±132 ms, \(P=0.05\)).

Cardiac denervation markedly reduced total RR variability to 116±124 ms² during awake periods, to 204±236 ms² during non-REM sleep, and to 245±292 ms² during REM sleep (all \(P<0.01\) versus age-matched subjects). The absolute HF variability of RR increased from 48±62 ms² during awake periods to 96±142 ms² during non-REM sleep (\(P<0.05\)) but did not differ from waking values during REM sleep.

**Discussion**

The novel findings of our study are (1) that the disappearance of deep sleep with aging impairs the nocturnal increase in cardiac vagal activity, as evidenced by a blunted increase in RR and HF RR variability, and (2) that mechanical effects of changes in the breathing pattern during sleep increase HF oscillatory profiles of RR during non-REM sleep.

**Aging, Sleep Architecture, and Heart Rate**

Twenty-four–hour ambulatory Holter recordings and heart rate recordings obtained during controlled conditions in awake subjects21,22 have revealed that the heart rate may increase as well as decrease with aging but that these changes are accompanied by a reduction in heart rate variability. The interpretation of these results is made difficult, however, by the confounding effects of modifications in physical activity23 and posture,16,17 higher cortical function,24 and the absence of polygraphic sleep recordings.18–22 Moreover, the magnitude and course of changes in the LF and HF components of heart rate variability depend on the age range studied, experimental conditions, and method used to assess heart rate variability.18–22

The mechanism responsible for the reduction in heart rate variability with aging remains speculative. Heart rate variability is greater in subjects with the lowest heart rate and decreases when sympathetic activity increases and vagal activity decreases.29 It has been shown that the decline in heart rate variability with aging is mainly, but not exclusively, due to a decline in parasympathetic function.21,26 However, several other components involved in the genesis of heart rate variability16,17 could also be specifically affected by aging, because the \(\beta\)-adrenergic modulation of cardiovascular function decreases with aging.30,31
function, renin-angiotensin system activity, and thermoregulation also decrease with age.

An important strength of our study resides in the fact that all recordings were obtained under carefully controlled supine conditions; thus, any possible confounding effects of changes in physical activity and posture on heart rate and heart rate variability were limited. Under these conditions, the supine resting heart rate did not differ between young and older subjects, but heart rate variability during awake periods was lower in the older subjects than in the younger volunteers.

Changes in heart rate variability were further assessed during sleep to determine whether aging altered the normal shifts in vagal predominance during non-REM sleep and sympathetic predominance during REM sleep. To the best of our knowledge, there are no previous published studies in which polysomnographic sleep recordings examine the effects of changes in sleep architecture with aging on heart rate and heart rate variability.

Our study revealed that aging decreased the amount of deep sleep and thereby impaired the nocturnal bradycardia and increase in HF variability of RR. Heart rate variability offers a unique insight into the autonomic modulation of heart rate and provides a marker of cardiac vagal outflow through the assessment of HF oscillations in RR. Thus, our data indicate that the vagal predominance during non-REM sleep in young subjects is lost with aging. These changes were observed despite the presence of 2 female subjects among the older volunteers. Age-related changes in sleep architecture affect male subjects earlier than females, but the difference in sex between the young and older subjects did not prevent detection of the effects of aging on non-REM sleep in our study.

Our results are in good accordance with previous observations that aging decreases sleep efficiency and deep sleep duration but increases the duration of light sleep. These changes are attributed to normal, age-related, neuronal alterations in brain areas that control sleep physiology. The originality of our study lies in the demonstration that these classic changes in sleep architecture with aging have a direct implication on nocturnal cardiovascular control. These findings are of importance, because the disappearance of nocturnal vagal predominance with aging is also seen after myocardial infarction and has been associated with an increased risk of cardiac events in this setting. Moreover, the incidence of cardiac arrhythmias increases with aging and the nonuniform nighttime distribution of acute cardiac events may implicate physiological triggers such as sleep state-dependent changes in autonomic nervous system activity.

Mechanical Effects of Breathing on RR Variability During Sleep

Respiratory oscillations in RR are mediated mainly by direct modulation of vagal effrent activity induced by baroreceptor responses to respiratory blood pressure fluctuations. However, cardiac-denervated patients also disclose limited oscillations in RR. These oscillations are synchronous with ventilation and are due to the mechanical effects of sinus node stretch induced by respiration-related changes in venous return. RR variability was markedly reduced in heart transplant patients (Their total power of RR was <4% of the total power of RR in the control subjects), and this finding argues strongly against a cardiac reinnervation in our patients. The analysis of changes in HF variability of RR in cardiac-denervated transplant recipients allowed us to determine whether the mechanical effects of changes in respiration affect the HF variability of RR during sleep. We are not aware of a previous study that has assessed heart rate variability during polygraphic sleep recordings in patients with heart transplants. Our study revealed that transition from wakefulness to non-REM sleep did not change RR but almost doubled the markedly depressed HF variability of RR in the heart transplant patients. This finding reveals that nonautonomic mechanisms favor, to a limited extent, increases in the HF variability of RR during non-REM sleep in humans. Breathing frequency and respiratory variance decreased during the shift from awake periods to non-REM sleep in our spontaneously breathing, recumbent, and sleeping transplant patients. Reducions in breathing frequency and tidal volume decrease HF oscillations in RR when seated transplant recipients breathe into a mouthpiece connected to a spirometer. Whether marked differences in the experimental conditions or peculiar changes in the breathing pattern, such as an enhanced contribution of rib cage movements to tidal volume during non-REM sleep, can explain why HF oscillations in RR increased despite reductions in breathing frequency and in respiratory variance requires further study. Further research is also needed to better delineate the effects of changes in tidal volume, not assessed in the present study, on RR variability during sleep in heart transplant recipients.

In conclusion, our study reveals that the normal, age-related disappearance of deep sleep impairs the nocturnal increase in cardiac vagal activity and (2) that nonautonomic mechanisms slightly increase HF oscillations in RR during non-REM sleep in humans.

Acknowledgments

These studies were supported by the Foundation for Cardiac Surgery, the National Fund for Research, Belgium (Dr van de Borne), a Pfizer Pharma grant, and the Marc Hurard Fondation (Dr Mezzetti). Belgium. We are indebted to Dr Karen Pickett for editorial assistance.

References

Effects of Aging and Cardiac Denervation on Heart Rate Variability During Sleep
Vincent Crasset, Silvia Mezzetti, Martine Antoine, Paul Linkowski, Jean Paul Degaute and Philippe van de Borne

Circulation. 2001;103:84-88
doi: 10.1161/01.CIR.103.1.84
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/103/1/84

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/