

Autonomic function in elderly uremics studied by spectral analysis of heart rate

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Background. Aging determines an altered response of the autonomic nervous system (ANS) to physiologic stresses. A widespread autonomic damage is well recognized in chronic renal failure (CRF).

Methods. We studied 30 CRF patients, aged 19 to 85 years, who were on bicarbonate hemodialysis. Surface electrocardiogram was recorded on lying and 65° head-up tilt standing positions. A dedicated software, using an autoregressive modeling technique, allowed to calculate power spectral analysis (PSA) of heart rate variability, assessing a low-frequency band in the range 0.03 to 0.15 Hz, and a high-frequency band in the range 0.15 to 0.33 Hz. Low-frequency and high-frequency components are regarded, but not invariably, as specific markers of sympathetic and parasympathetic activities, respectively, and the low-frequency/high frequency ratio as an index of sympathovagal balance.

Results. In normal controls, low-frequency band value and low-frequency/high-frequency ratio on standing resulted significantly reduced in the group older than 65 years when compared with those younger than 65 years; an opposite finding was seen in high-frequency band value on standing. In uremic patients, low-frequency band on lying resulted significantly lower only in elderly uremics when compared with elderly controls, whereas low-frequency band on standing was significantly lower in elderly than in younger uremics. Regression analysis showed a significant inverse relationship between aging and most low-frequency band values, especially in uremics. The comparison of linear regression models confirmed that a sympathetic autonomic derangement is greatly present in older uremics, in particular after 50 years of age.

Conclusion. Our data support assertion that combination of aging and CRF increases the chance of autonomic derangement being present.

A wide range of autonomic nervous system (ANS) dysfunction characterizes aging, as expression of an altered autonomic response to physiologic stresses. In particu-

lar, cardiovascular and thermoregulatory controls may be especially affected and the ANS derangement can be exacerbated by drugs or concomitant condition, such as prolonged bed rest or diabetes [1, 2]. In elderly, both sympathetic and parasympathetic nervous system pathways and baroreflex sensitivity are impaired and accordingly age-adjusted normal ranges have to be considered in the diagnostic workup of cardiovascular autonomic tests [3–6]. A recently developed more accurate method, able to demonstrate an early autonomic dysfunction, is represented by power spectral analysis (PSA) of heart rate variability in frequency domain [7, 8]. Using PSA of heart rate variability, an exponential decrease in both low-frequency and high-frequency bands has been demonstrated in healthy elderly individuals, but without change in sympathovagal balance during spontaneous breathing as well as in supine and standing positions [9–12].

In chronic renal failure (CRF), a widespread autonomic damage, confirmed by cardiovascular reflexes and PSA studies, has been well recognized as expression of damage most likely due to the action of still unknown toxins in the peripheral nervous system and in the central nervous system [13–15]. Robinson and Carr [16] have recently reviewed the subject. The influence of aging on autonomic neuropathy occurring in dialysis patients has been investigated in few studies, exclusively using cardiovascular reflex tests with different results. Vita et al [17] presented evidences for a higher vulnerability of ANS to uremic toxins in elderly than in middle aged uremics, whereas Jassal, Douglas, and Stout [18] failed to find a higher prevalence of autonomic dysfunction in aging population with uremia.

The aim of our study was to assess the relationship between CRF and aging in causing derangement of autonomic pathways, using PSA of heart rate variability.

METHODS

We studied 30 patients with chronic uremia, aged 19 to 85 years (mean \pm SD) (58 ± 15 years) (22 men and 8 women). They were on bicarbonate hemodialysis

Key words: uremia, hemodialysis, aging, autonomic neuropathy, power spectral analysis.

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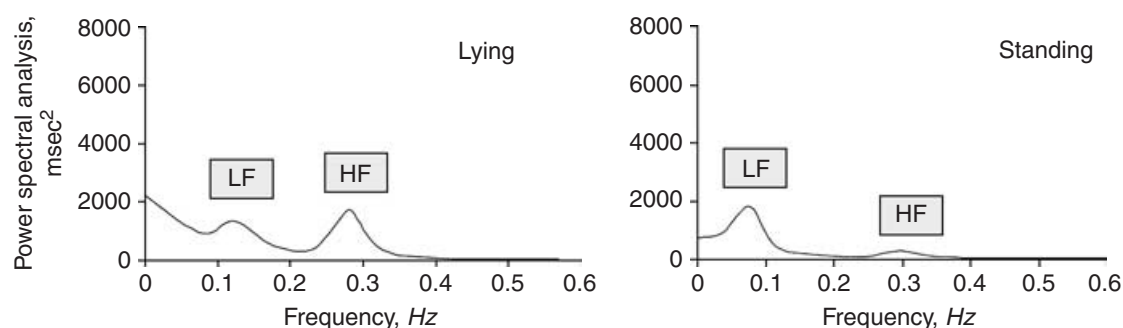


Fig. 1. Components of the power spectrum of heart rate variability in a normal subject on lying and on standing. LF is low-frequency band; HF is high-frequency band.

(4 hours, three times per week). The dialysis duration ranged from 1 month to 264 months (39 ± 58 months). None of them were taking medications acting on the ANS or had diabetes mellitus, severe heart failure, ischemic heart disease, bronchopneumopathy, or amyloidosis. Thirty-two age- and gender-matched normal individuals aged 22 to 85 years of age (55 ± 17 years) were investigated as control group.

After informed consent was obtained and each subject was requested to refrain from smoking and drinking coffee for at least 12 hours before the test, which was performed early in the morning or afternoon. The uremic patients were examined in a dialysis-free day.

After 10 minutes' rest, all subjects underwent a surface electrocardiogram from a thoracic lead taken while supine and R-R intervals were recorded for 10 minutes. They were then moved to a standing position ($0 \rightarrow 65^\circ$) by a tilting table, and again, after at least 4 minutes of stabilization, the heart rate was measured for another 10-minute period. Dedicated software (Sedico-HS srl, Padua, Italy) recognized the individual electrocardiographic R wave and the corresponding R-R intervals. By PSA, the series of 500 sequential R-R intervals was decomposed into a sum of sinusoidal functions of different amplitudes and frequencies by the Fourier transform algorithm. The result was displayed (power spectrum) with the magnitude of variability as a function of frequency. Thus, the power spectrum reflected the amplitude of the heart rate fluctuations present at different oscillation frequencies, providing a low-frequency band in the range 0.03 to 0.15 Hz, and a high-frequency band in the range 0.15 to 0.33 Hz (Fig. 1). Low-frequency and high-frequency components are regarded, but not invariably, as specific markers of sympathetic and parasympathetic activities, respectively, and the low-frequency/high-frequency ratio as reflecting sympathovagal balance [5, 6, 19].

Statistical analysis

The PSA values are expressed as mean \pm SEM. In some analysis, uremics and controls were divided in two sub-

groups on the basis of age: younger than 65 years ($N = 20$ and $N = 19$, respectively) or older than 65 years ($N = 10$ and $N = 13$, respectively). Student *t* test was used to determine differences between subgroups. The relationship between variables was determined by linear regression analysis. Linear regression models, assessing the relationship between each PSA parameter and age in normal controls and in uremic patients, were compared in regard to correlation coefficient (*r*), slope of regression line and intercept (analysis of covariance). A level of significance of $P < 0.05$ was considered.

RESULTS

In control subjects, total variance of heart rate, and low-frequency band value and low-frequency/high-frequency ratio on standing resulted significantly reduced in the group older than 65 years when compared with those younger than 65 years (Table 1). An opposite finding was seen in high-frequency band value on standing.

In uremic patients, total variance was significantly lower in the group younger than 65 years versus age-matched controls. Low-frequency band on lying resulted significantly lower only in elderly uremics when compared with elderly controls, whereas low-frequency band on standing was significantly lower in elderly than in younger uremics (Table 1).

Regression analysis showed a significant inverse relationship between aging and most low-frequency band values, especially in uremics, as expression of a predominant sympathetic damage with increasing age (Table 2). No significant relationship was found between dialytic age and PSA of heart rate components in uremic patients.

The comparison of linear regression models (age versus each PSA parameter) obtained in normal controls and uremics showed significant differences in three cases. Slope of regression line was significantly different for low-frequency band value in both lying and standing positions ($P < 0.03$ and $P < 0.04$, respectively) (Fig. 2). Low-frequency values in uremics were reduced with increasing age, in particular after 50 years. There were no significant differences for high-frequency band

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