*Kidney International, Vol. 67 (2005), pp. 1521–1525*

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

**RITA DI LEO, GIUSEPPE VITA, CORRADO MESSINA, and VINCENZO SAVICA**

*Clinica Neurologica 2, Department of Neurosciences, Psychiatry and Anaesthesiology, Policlinico Universitario, Messina, Italy; Chair of Nephrology, University of Messina, Nephrology and Dialysis Unit, Papardo Hospital, Messina, Italy*

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

*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 particular, 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 sympatovagal 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 ± SD) (58 ± 15 years) (22 men and 8 women). They were on bicarbonate hemodialysis

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

Received for publication July 31, 2004
and in revised form October 5, 2004
Accepted for publication October 27, 2004

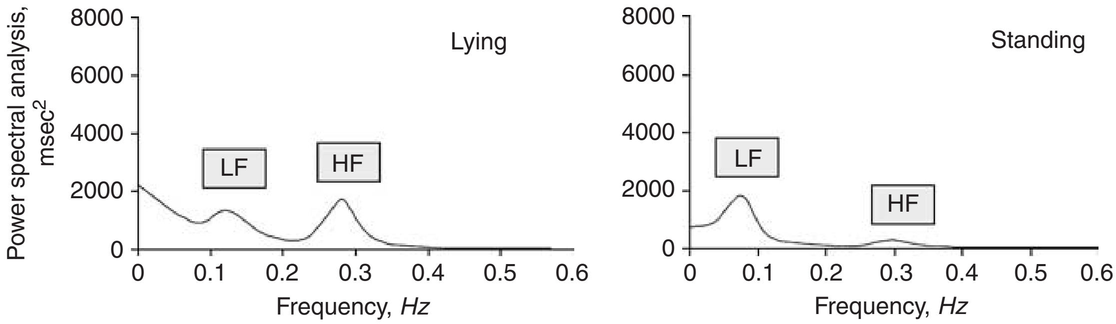


**Fig. 1. Components of the power spectrum of heart rate variability in a normal subject on lying and on standing.** LF is low-frequency band; HF is high-frequency band.

(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 subjects 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 → 65°) 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 ± SEM. In some analysis, uremics and controls were divided in two subgroups 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

**Table 1.** Total variance and spectral components normalized by total variance in uremics and controls

| | Younger than 65 years | | Older than 65 years | | |
|---|---|---|---|---|---|
| | Controls | Uremics | Controls | Uremics | Significance |
| Total variance *msec*$^2$ | 1826 ± 279 | 478 ± 102 | 817 ± 282 | 736 ± 306 | $P < 0.000005^a$<br>$P < 0.02^b$ |
| Lying | | | | | |
| Low-frequency *nu* | 58 ± 6 | 51 ± 7 | 52 ± 7 | 30 ± 8 | $P < 0.05^c$ |
| High-frequency *nu* | 21 ± 4 | 25 ± 5 | 31 ± 4 | 29 ± 7 | NS |
| Low-frequency/high-frequency ratio | 3.6 ± 4 | 7.1 ± 2 | 2.6 ± 0.7 | 2.3 ± 1.1 | NS |
| Standing | | | | | |
| Low-frequency *nu* | 75 ± 4 | 62 ± 7 | 45 ± 7 | 32 ± 9 | $P < 0.0004^b$<br>$P < 0.02^d$ |
| High-frequency *nu* | 16 ± 3 | 13 ± 3 | 27 ± 4 | 23 ± 5 | $P < 0.02^b$ |
| Low-frequency/high-frequency ratio | 7.3 ± 1.5 | 12.3 ± 3.8 | 2.9 ± 1.1 | 1.8 ± 0.7 | $P < 0.03^b$ |

[a]Controls younger than 65 years vs. uremics younger than 65 years; [b]controls younger than 65 years vs. controls older than 65 years; [c]controls older than 65 years vs. uremics older than 65 years; [d]uremics younger than 65 years vs. uremics older than 65 years. Values are expressed as the mean ± SEM. NS is not significant.

**Table 2.** Regression analysis of power spectral analysis (PSA) parameters vs. aging

| | r | Significance |
|---|---|---|
| Lying | | |
| Low-frequency controls | 0.094 | NS |
| Low-frequency uremics | −0.415 | $P < 0.03$ |
| High-frequency controls | 0.105 | NS |
| High-frequency uremics | 0.122 | NS |
| Low-frequency/high-frequency controls | 0.062 | NS |
| Low-frequency/high-frequency uremics | −0.248 | NS |
| Standing | | |
| Low-frequency controls | −0.371 | $P < 0.04$ |
| Low-frequency uremics | −0.618 | $P < 0.0003$ |
| High-frequency controls | 0.269 | NS |
| High-frequency uremics | 0.321 | NS |
| Low-frequency/high-frequency controls | −0.206 | NS |
| Low-frequency/high-frequency uremics | −0.547 | $P < 0.002$ |

NS is not significant.

value (Fig. 3). Comparison of regression lines for low-frequency/high-frequency ratio on standing showed a significantly different slope between controls and uremics ($P < 0.05$) (Fig. 4).

## DISCUSSION

Although traditional cardiovascular autonomic tests still remain the cornerstone in the clinical approach to individual patients with suspected autonomic dysfunction, they have been criticized as being dependent on patient's cooperation and of little use in the investigation of the sympathetic pathway. Several studies have provided evidence that specific heart rate PSA components, revealed in a frequency domain, may better allow to explore in detail cardiovascular regulatory mechanisms. Conversely, although PSA of heart rate variability is an accurate method for investigating the autonomic function in a given population, its clinical usefulness is still limited and great caution is needed in the evaluation of single individuals [7, 8].

In healthy conditions, PSA studies showed with aging a reduction of low-frequency power as expression of a lower sympathetic activity, which has been explained as protective feature making individuals of advanced age less vulnerable to coronary artery accidents and sudden death, and also an increase of high-frequency power that could provide protection against arrhythmias and acute cardiac events [11, 12].

Only few studies investigated the relationship between aging and uremia showing, not invariably, in elderly uremics a more extensive parasympathetic and sympathetic dysfunction. Vita et al [17] found a higher parasympathetic and sympathetic damage using age-adjusted confidence limits of cardiovascular autonomic tests. However, Jassal, Douglas, and Stout [18] demonstrated that older dialysis patients have the highest prevalence of cardiovascular autonomic impairment but that no potentiation occurs when both advanced age and CRF coexist.

The present study has examined for the first time the relationship between aging and uremia using PSA of heart rate. The results obtained in normal individuals confirmed previous reports, showing a reduction of low-frequency band value and low-frequency/high-frequency ratio and an increase of high-frequency band value with increasing age. In older uremics, a predominant sympathetic damage was evidenced by reduced low-frequency band values on lying as well on standing positions. This finding was supported also by the existence of an inverse relationship between age and low-frequency values as well as low-frequency/high-frequency ratio, considered a good indicator of sympathovagal balance. All together our results agree with previous conclusion coming out from PSA evaluation that the conviction of a major parasympathetic damage in CRF patients had to be modified in favor of a more widespread autonomic dysfunction involving both sympathetic and parasympathetic pathways [14]. Actually, just using conventional cardiovascular autonomic tests, we had already observed both

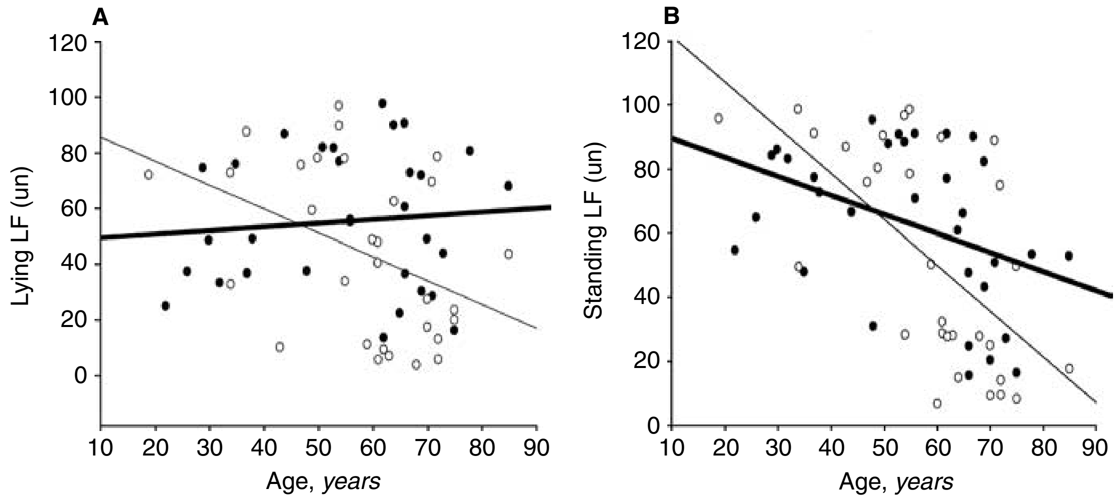


**Fig. 2. Comparison of linear regression models [age vs. low-frequency (LF) band value] obtained in controls (● and thick line) and in uremics (○ and thin line) on lying (*A*) and on standing (*B*) positions.** There was a significant difference in the slope of regression line on lying ($P < 0.03$) and on standing ($P < 0.04$).

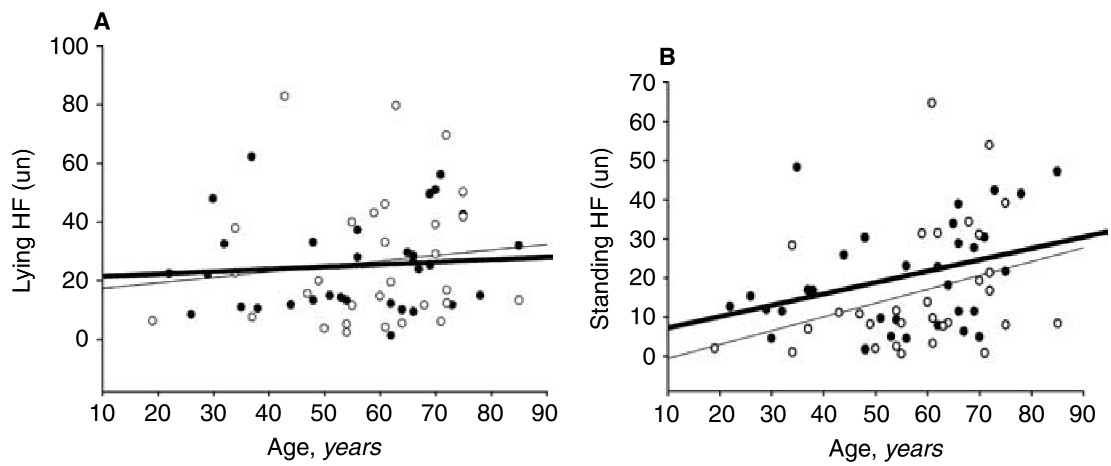


**Fig. 3. Comparison of linear regression models [age vs. high-frequency (HF) band value] obtained in controls (● and thick line) and in uremics (○ and thin line) on lying (*A*) and on standing (B) positions.** There was no significant difference.

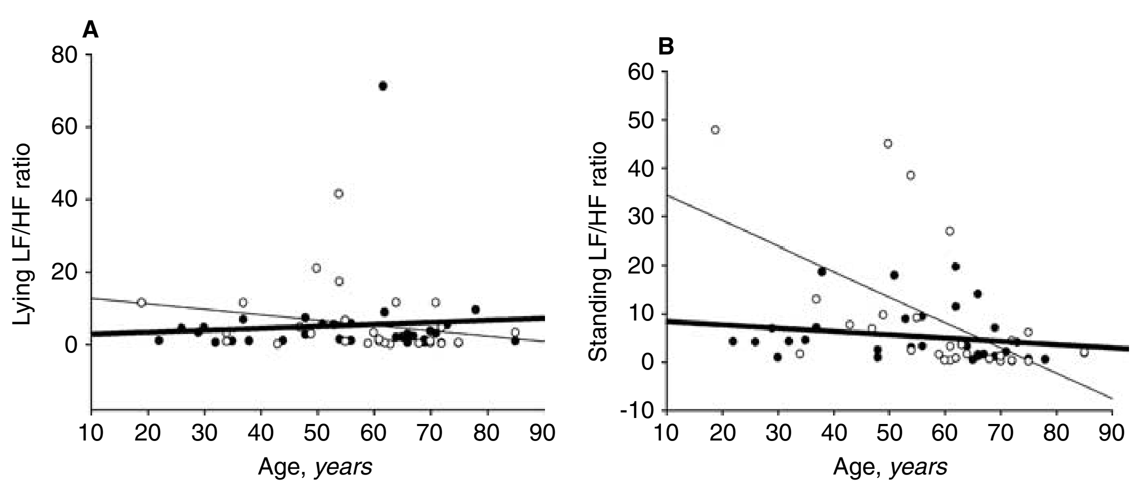


**Fig. 4. Comparison of linear regression models [age vs. low-frequency/high-frequency (LF/HF) value] obtained in controls (● and thick line) and in uremics (○ and thin line) on lying (*A*) and on standing (*B*) positions.** There was a significant difference in the slope of regression line only on standing ($P < 0.05$).

sympathetic and parasympathetic damage in aging uremics [17]. Moreover, dialytic age seems not to influence occurrence of autonomic dysfunction. High-frequency power on standing showed a trend toward an increase with aging in uremics, but not reaching a statistical significance. It could demonstrate an impairment of the physiologic protection against arrhythmias and sudden death [12], and express a hazard for life.

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. A steeper slope of regression line indicates a higher age-related deterioration of autonomic function in uremia than that occurring in elderly healthy population as consequence of an impaired cardiovascular homeostasis [12].

## CONCLUSION

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

*Reprint requests to Dr. Rita Di Leo, Clinica Neurologica 2, Policlinico Universitario, 98125 Messina, Italy.*
*E-mail address: rita_dileo@tin.it*

## REFERENCES

1. Kaijser L, Sachs C: Autonomic cardiovascular responses in old age. *Clin Physiol* 5:347–357, 1985
2. Collins KJ, Exton-Smith AN, James MH, Oliver DJ: Functional changes in autonomic nervous responses with ageing. *Age Ageing* 9:17–24, 1980
3. Piha SJ: Cardiovascular autonomic reflex tests: normal responses and age-related reference values. *Clin Physiol* 11:277–290, 1991
4. Vita G, Princi P, Calabrò R, *et al*: Cardiovascular reflex tests. Assessment of age-adjusted normal range. *J Neurol Sci* 75:263–274, 1986
5. Lipstitz LA: Ageing and the autonomic nervous system, 55, in *Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System*, 4th ed., edited by Mathias CJ, Bannister R, Oxford, Oxford University Press, 1999, pp 535–544
6. O'Mahony D, Bennett C, Green A, Sinclair AJ: Reduced baroreflex sensitivity in elderly humans is not due to efferent autonomic dysfunction. *Clin Sci* 98:103–110, 2000
7. Pagani M, Malfatto G, Pierini S, *et al*: Spectral analysis of heart rate variability in the assessment of autonomic diabetic neuropathy. *J Auton Nerv Syst* 23:143–153, 1988
8. Omboni S, Parati G, Di Rienzo M, *et al*: Blood pressure and heart rate variability in autonomic disorders: A critical review. *Clin Auton Res* 6:171–182, 1996
9. Schwartz JB, Gibb WJ, Tran T: Aging effects on heart rate variation. *J Gerontol* 46:99–106, 1991
10. Lipstitz LA, Mietus J, Moody GB, Goldberger AL: Spectral characteristics of heart rate variability before and during postural tilt. Relation to aging and risk of syncope. *Circulation* 81:1803–1810, 1990
11. Piccirillo G, Fimognari FL, Viola E, Marigliano V: Age-adjusted normal confidence intervals for heart rate variability in healthy subjects during head-up tilt. *Int J Cardiol* 50:117–124, 1995
12. Piccirillo G, Bucca C, Bauco C, *et al*: Power spectral analysis of heart rate in subjects over hundred years old. *Int J Cardiol* 63:53–61, 1998
13. Vita G, Dattola R, Calabro R, *et al*: Comparative analysis of autonomic and somatic dysfunction in chronic uraemia. *Eur Neurol* 28:335–340, 1988
14. Vita G, Bellinghieri G, Trusso A, *et al*: Uremic autonomic neuropathy studied by spectral analysis of heart rate. *Kidney Int* 56:232–237, 1999
15. Savica V, Musolino R, Di Leo R, *et al*: Autonomic dysfunction in uraemia. *Am J Kidney Dis* 38(Suppl 1):S118–S121, 2001
16. Robinson TG, Carr SJ: Cardiovascular autonomic dysfunction in uraemia. *Kidney Int* 62:1921–1932, 2002
17. Vita G, Savica V, Marabello L, *et al*: Occurrence of uraemic autonomic dysfunction in relation to age. *Acta Neurol Scand* 76:468–472, 1987
18. Jassal SV, Douglas JF, Stout RW: Prevalence of central autonomic neuropathy in elderly dialysis patients. *Nephrol Dial Transplant* 13:1702–1708, 1998
19. Bellavere F, Balzani I, De Masi G, *et al*: Power spectral analysis of heart-rate variations improves assessment of diabetic cardiac autonomic neuropathy. *Diabetes* 41:633–640, 1992