Autonomic nervous function during haemodialysis assessed by spectral analysis of heart-rate variability

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INTRODUCTION

Acute hypotension has been recognized as being the most important and frequent complication of haemodialysis treatment occurring in up to 30% of patients [1, 2]. It is well known that the reduction in circulating blood volume due to both ultrafiltration of plasma water through the dialyser and osmotic shift of extracellular fluid into the intracellular compartment is one of the main determinants for haemodialysis-induced cardiovascular collapse [3–5]. Although the underlying mechanisms of the acute event are still poorly understood, it appears clear that cardiovascular regulatory mechanisms that are unable to compensate for haemodialysis-induced hypovolaemia play a critical role in the pathogenesis of acute hypotension. In fact, several factors involved in haemodialysis-induced hypotension may weaken the compensatory response to hypovolaemia: impaired cardiac performance in left ventricular hypertrophy and myocardial interstitial fibrosis [6–8], inadequate increase in total peripheral resistance due to heat stress [9] or acetate dialysate [10, 11] and organic damage of the autonomic nervous system, as occurs in patients with diabetes [11–13] or hypertension [14] and in the elderly [15]. These factors may cause a decrease in the overall sensitivity of the baroreceptor-mediated reflex [16], and a consequent inefficiency in the short-term regulation of arterial pressure.

The present study was undertaken to evaluate the efficiency of autonomic control in haemodialysis patients. We assessed the state of short-term autonomic regulation by analysing heart-rate variability during a haemodialysis session. In fact, spontaneous fluctuations in heart period carry a great deal of information about the state of cardiovascular neural controls [17–20], and spectral analysis of such fluctuations seems to be a reliable tool for investigating the efficiency of short-term compensatory response to perturbations of the circulatory system.

Several aspects of heart-rate variability have been explored in both physiological and clinical studies (see e.g. [18, 21, 22]), and it has been shown that, in healthy subjects, three significant physiological...
rhythms, oscillating at specific frequencies, are hidden in heart-period fluctuations. Such rhythms can be detected by means of spectral analysis (Fig. 1) and can be characterized by the powers in the three bands [17]: very low frequency (VLF; <0.06 Hz), low frequency (LF; 0.06–0.15 Hz) and high frequency (HF; 0.15–0.4 Hz). The power component in the HF band is correlated with the vagal tone on the sinus node, so that this spectral component of variability is regarded as a marker of efferent parasympathetic activity [19]. The component in the LF band is due to baroreceptor-mediated regulation and includes contributions from both sympathetic and parasympathetic divisions [20]. Finally, the power in the VLF band has been linked with humoral and temperature regulations and with slow vasomotor activity [22].

On the basis of this spectral decomposition, we studied the beat-to-beat variability of the heart period in 30 patients with chronic renal failure, with and without a past history of acute hypotension. Spectral analysis was used to calculate the powers in LF and HF bands, and the LF/HF power ratio was considered an index to assess the short-term autonomic response to haemodialysis-induced hypovolaemia. A preliminary report of this study has appeared [23].

MATERIALS AND METHODS

Patient selection

Patients were studied at the Nephrology and Dialysis Unit of the Ospedale Maggiore in Trieste (Italy). The protocol of the study was approved by our institutional review board and consent was obtained from each patient after detailed description of the procedures.

Two groups of patients with end-stage renal failure undergoing regular haemodialysis treatment were selected. The first group included 15 hypotension-resistant patients, classified as stable, none of whom had collapsed during the last 12 treatments (4 female, 11 male; age 54.9 ± 11.2 years; duration of dialysis 79.9 ± 58.8 months; body weight 65 ± 9.7 kg); the second group consisted of 15 hypotension prone patients, classified as unstable, whose last twelve treatments were complicated by at least two episodes of cardiovascular collapses (14 female, 1 male; age 73.6 ± 9.1 years; duration of dialysis 46.2 ± 42.2 months; body weight 59 ± 14.7 kg).

Cardiovascular collapse was defined as a fall of systolic blood pressure below 95 mmHg with either a drop in blood pressure of at least 20 mmHg or the presence of symptoms related to hypotension. All the sessions considered in this study ended without the occurrence of collapse.

Etiology of renal failure in stable patients was glomerular disease (7), nephroangiosclerosis (2), vasculitis (1), vesicoureteral reflux nephropathy (2), renal tuberculosis (1), unknown (2). In unstable patients renal failure was secondary to: glomerular disease (3), nephroangiosclerosis (3), vasculitis (1), pyelonephritis (1), renal tuberculosis (2), polycystic kidney disease (2) and unknown (3).

None of the patients had a past clinical history of diabetes mellitus or congestive heart failure, or were receiving medications that may affect the cardiovascular or autonomic nervous system. No one showed signs of autonomic neuropathy. No significant differences in respiratory patterns were observed during dialysis between the two groups.

Protocol

All patients were treated three times a week, for 3–4 h, with a cuprophan dialyser of 1.3 m², blood flow of 300 ml/min and dialysate flow of 500 ml/min. Dialysate composition was (mmol/l): Na⁺, 143; K⁺, 2; Ca²⁺, 1.75; Mg²⁺, 0.5; Cl⁻, 110.5; HCO₃⁻, 35; acetate, 4 mmol/l; and glucose, 1 g/l. The temperature of the dialysate was kept constant at 37°C. Ultrafiltration was constant at a mean rate of 793 ± 145 ml/h and ultrafiltration rates, normalized with respect to the body weight, were 12.3 ± 2.4 ml h⁻¹ kg⁻¹ (stable) and 13.4 ± 2.6 ml h⁻¹ kg⁻¹ (unstable) with no significant difference between the two groups.

Per cent changes in blood volume were continuously estimated as the ratio between the current and the initial haemoglobin concentration, measured by an optical probe placed in the arterial line of the extracorporeal circuit (Hemoscan, HOSPAL-DASCO S.p.A., Medolla, Italy). Blood pressure was measured non-invasively every 10 min with an automatic blood-pressure monitor. During the entire
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Heart-rate variability analysis

For each R–R sequence, missing beats were automatically detected and filled in. Beats thus inserted were 6.1 ± 2.6% of the total beats for the stable patients and 6.5 ± 2.4% for the unstable ones. In order to characterize heart-period variability in the time domain, for each R–R sequence the root mean square of consecutive R–R interval differences (MSSD) [24] was calculated over 30-min intervals.

For the power-spectrum computation, an evenly spaced time series was derived by using the method proposed by Berger et al. [25], with an oversampling frequency of 4 Hz. From the entire oversampled R–R time series, 120 epochs were extracted by shifting a rectangular window 3-min long (720 R–R samples) with a step of 1.5 min, producing epochs overlapped by one-half. Since we were interested in short-term autonomic regulation, long-term fluctuations with a period equal to or greater than the window length, and then assignable to the VLF band, were removed from each epoch by linear regression [26]. In this way, the effects of circulating hormones involved in long-term autonomic regulation, such as noradrenaline, adrenaline, angiotensin II, etc., that influence heart-period fluctuations within the VLF band [27], were neglected.

Epoch by epoch, power-spectral-density was estimated by means of an autoregressive technique that yields an efficient filtering of noise effects and an accurate frequency resolution, compared with fast Fourier transform, even when using short data series [26]. In fact, with autoregressive techniques, a few parameters are estimated over a large set of data, with pre-selection of an appropriate autoregressive model order. Model order was chosen by a statistically based criterion (the minimum description length [28]) after having previously verified its substantial independence of the patient status.

Spectral analysis techniques require that the heart-period series be analysed during epochs in which the cardiovascular system is in a steady state. Since haemodialysis-induced perturbation occurs over a long time-scale (3–4 h), the steadiness of the phenomenon was assumed in the short-term and, after specific tests, the epoch length was chosen sufficiently short to satisfy this assumption. However, specific tests with shorter windows (up to 2 min) allowed us to verify the low sensitivity of the results on this parameter [29].

The autoregressive spectrum was calculated through the modified covariance method, which is the most effective among those based on least-squares linear prediction [26]. Powers in LF and HF bands were then computed by integrating the spectrum in the ranges 0.06–0.15 Hz and 0.15–0.4 Hz respectively.

Statistical analysis

The median value over periods of dialysis was used to average the time course of parameters. To characterize stable and unstable groups, mean and SD were used. Mean values calculated in the two groups were compared by using one-way analysis of variance (ANOVA). Differences were considered statistically significant for \( P \leq 0.05 \).

RESULTS

No significant differences were observed when comparing the time course of blood volume per cent reduction in stable and unstable patients (Fig. 2). At the end of the third hour of dialysis the per cent blood volume was 85 ± 3.5 in the stable group and 86 ± 2.8 in the unstable one, hence the hypovolaemia induced by haemodialysis was similar in the two groups of patients.

To evaluate the changes in systolic pressure and heart rate during the dialysis, for each patient the median value of these haemodynamic parameters was calculated within the first 3 min of dialysis and over consecutive 30-min intervals. Systolic pressure in hypotension-resistant patients tends to remain stable during the dialysis, with no significant changes with respect to the initial value (Fig. 3). On the other hand, the hypotension-prone group, after the first hour of dialysis, showed a slight decrease in systolic arterial pressure (Fig. 3). Pressure response only partially reflected the classification of patients as hypotension prone and hypotension resistant, since acute hypotension did not occur in the sessions.

Fig. 2. Blood volume reduction during dialysis in stable (○) and unstable (+) groups. Mean values and SDs of the per cent volume with respect to the initial value, calculated every 30 min, are shown. No significant difference was observed between the two groups \((P > 0.05)\).
considered in this study. In fact, the difference in the pressure response between stable and unstable groups was not statistically significant. A continuous reduction in heart period was observed during dialysis in both groups (Fig. 4). However, at the end of dialysis the difference with respect to the beginning was significant ($P < 0.05$) only in the unstable group.

In order to quantify the heart-period variability in the time domain, MSSD, considered to be an indicator of parasympathetic activity [24], was calculated over 30-min intervals. The time course of this index for the two groups of patients is given in Fig. 5. The unstable group was characterized by higher values, which could denote a predominant parasympathetic activity. However, because of high SDs, no significant differences in this index were found on comparing stable and unstable groups.

Since no relevant differences were observed by comparing, in the time domain, the haemodynamic parameters of stable and unstable groups, analysis of heart-period variability in the frequency domain was performed. Representative time patterns of the heart-period power spectrum for stable and unstable patients are shown in Fig. 6. In this Figure, the spec-
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trum calculated over 3-min epochs is progressively represented, in a pseudo-three-dimensional view, as a function of dialysis time. On comparing spectral time patterns it was evident that in a stable patient the power was mainly in the LF band (Fig. 6, upper panel), whereas in an unstable patient it tended to prevail in the HF band (see Fig. 6, lower panel). This observation was confirmed in all the R–R series analysed in the present study: 198 ± 200 compared with 60 ± 82 ms⁻¹ for stable and 72 ± 46 compared with 95 ± 67 ms⁻¹ for unstable patients (LF versus HF).

In order to make a more direct quantification of this phenomenon, for each R–R series the median values over the entire dialysis of the power in the HF and in the LF band were calculated and then compared, as shown in Fig. 7. Stable and unstable patients lie in two different regions of the plane, clearly separated by a bisector. For both stable and unstable groups the power in the LF band was nearly proportional to that in the HF band. It is worth noting that the slope of the regression lines was significantly different and the ratio between the power in LF and in HF bands (subsequently referred to as the LF/HF ratio) was systematically greater in stable patients (2.15 ± 0.69) than in unstable ones (0.57 ± 0.25). For this reason the LF/HF ratio rather than the single LF or HF powers was used to characterize the two groups of patients.

During the entire dialysis a markedly different time course of the LF/HF ratio was observed in stable and unstable patients (see e.g. Fig. 8): the LF/HF ratio tended to remain > 1 in stable and < 1 in unstable patients. This result was confirmed in all patients and it was independent of the LF/HF value at the initial stage of dialysis (0–10 min). In particular, there were several unstable patients (40%) whose LF/HF ratio was > 1 at the beginning of the session and became lower than the unity threshold after a few epochs (see Fig. 8). The opposite was observed in some stable patients (30%). Moreover, it was noted that stable patients showed a time evolution of the LF/HF ratio with larger variations than the unstable patients (see Fig. 8).

The median value of the LF/HF ratio was computed for each patient over consecutive 30-min intervals (Fig. 9). After the first 30 min of dialysis, stable and unstable patients showed clearly different LF/HF values, and the difference persisted during the following intervals. Although single patients showed slight trace-to-trace variations, during the second hour the two ranges of the LF/HF ratio did not overlap and stable and unstable groups were completely separated. Moreover, the median calculated over 3 h of dialysis was clearly different in the two groups of patients (Fig. 9, bottom right panel).

One-way ANOVA performed on the values of LF/HF is shown in Fig. 10 where each box includes from the 25th to 75th percentiles of data. During the first 6 min of dialysis the two groups partially overlapped because of the initial value of the LF/HF ratio, which was < 1 in some stable patients and > 1 in some unstable patients. The distance between boxes increased during dialysis and the probability, P, of equal means for the two groups became < 0.01 after the first 30 min.

**DISCUSSION**

Spectral analysis of the beat-to-beat heart-period variability was used in the present study to assess how hypotension-prone and hypotension-resistant patients with chronic renal failure respond to hypovolaemia induced by haemodialysis. In both stable and unstable groups there was a strict correlation between the power in LF and HF bands in accordance with previous investigations showing that autonomic activation influences both bands [18, 22]. Nevertheless, this study importantly points out that hypotension-prone and hypotension-resistant patients exhibit markedly different spectral patterns (Fig. 6) with a considerably different value of the LF/HF power ratio. In particular, in stable patients
this ratio was >1, and tended to increase, while blood volume progressively decreased because of the dialysis process. On the other hand, in unstable patients the ratio remained <1 during the entire dialysis session (Fig. 10). The LF/HF ratio, formerly proposed by several authors as a marker of the sympatho-vagal balance [30–33], proved to be an efficient index to discriminate between hypotension-prone and hypotension-resistant patients and no other haemodynamic parameter considered in this study was found to be as efficient.

Since the per cent blood-volume reduction in the course of dialysis was similar in stable and unstable groups, the different LF/HF ratio cannot be explained as being a consequence of different circulatory perturbations.

It has been observed that in elderly subjects the increase in power in the LF band in response to standing was not as large as in young subjects [34]. The two groups under study reflect the fact that older patients are more frequently subject to collapse than younger ones and, therefore, the age in the unstable group was significantly higher than that in the stable one. In order to assess the influence of aging on the discrimination between stable and unstable patients by means of the LF/HF ratio, two subgroups, each of eight patients, with no significant difference in age, were pooled (see Fig. 9). The LF/HF ratio was slightly lower in the stable subgroup rather than in the entire stable group (1.9 ± 0.5 compared with 2.3 ± 0.8), whereas no significant changes were observed in the unstable sub-

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**Fig. 9.** Individual (main panels) and cumulative (inset panels) LF/HF ratios in stable (white) and unstable (grey) patients. The individual values indicate the medians of the LF/HF ratios computed over the 30-min interval indicated. Cumulative values refer to the mean and SD of the individual values of the stable and unstable groups. The last panel refers to the entire dialysis and demonstrates the clear distinction between the two groups that the index provides (P<0.001). Circles indicate two age-matched subgroups (see Discussion).
The LF/HF ratio during dialysis showed significant differences between stable (upper boxes) and unstable (lower boxes) patients. The 'notches' in the boxes indicate the 95% confidence intervals for the estimated means. In stable patients, the power in the LF band rises during dialysis, whereas a moderate decrease is observed in unstable patients. This result is consistent with previous studies on nocturnal pressure and heart rate variability in uraemic patients.

In stable patients, the LF/HF ratio decreased during dialysis, whereas a greater value was observed in unstable patients. This ratio was found to be a representative marker of the baroreceptor-mediated autonomic response. The LF/HF ratio in unstable patients tended to remain significantly different from the stable group, even after adjusting for baseline values.

When the cardiovascular system is stressed with a loss of blood volume, such as mild haemorrhage, or in haemodialysis-induced hypovolaemia, heart-period fluctuations tend to synchronize on the LF oscillation and, as a consequence, the LF/HF ratio rises. The increase in the LF/HF ratio during the first 2 h of dialysis in stable patients indicates a reduction in overall cardiovascular variability, observed in uraemic patients with normal baroreflex function before haemodialysis. In unstable patients, this ratio was found to be a representative marker of the baroreceptor-mediated autonomic response.

Previous research comparing the autonomic function in hypotension-prone and hypotension-resistant uraemic patients led to apparently contrasting results. Lilley et al. [50] suggested a defect in the afferent limb of baroreceptor or cardiopulmonary arcs of unstable patients. Subsequent studies have failed to demonstrate autonomic control impairment in a hypotension-prone dialysis population. In particular, Converse et al. [54] did not observe significant differences between the autonomic function of hypotension-prone and hypotension-resistant patients during the inter- and intra-dialysis periods. In accordance with our results, they observed only a moderate decrease in arterial pressure and a proportionate rise in heart rate in hypotension-prone patients. They assessed peripheral-resistance baroreflex regulation, which seemed to operate normally until the onset of vasovagal collapse.

When acute hypotension occurred, a fast, paradoxical withdrawal of sympathetic vasocon-
stricter drive was observed. As these authors suggested, this event was probably caused by a very low level of atrial pressure that triggered a paradoxical sympatho-inhibitory reflex through the cardiac receptors.

It is well known that pressure levels in the circulatory system are kept quite stable as long as cardiovascular perturbations remain within the operative range of the regulatory mechanisms. A reduced sensitivity in baroreceptor-mediated pressure regulation could cause a contraction of this operative range, reducing the regulatory capability. On this basis, one might speculate that as long as cardiovascular perturbations, due to blood volume reduction, lie within the baroreflex operative range, unstable and stable patients seem to regulate alike and, as shown in this paper, no significant differences can be found between stable and unstable groups on the basis of classical haemodynamic parameters. Only when circulatory perturbations overcome the limits of the operative range of regulatory mechanisms do the effects of perturbation become dramatically evident. Parameters obtained by spectral analysis of heart-rate variability, in particular the LF/HF ratio, can be used to evaluate the autonomic function, aside from the circulatory perturbation. For this reason, spectral analysis of heart-rate variability seems to represent an adequate tool for quantifying the short-term autonomic response of patients under haemodialysis treatment, allowing a clear distinction between hypertension-prone and hypotension-resistant patients even when they behave alike haemodynamically.

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REFERENCES


