Hemodynamic Patterns and Spectral Analysis of Heart Rate Variability during Dialysis Hypotension

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Abstract. Intradialytic hypotension, a major source of morbidity during hemodialysis and ultrafiltration, is often accompanied by paradoxical bradycardia. Relatively little is known about the sequential changes in autonomic nervous system activity up to and during the hypotensive episode. Continuous, beat-to-beat measurements of BP and heart rate were made during hemodialysis in patients prone ($n = 8$) and not prone ($n = 11$) to develop intradialytic hypotension. Off-line spectral analysis of heart rate variability (HRV) was performed to assess changes in autonomic nervous system activity during dialysis sessions both with and without hypotension. The low frequency (LF) component of HRV is thought to correlate with sympathetic nervous system activity, the high frequency (HF) component with that of the parasympathetic nervous system. In the sessions not complicated by symptomatic hypotension ($n = 26$), mean arterial BP (MAP) hardly fell, whereas heart rate increased from 77 ± 2 to 89 ± 5 bpm ($P < 0.05$). The LF component of HRV increased from 45.2 ± 5.0 normalized units (nu) to 59.9 ± 4.9 nu ($P < 0.05$), whereas the HF component fell from 54.8 ± 5.0 to 40.2 ± 4.4 nu ($P < 0.05$). These changes agree with compensatory baroreflex-mediated activation of the sympathetic nervous system (and suppressed parasympathetic activity) during ultrafiltration-induced intravascular volume depletion. In the sessions complicated by severe symptomatic hypotension ($n = 22$), the changes in heart rate and the results of spectral analysis of HRV were similar to those reported above up to the moment of sudden symptomatic (nausea, vomiting, dizziness, cramps) hypotension, whereas MAP had already fallen gradually from 94 ± 3 to 85 ± 3 mmHg ($P < 0.05$). The sudden further reduction in MAP (to 55 ± 2 mmHg, $P < 0.02$) was invariably accompanied by bradycardia (heart rate directly before hypotension 90 ± 2 bpm, during hypotension 69 ± 3 bpm, $P < 0.002$). The LF component of HRV fell from 62.8 ± 4.6 nu directly before to 40.0 ± 3.7 nu ($P < 0.05$) during hypotension, whereas the HF component increased from 37.9 ± 4.7 to 60.3 ± 3.7 nu ($P < 0.05$). These findings agree with activation of the cardiodepressor reflex, involving decreased sympathetic and increased parasympathetic nervous system activity, respectively. These findings indicate that activation of the sympatho-inhibitory cardiodepressor reflex (Bezold-Jarisch reflex), which is a physiologic response to a critical reduction in intravascular volume and cardiac filling, is the cause of sudden intradialytic hypotension.

Dialysis-induced hypotension is still an important problem of hemodialysis treatment that may complicate up to one-third of dialysis sessions. Recent reviews note that the critical issue is the decrease in blood volume induced by ultrafiltration (1–3). Clinically, two types of dialysis-induced hypotension have been recognized. The first is a relatively asymptomatic gradual reduction in BP accompanied by an increase in heart rate, the second a more abrupt and severe fall in BP associated with bradycardia and symptoms such as cramps, nausea, and vomiting (4,5). Generally, these two types of hypotension tend to be regarded as separate entities, and their temporal and pathophysiologic relations have not been well defined.

By using direct measurements of muscle sympathetic peroneal nerve activity, Converse *et al.* recently reported that the bradycardic type of dialysis-induced hypotension was associated with marked sympatho-inhibition, and they pointed out the analogy with activation of the Bezold-Jarisch reflex (5). This reflex, which involves sympatho-inhibition, bradycardia, vasodilation, and sudden hypotension, can also be triggered by interventions that reduce venous return such as lower body negative pressure, tilting, and hemorrhage (6,7). It is typically preceded by a phase of compensatory sympatho-activation (tachycardia, vasoconstriction, relatively preserved BP) and is thought to protect the heart against ischemia during severe hypovolemia by reducing its workload (bradycardia, negative inotropy, afterload reduction) (8).

We hypothesize that the different types of hypotension described in dialysis patients are inter-related and are part of the above-mentioned integrated hemodynamic response to progressive hypovolemia, which in the case of hemodialysis is triggered by ultrafiltration. To test this hypothesis, it is essential to obtain information not only on hemodynamic variables, but also on changes in the activity of the autonomous nervous system. However, measurement of muscle sympathetic peroneal nerve activity is difficult in patients with symptomatic dialysis-induced hypotension due to inadvertent leg movements. Converse *et al.* completed measurements in only two patients (5). We therefore decided to use continuous spectral

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analysis of heart rate variability as a noninvasive tool to assess changes in sympatho-vagal balance before and during dialysis-induced hypotension (9).

In the present study, we characterized the hemodynamic patterns that may occur during hemodialysis and ultrafiltration by continuous, beat-to-beat measurement of BP and heart rate. The objective was to define any relations between different hemodynamic patterns, more specifically between hypotensive episodes associated with either tachycardia or bradycardia. An additional aim was to define which predialysis patient characteristics predispose a particular dialysis session to culminate in symptomatic hypotension.

Materials and Methods

The protocol of the study was approved by the Medical Ethical Committee of the University Hospital Utrecht. All patients provided informed consent before participation.

Patients and Dialysis Prescription

In our population of 40 to 45 patients, about 25 to 30% were prone to dialysis hypotension. We performed the measurements outlined below during 48 dialysis sessions in 19 patients with end-stage renal failure undergoing sessions of hemodialysis three times a week of 3 to 4 h duration. Their characteristics are shown in Table 1. Eight patients (42%) were hypotension prone (dialysis-induced fall in mean arterial pressure to <65 mmHg in more than 25% of the dialysis sessions in the previous 2 mo). This relative preponderance of patients prone to hypotension was deliberate to assure inclusion of a sufficient number of dialysis sessions complicated by hypotension. Causes for renal failure were analgesic-induced nephropathy ($n = 2$), obstructive uropathy ($n = 1$), polycystic kidney disease ($n = 1$), nephrosclerosis ($n = 1$), diabetic nephropathy ($n = 6$), and lupus nephritis ($n = 1$), the cause being unknown in seven patients. Seven patients received antihypertensive medication (angiotensin-converting enzyme inhibitor, $n = 3$; calcium-entry blocker, $n = 2$; beta blocker, $n = 2$). All patients used phosphate binding agents, vitamin supplements, and erythropoietin. Dry weight was established by the attending physician on clinical grounds, chest x-ray, or vena cava collapse index. Patients were dialyzed with Gambro AK 100 volumetric control machines (Gambro, Lund, Sweden), using either the BIO-750WET dialyzer (Asahi Medical, Tokyo, Japan) or the F50S dialyzer (Fresenius, Bad Homburg, Germany). Blood flow rates ranged from 200 to 250 ml/min, the dialysate flow rate was 500 ml/min, and the dialysate temperature was 37°C. Ultrafiltration was linear and the ultrafiltration rate was adapted to reach the dry weight in the preset dialysis time. No sodium or blood volume profiling was performed. The dialysate composition was: 140 mmol/L Na^+, 2 mmol/L K^+, 35 mmol/L HCO_3^-, 105 mmol/L Cl^-, 1.5 mmol/L Ca^{2+}, 0.25 mmol/L Mg^{2+}, and 11 mmol/L glucose.

Table 1. Patient characteristics[a]

Characteristic	Hypotension Resistant	Hypotension Prone	*P* Value
No. of patients	11	8	
No. of measurements	18	30	
No. of hypotensive episodes	3 of 18 (17%)	19 of 30 (63%)	<0.01
Age (yr)	59 ± 5	68 ± 3	NS
Height (m)	1.67 ± 0.02	1.66 ± 0.02	NS
Weight (kg)	73.5 ± 5.0	72.4 ± 5.2	NS
Male/female	5/6	1/7	NS
Dialysis duration (mo)	19.7 ± 5.6	18.7 ± 8.3	NS
Diabetes mellitus	3 of 11	4 of 8	NS
Cardiovascular drugs	3 of 11	1 of 8	NS
Mean arterial pressure (mmHg)	93 ± 5	93 ± 5	NS
Heart rate (bpm)	71 ± 4	81 ± 2	0.06
Stroke volume (ml)	74 ± 8	54 ± 3	0.06
Cardiac output (L/min)	5.4 ± 0.7	4.3 ± 0.1	NS
LF/HF ratio	1.65 ± 0.44	1.12 ± 0.29	NS

[a] Data are presented as mean ± SEM. LF/HF ratio, ratio between low-frequency and high-frequency power of heart rate variability.

General Procedures/Protocol

All measurements were performed while the patients were seated in a multiadjustable chair. The start position was semirecumbent. When hypotension occurred, patients were put in the reverse Trendelenburg position, and isotonic saline boluses were give as needed. Beat-to-beat recordings of heart rate, electrocardiogram, BP, cardiac output, and stroke volume were obtained noninvasively. The hematocrit and respiration rate were also measured continuously, whereas forearm blood flow was measured intermittently at 30-min intervals and more often during hypotension. On-line data acquisition and storage on a Pentium 133-MHz 1.3-Gb hard disk personal computer system was performed with *m*-POLY 5 (Inspektor Research Systems, Amsterdam, The Netherlands). Spectral analysis of heart rate variability was performed off-line.

Cardiac Output and Stroke Volume

Stroke volume and cardiac output (and electrocardiogram and heart rate) were estimated using thoracic impedance cardiography (BoMed NCCOM3 R-7, BoMed Medical Manufacturing, Irvine, CA). Eight electrodes were configured on the thorax, from which changes in thoracic impedance during cardiac cycle were derived. These reflect changes in thoracic aortic volume, *e.g.*, left ventricular outflow. Stroke volume is calculated from the formula $SV = V_{EPT} \times LVET \times (dZ/dt)_{max}/Z_0$. V_{EPT} is a factor based on anthropometric measurements (gender, height, and weight), *LVET* is left ventricular ejection time, Z_0 is baseline thoracic impedance, $(dZ/dt)_{max}$ is the maximal rate of change of thoracic impedance, and *SV* is the stroke volume (absolute). Previous studies (10) have shown that this method follows relative changes in stroke volume accurately.

Blood Pressure

Arterial pressure and heart rate were recorded continuously on the hand of the arm without the dialysis access by using finger photo plethysmography (2300 Finapres™; Ohmeda, Englewood, CO). A finger cuff was wrapped around the mid-phalanx of the middle finger and supported at heart level during the entire dialysis session by adjusting the elbow rest. The hand was warmed with a small hand-made electrical-heated blanket during the entire procedure to prevent distortion of the arterial pressure waves due to cold-induced vasoconstriction. BP was frequently checked manually to compare values. No mismatches occurred as long as the Servo Self Adjust (fine tuning of

the set point and correction of slow moving physiologic changes) was turned on. Because this adjustment occurs automatically every 70 beats or less, spectral analysis of BP was not performed (11).

Forearm Blood Flow

Forearm blood flow was measured by R-wave-triggered venous occlusion plethysmography (EC 5R Plethysmograph; Hokanson, Bellevue, WA) on the arm without the dialysis access using a cuff occlusion pressure of 60 mmHg. During measurements, the forearm was stabilized slightly above the level of the heart. The average value of forearm blood flow was obtained from six consecutive recordings performed at 15-s intervals. Forearm vascular resistance was calculated as the ratio of mean arterial BP to forearm blood flow, and is expressed in units of resistance. Shortly before and during hypotension, some measurements were not reliable due to movement artifacts and these were excluded from the data analysis.

Spectral Analysis

Spectral analysis of heart rate variability (*e.g.*, heart rate fluctuations around mean heart rate or beat-to-beat changes in heart rate) is used to assess sympathetic and parasympathetic function of the autonomic nervous system (12–14). Using this method, the degree of variability and frequency-specific oscillations can be defined. The basis of this method is analysis of the tachogram of R-R intervals derived from an electrocardiographic signal. A Fast Fourier Transform algorithm is applied to assess oscillatory components (*i.e.*, the power spectrum). This power spectrum of heart rate variability reveals two important frequency components, namely low-frequency (LF, 0.04 to 0.15 Hz), a putative marker of sympathetic modulation, and high-frequency (HF, 0.15 to 0.40 Hz), considered a marker of vagal activity. A third component, very low frequency (VLF, <0.04 Hz), can be recognized, with as yet no clearly defined physiologic correlate. Summation of these three components reveals total power. We used relative powers of LF and HF, that is, LF or HF power divided by total power minus the VLF component, expressed in normalized units (nu) as markers of sympathetic or vagal modulation. Their ratio (LF/HF ratio) is considered to reflect sympatho-vagal balance (15). This method tends to minimize the effect of changes in total power on the values of LF and HF components and stresses the balanced interplay between the components of autonomic modulation.

Statistical Analyses

Data are presented as mean ± SEM. Statistical analyses were performed using unpaired/paired *t* test for comparison of baseline values between two groups of dialysis patients. ANOVA for repeated measures followed by Student-Newman-Keuls test was used for comparison of group differences in hemodialysis sessions. A P value <0.05 was considered significant.

Results

Patterns in BP and Heart Rate Response

Analyzing all 48 measurements, we could reduce these data to four basic patterns, of which typical examples are shown in Figure 1. Sessions without hypotension showed Pattern I, II, or III. In dialysis sessions showing Pattern I ($n = 12$), BP was stable and no increase or a minimal increase in heart rate occurred (0 to 5 bpm). Pattern II ($n = 9$) differed from this pattern in that heart rate increased markedly (5 to 20 bpm). Patients showing these patterns had no subjective complaints. Pattern III ($n = 5$) is compatible with near-hypotension. In these sessions, pulse pressure decreased strongly toward the end of hemodialysis (mainly because of lowering of the systolic BP) combined with the increase in heart rate. Vague presyncopal symptoms often occurred at the end of Pattern III.

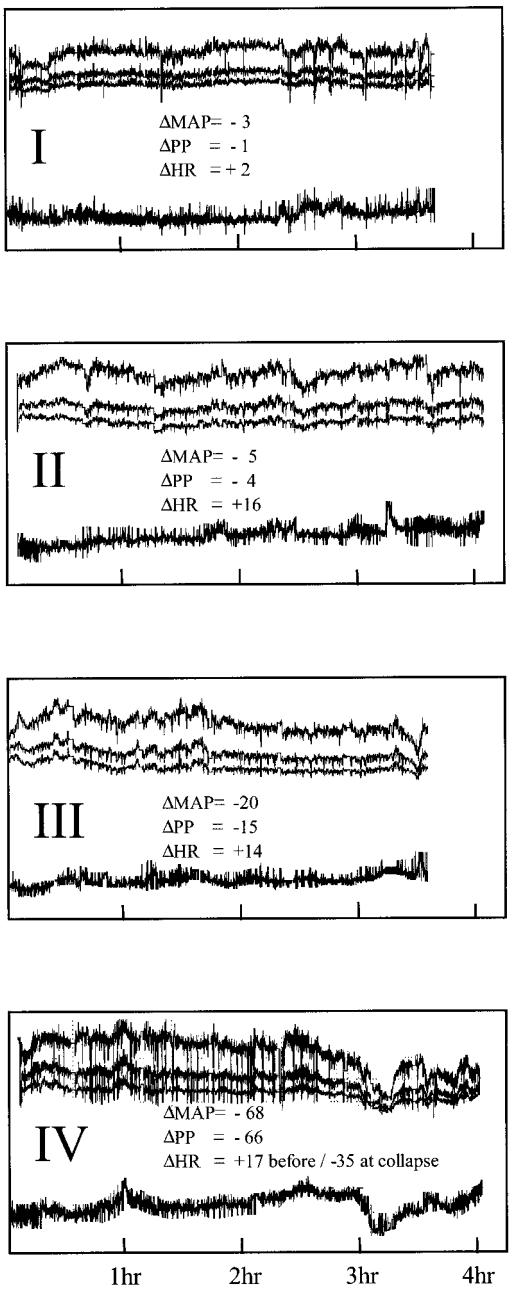

Figure 1. Typical examples of dialysis sessions without symptomatic hypotension (Patterns I through III) and with symptomatic hypotension and bradycardia (Pattern IV). Dialysis time (horizontal axis) was 3.5 to 4 h. In all panels, the top three tracings represent the systolic, mean, and diastolic arterial pressure, respectively. The bottom tracing represents the heart rate. Pattern I: blood pressure and heart rate stable; Pattern II: blood pressure stable, increasing heart rate; Pattern III: decreasing pulse pressure, increasing heart rate, near hypotension; Pattern IV: recognizable decrease in blood pressure followed by bradycardia and hypotension. MAP, mean arterial pressure (mmHg); PP, pulse pressure (mmHg); HR, heart rate (beats/min).

In sessions with frank, symptomatic hypotension, defined as Pattern IV ($n = 22$), there was a steady decrease of pulse pressure accompanied by an increase in heart rate (as in Pattern III), followed by severe symptomatic hypotension with bradycardia. Syncopal symptoms occurred approximately 20 min before collapse and were full-blown during collapse. In most hypotensive patients, they included abdominal discomfort, yawning, sighing, vomiting, restlessness, cramping, and anxiety. Remarkable to the investigating staff (not to experienced dialysis nurses) was the occurrence of coughing and hoarseness shortly before the actual collapse in most patients.

Baseline Characteristics and Ultrafiltration Volume in Hypotensive and Nonhypotensive Dialysis Sessions

Body temperature was slightly but significantly lower before dialysis sessions complicated by hypotension (Table 2). Other significant differences were the interdialytic weight gain, the net and gross ultrafiltration volume, and the ultrafiltration rate, which were all significantly greater in dialysis sessions complicated by hypotension. Differences in hemodynamic variables did not reach statistical significance.

Analysis of Nonhypotensive Dialysis Sessions

Hemodynamics. Table 3 shows the values for all sessions without bradycardic hypotension (Patterns I through III). Mean arterial pressure remained stable, whereas pulse pressure fell by 8.5 ± 7.0% due to a statistically nonsignificant fall in systolic pressure and a rise in diastolic pressure, respectively. Heart rate increased significantly (16.4 ± 5%). Cardiac output (−6.0 ± 2.2%) and stroke volume (−13.3 ± 3.8%) both fell during volume withdrawal. These observations point to an increase in peripheral vascular resistance, which is in agreement with the gradual increase in forearm vascular resistance.

Spectral Analysis of Heart Rate Variability. In the aggregate of all sessions without hypotension, the HF power decreased significantly from 54.8 ± 5.0 nu before dialysis to 40.2 ± 4.9 nu at the end of dialysis (Figure 2A), whereas the LF power increased significantly from 45.2 ± 5.0 to 59.9 ± 4.9 nu. Consequently, the LF/HF ratio, considered to reflect sympatho-vagal balance, increased significantly at the end of dialysis (Table 3).

Table 2. Baseline values in dialysis sessions without ($n = 26$) and with ($n = 22$) hypotension[a]

Parameter	Without Hypotension	With Hypotension	*P* Value
Mean arterial pressure (mmHg)	101 ± 4	94 ± 3	NS
Heart rate (bpm)	77 ± 2	78 ± 2	NS
LF/HF ratio	1.16 ± 0.2	0.99 ± 0.2	NS
Body temperature (°C)	37.0 ± 0.1	36.5 ± 0.1	<0.05
Interdialytic weight gain (kg)	2.0 ± 0.2	2.7 ± 0.1	<0.02
Ultrafiltration volume (net) (ml)	1850 ± 158	2572 ± 95	<0.02
Ultrafiltration rate (L/h)	0.75 ± 0.04	1.00 ± 0.04	<0.02

[a] Data are presented as mean ± SEM.

Analysis of Hypotensive Dialysis Sessions

Hemodynamics. Table 4 shows the values for all sessions with hypotension. Because collapse occurred at different moments, albeit usually during the second half of dialysis (time of hypotension 147 ± 29 min), data from continuous measurements in these dialysis sessions were analyzed as follows. Comparisons were made between values obtained at the start of dialysis, at half-time between start of dialysis and collapse, at collapse minus 20 and 10 min, at collapse, and finally at collapse plus 10 min. Because of various interventions (for example, isotonic saline infusion or reverse Trendelenburg position), data after the collapse were very variable and show a great standard error. From various moments after the start of dialysis and ultrafiltration until 20 min before hypotension, we observed a gradual decrease in mean arterial pressure (−3.9 ± 3.0%), cardiac output (−3.6 ± 3.9%), and stroke volume (−11.7 ± 3.5%), accompanied by increases in heart rate (8.8 ± 2.7%) and forearm vascular resistance (24.1 ± 9.2%). Pulse pressure diminished by 12.8 ± 5.9%, mostly because of lowered systolic BP. These changes were even more pronounced 10 min before hypotension.

During hypotension, mean arterial BP fell abruptly when compared to 10 min before collapse (−33.0 ± 3.0%), together with heart rate (−20.7 ± 2.4%) and forearm vascular resistance (−35.2 ± 8.0%). Pulse pressure was narrowed to 29 mmHg. Stroke volume remained unaltered, while cardiac output fell by 10.9 ± 1.7%.

Spectral Analysis of Heart Rate Variability. In the sessions with hypotension, the HF power decreased and the LF power increased up to the moment of circulatory collapse (Figure 2B), and the LF/HF ratio increased (Table 4). The values that were reached were similar to those reached at the end of dialysis in the nonhypotensive sessions (Figure 2A, Table 3). At the time of collapse, however, the LF power decreased significantly, whereas the HF power increased (Figure 2B) and the LF/HF ratio fell markedly (Table 4).

Analysis of Paired Observations

Table 5 shows results of paired observation in six patients who were studied both during a dialysis session with and without hypotension. BP, heart rate, stroke volume, cardiac output, and LF/HF ratio were not different before the two sessions. The interdialytic interval tended to be longer for dialysis sessions complicated by hypotension, and the interdialytic body weight increase was significantly greater. During dialysis sessions complicated by hypotension, the ultrafiltration rate was significantly greater during sessions with hypotension (1.0 ± 0.1 L/h) than during those without hypotension (0.7 ± 0.1 L/h).

Discussion

The present study showed that volume removal by ultrafiltration during hemodialysis can elicit a characteristic phased

Table 3. Dialysis sessions without hypotension ($n = 26$)[a]

Parameter	Start	t¼	t½	t¾	End
Systolic BP (mmHg)	151 ± 6	156 ± 7	152 ± 7	150 ± 6	144 ± 6
Diastolic BP (mmHg)	78 ± 3	80 ± 3	80 ± 4	78 ± 3	80 ± 3
Pulse pressure (mmHg)	73 ± 4	76 ± 4	72 ± 5	71±	65 ± 5[b,c]
Heart rate (bpm)	77 ± 2	77 ± 2	78 ± 3	84 ± 4	89 ± 5[b,c]
Stroke volume (ml)	65 ± 4	62 ± 4	61 ± 4	58 ± 4	55 ± 4[b,c]
Cardiac output (L/min)	5.0 ± 0.3	4.7 ± 0.3	4.7 ± 0.3	4.6 ± 0.2	4.6 ± 0.3[b]
Forearm resistance (ml/min per 100 ml)	32.0 ± 3.7	38.9 ± 4.6	43.8 ± 7.6	40.8 ± 8.4	44.0 ± 7.2
LF/HF ratio	1.16 ± 0.2	1.75 ± 0.4	2.18 ± 1.0	1.54 ± 0.2	2.40 ± 0.4[b]

[a] Data are presented as mean ± SEM. Start, start of dialysis; End, end of dialysis; t¼, t½, and t¾: 25, 50, and 75% of dialysis duration, respectively.
[b] $P < 0.05$ *versus* baseline.
[c] $P < 0.05$ *versus* t½.

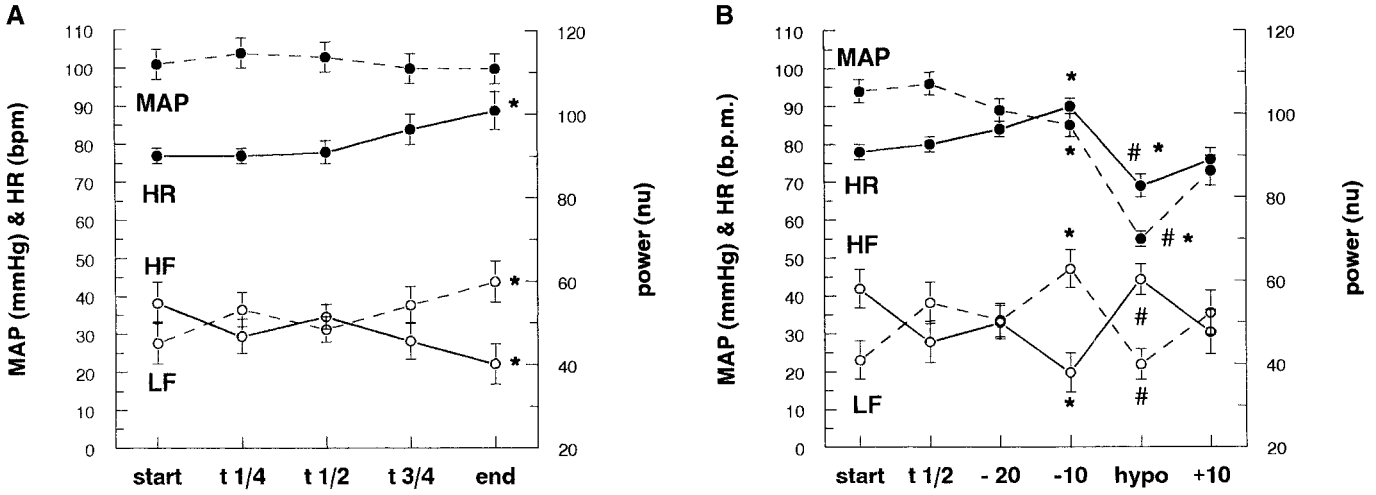

Figure 2. MAP, HR, and low frequency (LF) and high frequency (HF) power (nu, normalized units) in dialysis sessions without (A) and with (B) symptomatic hypotension. Start, start of dialysis; end, end of dialysis. Panel A: t1/4, t1/2, and t3/4: 25, 50, and 75% of dialysis duration, respectively. Panel B: t1/2, halfway between start of dialysis and moment of hypotension; −20, −10, 20 min and 10 min before hypotension, respectively; hypo, moment of hypotension. *$P < 0.05$ *versus* baseline; #$P < 0.05$ versus −10 min.

hemodynamic response, which, however, is not always fully expressed in all dialysis sessions. When expressed completely, subsequent phases of a stable BP with minor or more pronounced increments in heart rate, a progressive decline in pulse pressure with tachycardia, and finally circulatory collapse with severe symptomatic hypotension and bradycardia can be recognized. Results of spectral analysis of heart rate variability were consistent with progressive sympatho-activation in the early phases of this response and marked sympatho-deactivation in the final phase.

In the dialysis sessions that were not complicated by abrupt hypotension and bradycardia, we defined three hemodynamic patterns. In the first, BP and heart rate hardly changed, whereas in the second BP was also stable but a clear rise in heart rate could be observed. In the third pattern, a progressive but gradual decline in mean arterial and pulse pressure occurred, usually after an initial period of variable duration with a stable BP. Heart rate increased as in the second pattern and presyncopal symptoms were sometimes reported. In the aggregate of these sessions without overt symptomatic hypotension, forearm vascular resistance increased and cardiac output fell, indicating that vasoconstriction occurred. In agreement with this, the results of spectral analysis of heart rate variability were compatible with progressive sympathetic activation (increasing LF power) and parasympathetic withdrawal (decreasing HF power).

In dialysis sessions characterized by a fourth pattern, the hemodynamic changes were initially similar to those observed in sessions showing the third pattern, but abrupt hypotension and bradycardia occurred in the final stages of dialysis (approximately 2.5 h after starting dialysis). Forearm vascular resistance fell abruptly when compared to precollapse levels. Cardiac output fell, but to a much smaller extent than BP. These findings indicate that vasodilation occurred in the phase

Table 4. Dialysis sessions with hypotension ($n = 22$)[a]

Parameter	Start	t½	−20 min	−10 min	Hypotension	+10 min
Systolic BP (mmHg)	147 ± 6	148 ± 6	134 ± 6	126 ± 7	75 ± 3[b,c]	108 ± 6
Diastolic BP (mmHg)	71 ± 3	73 ± 3	70 ± 2	67 ± 2	46 ± 2[b,c]	58 ± 4
Pulse pressure (mmHg)	76 ± 5	74 ± 5	64 ± 5	59 ± 5	29 ± 3[b,c]	50 ± 4
Heart rate (bpm)	78 ± 2	80 ± 2	84 ± 2	90 ± 2[d]	69 ± 3[b,c]	76 ± 3
Stroke volume (ml)	55 ± 3	50 ± 2	47 ± 2	46 ± 2[d]	48 ± 2[b,c]	49 ± 2
Cardiac output (L/min)	4.2 ± 0.2	4.0 ± 0.1	3.9 ± 0.1	4.0 ± 0.2	3.5 ± 0.2[b,c]	3.7 ± 0.2
Forearm resistance (ml/min per 100 ml)	23.9 ± 1.9	29.4 ± 2.6	28.6 ± 2.9	31.9 ± 4.5	19.2 ± 1.8[c]	25.1 ± 1.9
LF/HF ratio	0.99 ± 0.2	1.64 ± 0.3	1.39 ± 0.3	2.93 ± 0.5[d]	0.73 ± 0.1[b,c]	2.36 ± 0.6

[a] Data are presented as mean ± SEM. Data are synchronized to the time of hypotension, which occurred on average 147 ± 29 min after the start of dialysis. Start, start of dialysis; t½, halfway between start of dialysis and hypotension; −20, −10, and +10, 20 and 10 min before and 10 min after hypotension occurred; LF/HF ratio, ratio of low-frequency and high-frequency power of heart rate variability.
[b] $P < 0.002$ *versus* baseline.
[c] $P < 0.002$ *versus* −10 min.
[d] $P < 0.02$ *versus* baseline.

Table 5. Paired observation in patients studied during a dialysis session without and with hypotension ($n = 6$)

Parameter	Without Hypotension	With Hypotension	*P* Value
Mean arterial pressure (mmHg)	98 ± 9	100 ± 6	NS
Heart rate (bpm)	82 ± 4	78 ± 3	NS
Stroke volume (ml)	53 ± 10	50 ± 11	NS
LF/HF ratio	1.23 ± 0.41	1.30 ± 0.40	NS
Cardiac output (L/min)	4.4 ± 0.4	4.0 ± 0.3	NS
Interdialytic interval (d)	1.2 ± 0.1	1.5 ± 0.1	NS
Interdialytic weight gain (kg)	1.62 ± 0.20	2.50 ± 0.20	<0.02
Ultrafiltration volume (net) (ml)	1680 ± 310	2380 ± 180	<0.02
Ultrafiltration rate (L/h)	0.7 ± 0.1	1.0 ± 0.1	<0.02

of hypotension. Up to the moment of circulatory collapse, the changes in the indicators of activity of the autonomic nervous system were the same as in the final stages of dialysis sessions without severe hypotension, pointing to initial sympatho-activation and parasympathetic withdrawal. In the phase of circulatory collapse and bradycardia, however, the LF power decreased markedly and the HF power increased, changes compatible with sudden sympathetic withdrawal and parasympathetic dominance.

The patterns described above can be recognized as parts of the spectrum of the normal autonomic cardiovascular response to progressive intravascular volume depletion and are likely to represent transitions from one stage to the next. The initial response to hypovolemia is activation of the sympathetic nervous system due to baroreceptor deactivation. Mean arterial BP is preserved relatively well due to vasoconstriction, but pulse pressure may fall and tachycardia develops. Elements of this initial response to volume depletion can be recognized not only in the dialysis sessions not complicated by sudden hypotension, but also in the early phase of those that were complicated by this event. With progressive hypovolemia, blood volume and cardiac filling become critically reduced, which activates the cardiodepressor or Bezold-Jarisch reflex (8,16–18). This reflex probably originates in the heart and is triggered by activation of myocardial mechanoreceptors, which are stimulated by vigorous contractions around a nearly empty left ventricular cavity (19). As a result, vagal afferents inhibit central cardiovascular centers, overrule their baroreflex-mediated activation, and deactivate the sympathetic nervous system. Sudden vasodilation and bradycardia occur, resulting in severe hypotension with vasovagal complaints. This later phase of the autonomic cardiovascular response to hypovolemia can be clearly recognized in the final stages of dialysis sessions complicated by symptomatic hypotension and bradycardia. The Bezold-Jarisch reflex is thought to be a protective response, defending the heart against ischemia during severe hypovolemia by reducing its workload through induction of bradycardia, negative inotropy, and afterload reduction (17).

Depending on the definition of hypotension that is used, some patients showing Pattern III could be classified as having the tachycardic type of hypotension, whereas patients showing Pattern IV would be classified as having the bradycardic type. Observing the examples of the patients displaying these patterns in Figure 1, it can be appreciated that the patient showing Pattern III was actually very close to reaching the next stage. This figure clearly illustrates that tachycardic and bradycardic types of hypotension are not completely unrelated phenomena, but represent different stages of the cardiovascular response to volume depletion.

As discussed above, it may be partly a matter of definition and timing whether a hypotensive episode is defined as being of the tachycardic or bradycardic type. This could explain the

relatively low frequency of bradycardic hypotensive episodes reported in other studies (4,20). In this respect, however, it is relevant that Enzmann *et al.* reported that episodes of hypotension not accompanied by a substantial change in heart rate are characterized (spectral analysis) mainly by sympathetic withdrawal without much alteration in parasympathetic activity (21). It is indeed known that manipulations that elicit cardioinhibitory responses may be classified as either predominantly vasodepressor (hypotension), cardioinhibitory (bradycardia), or mixed (hypotension and bradycardia). Hypotension and bradycardia are not always tightly linked, the suggestion being that stronger degrees of cardiac mechanoreceptor stimulation are needed to also evoke a bradycardic response (17). Finally, it is also possible that in some of the studies reporting a relatively low frequency of bradycardic hypotension, subtle or relatively short-lasting episodes of bradycardia were missed due to noncontinuous heart rate measurement. In our study, in which both the duration and magnitude of the heart rate-slowing response certainly varied among the different hypotensive episodes, continuous, beat-to-beat heart rate measurement virtually guaranteed the detection of any episodes of bradycardia. It remains to be determined, however, how often predominant vasodepressor, bradycardic, or mixed responses are observed in large groups of patients suffering from frequent dialysis hypotension, as well as how these patterns correlate with measures of autonomic nervous system activity.

Our study extends and confirms the observations of Converse *et al.* made in two patients during dialysis-induced hypotension (5). By direct measurements of sympathetic peroneal nerve activity, they showed that sudden dialysis hypotension with bradycardia was characterized by abrupt withdrawal of muscle sympathetic nerve activity. These authors were the first to suggest that the abrupt dialysis-induced hypotension of the bradycardic type was a form of vasodepressor syncope, resulting from activation of the Bezold-Jarisch reflex. It is of note that they also observed that the hypotensive episode was preceded by a gradual increase in sympathetic nerve traffic and tachycardia, which suggested appropriate baroreflex reactivity during ultrafiltration-induced volume reduction before the hypotensive episode. Our findings of an increasing LF/HF power ratio in dialysis sessions without hypotension and in the initial phase of dialysis sessions with hypotension, as well as a preliminary report by Enzmann *et al.* (21) showing the same, agree with this notion.

Spectral analysis of heart rate variability has been advanced as a noninvasive tool to assess short-term changes in the activity of the autonomic nervous system (9,13,14), but the validity of this method has recently become a matter of debate (22,23). Although the method may not be valid under all conditions, there is, however, little reason to question the results of spectral analysis of heart rate variability in our study as the changes observed clearly agree with what might be expected from normal physiology (24). More importantly, the spectral analysis results are entirely consistent with the limited direct measurements of muscle sympathetic nerve activity before and during dialysis-induced hypotension referred to earlier (5).

Patients apparently do not always traverse all subsequent hemodynamic phases of the cardiovascular response to volume depletion during hemodialysis and ultrafiltration. This is in particular also true in those patients defined as being hypotension prone, who in our study developed severe hypotension and bradycardia in 19 of 30 (63%) of dialysis sessions. It is of course of interest to assess what predisposes a dialysis session to culminate in severe hypotension and bradycardia. Ligtenberg *et al.* suggested that subtle fluctuations in sympathetic tone during increasing sympatho-activation and falling cardiac output could trigger activation of the cardiodepressor reflex (25). In this respect, it is of note that cardiac output and stroke volume tended to be lower in the beginning of the aggregate of dialysis sessions complicated by hypotension, suggesting that the starting position was less favorable in this respect. Another option is that the patients were somewhat less volume-overloaded before the dialysis sessions, culminating in hypotension. Applying ultrafiltration would then lead to earlier attainment of the critical level of circulatory or cardiac filling, which would trigger the cardiodepressor response. It has indeed been shown in healthy subjects that volume depletion facilitates activation of the cardiodepressor reflex by applying lower body negative pressure, a model for progressive intravascular volume depletion (26). However, the finding that the interdialytic weight gain was significantly greater before dialysis sessions complicated by hypotension argues against this possibility. This latter observation points to another potential and perhaps more important discriminating factor. When paired observations were analyzed in six patients who were investigated both during a session with and without hypotension and bradycardia, no differences in predialysis BP, heart rate, stroke volume, and cardiac output could be found. Likewise, the degree of autonomic cardiovascular modulation was not different on the two occasions as reflected by the similar predialysis LF/HF ratios. The only difference in this analysis was a significantly greater interdialytic weight gain before dialysis sessions complicated by hypotension, which necessitated significantly higher ultrafiltration rates. It is conceivable that these higher ultrafiltration rates exceeded the refill capacity to such an extent that blood volume and cardiac filling were reduced to a greater degree during dialysis leading to activation of the Bezold-Jarisch reflex.

In summary, our study suggests that the tachycardic and the bradycardic types of hypotension induced by ultrafiltration are part of the spectrum of the normal cardiovascular autonomic response to progressive hypovolemia. Spectral analysis of heart rate variability agrees with increasing, baroreflex-mediated sympathetic activity during dialysis sessions without symptomatic hypotension. However, severe bradycardic hypotension, which is preceded by increased sympathetic activity, is characterized by marked sympatho-inhibition and parasympathetic activation, which is consistent with activation of the Bezold-Jarisch reflex. Factors predisposing a dialysis session to culminate in activation of this reflex possibly include reduced predialysis stroke volume and cardiac output, as well as the necessity for high ultrafiltration rates.

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