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PERSPECTIVES IN RENAL MEDICINE

Cardiovascular autonomic dysfunction in uremia

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Cardiovascular autonomic dysfunction in uremia. Cardiovascular morbidity and mortality is common in chronic renal failure patients, and may be explained in part by abnormalities in cardiovascular autonomic regulation. This review discusses the results of cardiovascular autonomic function studies in chronic renal failure patients. While covering most methods of assessing autonomic function, we focus particularly on power spectral analysis methods. These newer techniques are non-invasive, reproducible, and allow the rapid assessment of the integrity of cardiovascular autonomic reflexes at the bedside. The abnormalities of parasympathetic, sympathetic and cardiac baroreceptor function seen in dialysis-dependent patients are highlighted, and their significance in intra-dialytic hypotension and cardiovascular mortality as well as the effects of dialysis and transplantation on these parameters examined. Importantly, studies of cardiovascular autonomic dysfunction in pre-dialysis chronic renal failure patients, when abnormalities may be amenable to intervention to prevent progression and premature cardiovascular morbidity and mortality, are reviewed.

Cardiovascular disease is the leading cause of mortality in hemodialysis patients, accounting for 44% of the overall mortality [1]. Indeed, for hemodialysis patients 15 to 30 years old, the incidence of cardiovascular death is 150 times greater than the general population [2]. A number of mechanisms have been proposed to explain this excess cardiovascular mortality, including hypertension, arterial stiffness and cardiovascular autonomic dysfunction. This review focuses on the reported abnormalities in cardiovascular autonomic function with studies utilizing both traditional invasive and recent non-invasive techniques, in particular discussing the possible differential effects on parasympathetic and sympathetic nervous system dysfunction. The effects of dialysis and renal transplantation on cardiovascular autonomic dysfunction are covered as well as its significance with regard to dialysis complications, including intra-dialytic hypotension, and cardiovascular mortality.

Key words: baroreceptor reflex arc, blood pressure, heart, parasympathetic nervous system, power spectral analysis techniques, sympathetic nervous system, dialysis, hemodialysis, intradialytic hypotension, peritoneal dialysis, renal transplantation, chronic renal failure.

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CARDIAC BARORECEPTOR SENSITIVITY

The baroreceptor reflex arc is the principal mechanism in the short-term regulation of the cardiovascular system, including blood pressure changes. The main baroreceptor sites are in the carotid sinuses, the enlarged parts of the internal carotid arteries just above the bifurcation of the common carotid arteries, as well as the aortic arch and its proximal branches. Free and encapsulated baroreceptor nerve endings are embedded in the adventitial layer of the arterial wall. These tonically discharge via afferent fibers in the glossopharyngeal (carotid) and vagus (aortic) nerves to specialized nuclei within the brainstem, including the nucleus tractus solitarius, nucleus ambiguous, and the ventrolateral nuclei of the medulla oblongata. Afferent discharge is increased by stimulation of the baroreceptor nerve endings secondary to stretching of the arterial wall brought about by increased transmural pressure related to increased blood pressure. Equally afferent discharge is decreased by reduced blood pressure, reduced transmural pressure, and reduced stretch. Central fibers in the brainstem nuclei may be influenced by the hypothalamus, cerebral cortex, and other higher brain centers. Efferent discharge via the parasympathetic and sympathetic outflow tracts influences sinoatrial node, ventricular wall, arteriolar and capacitance vessel function in responses to the precipitating blood pressure change. Therefore, assessments of baroreceptor sensitivity can provide a measure of the overall integrity of autonomic nervous system function.

Intra-arterial techniques

Classically, invasive intra-arterial techniques are used to assess heart rate responses to either pressor (phenylephrine, angiotensin) or depressor stimuli (amyl nitrite, sodium nitroprusside). The regression of pulse interval on systolic blood pressure represents an index of baroreceptor sensitivity [3]. In a study of 32 hemodialyzed patients, Pickering and colleagues were the first to report

Table 1. Results of studies assessing baroreceptor sensitivity in chronic renal failure patients

Study	Population	Test	Findings
Pickering et al, 1972 [4]	32 HD	IV bolus phenylephrine	– Reduced BRS in HD compared to controls (historical) – BRS inversely correlated with age and hypertension, though correlation weaker in HD patients
Lazarus et al, 1973 [5]	13 CRF (9 hypertensive) 5 Controls	IV bolus angiotensin Inhaled amyl nitrite	– Reduced BRS in normotensive (2.1 msec/mm Hg) and hypertensive CRF (−1.3) compared to controls (9.1) for pressor stimulus (angiotensin) – Reduced BRS in normotensive (2.5 msec/mm Hg) and hypertensive CRF (2.3) compared to controls (9.1) for depressor stimulus (amyl nitrite)
Bondia et al, 1988 [6]	10 HD 8 Controls	IV bolus phenylephrine	– Reduced BRS in HD (3.08 vs. 11.35 msec/mm Hg)
Heber et al, 1989 [7]	10 HD 5 Controls	VS	– All but 1 patient had square wave (abnormal) response (initial BP increase, plateau with no fall, post-release gradual BP reduction with no overshoot)
Agarwal et al, 1991 [8]	25 CRF 8 Controls	IV bolus phenylephrine	– Reduced BRS in CRF (3.88 vs. 11.2 msec/mm Hg) – 8 patients restudied on HD, BRS lower in hypotension-prone vs. normotensive group (3.10 vs. 5.32 msec/mm Hg) – 12 patients restudied after RT, BRS improved (7.46 vs. 3.95 msec/mm Hg)
Gerhardt et al, 1999 [17]	20 HD 20 RT 20 Controls	2- to 4-beat sequences of concordant increases or decreases in BP and PI	– Reduced BRS in CRF vs. Controls (5.2 vs. 13.4 msec/mm Hg) – Similar BRS in RT and Controls (11.2 vs. 13.4 msec/mm Hg)
Bald et al, 2001 (abstract)	27 CRF 20 HD 27 Controls	Sequence analysis	– Reduced BRS in HD, not CRF, vs. Controls
Carr et al, 2001 (abstract)	83 CRF 24 Controls	Combined α-index (FFT)	– Reduced BRS in 54 severe CRF (7.3 msec/mm Hg) compared to 29 mild-to-moderate CRF patients (12.0) and Controls (10.5)

Abbreviations are: CRF, chronic renal failure; HD, hemodialysis; BRS, baroreceptor sensitivity; VS, Valsalva maneuver; RT, renal transplant; BP, blood pressure; PI, pulse interval; FFT, fast Fourier Transform.

impaired baroreceptor sensitivity in chronic renal failure. Furthermore, there was an inverse relationship between baroreceptor sensitivity and age and blood pressure, but this was less marked than in control subjects. Finally, baroreceptor sensitivity appeared to improve with long-term hemodialysis in the six patients re-studied (Table 1) [4].

This observation of impaired baroreceptor sensitivity in chronic renal failure has been confirmed by a number of other studies, utilizing different techniques [5–8] (Table 1). Lazarus and colleagues reported impaired baroreceptor sensitivity in both four normotensive and nine hypertensive dialysis-independent chronic renal failure patients using pressor (angiotensin) and depressor (amyl nitrite) techniques [5]. Bondia and colleagues initially studied 52 hemodialysis patients, and identified ten with an abnormal Valsalva ratio. This group was then studied in more detail to identify the segments of the autonomic reflex arc affected. Abnormalities were identified in response to bolus phenylephrine (afferent common) and atropine (efferent vagal) [6]. Heber and colleagues assessed intra-arterial blood pressure responses to the Valsalva maneuver, and reported a square wave response, that is, an initial blood pressure increase with a plateau thereafter and a gradual reduction with no overshoot following release. This is consistent with an impaired baroreceptor reflex arc, and was hypothesized to be secondary to chronic fluid overload and arterial stretching [7].

Non-invasive techniques

The advent of newer, reliable, non-invasive techniques of beat-to-beat blood pressure measurement [9, 10], together with the increased availability of powerful microcomputers and appropriate analysis techniques has made possible the calculation of cardiac baroreceptor sensitivity from the assessment of continuous blood pressure and pulse interval recordings taken at rest. Blood pressure and pulse interval variability can be described in terms of the underlying rhythmic factors affecting the cardiovascular system, including the cardiac cycle, the respiratory cycle, and vasomotor activity [11]. The technique of power spectral analysis with the use of fast Fourier Transform can be used to detect such underlying rhythmicity by assessing the number, frequency, and amplitude of the oscillatory components (frequency domain analysis) [12]. Cardiac baroreceptor sensitivity can be estimated by calculation of the square root of the ratio of powers of pulse interval to systolic blood pressure, the α-index, which has been shown to correlate well with cardiac baroreceptor sensitivity calculated by means of the 'gold standard' pharmacological techniques [13, 14]. Utilizing these techniques, we have recently reported reduced cardiac baroreceptor sensitivity in dialysis-independent chronic renal failure patients with severely impaired function [glomerular filtration rate (GFR) <30 mL/min] compared to those patients with mildly impaired

function (GFR 30 to 80 mL/min) and control subjects (Table 1) (abstract; Carr et al, *J Am Soc Nephrol* 12: A0352, 2001).

Blood pressure and pulse interval also can vary as a function of time. Therefore, analysis of beat-to-beat blood pressure and pulse interval recordings of at least 10 minutes taken at rest can be used to assess cardiac baroreceptor sensitivity (time domain analysis). Recordings are analyzed to document sequences of typically at least three beats associated with increasing blood pressure and pulse interval (pressor sequences) or decreasing blood pressure and pulse interval (depressor sequences). These are associated with the baroreceptor reflex, and account for at least 20% of beats in typical recordings [15, 16]. Utilizing this technique, Gerhardt and colleagues have reported impaired baroreceptor sensitivity for both pressor and depressor sequences in 20 hemodialysis chronic renal failure patients compared to control subjects (Table 1) [17]. In a study of 27 dialysis-independent children with impaired renal function, Bald and colleagues have provisionally reported no significant difference in baroreceptor sensitivity to an age-matched control population, though the control group had lower systolic blood pressure values (Table 1) [abstract; Bald et al, *J Hypertens* 19(Suppl 2):S212, 2001].

PARASYMPATHETIC NERVOUS SYSTEM

Classical techniques

Standard assessments of the integrity of the parasympathetic nervous system include the measurement of heart rate responses to respiration, orthostatic change and the Valsalva maneuver [18]. A number of studies have consistently reported impairment of parasympathetic nervous system function in both pre-dialysis [8, 19–22] and hemodialysis-dependent chronic renal failure patients using these techniques (Table 2) [6, 19–21, 23–35]. Only one study has reported intact parasympathetic nervous system function, though this was a small study of 10 hemodialysis patients utilizing heart rate responses to orthostatic change as the only assessment of parasympathetic function (Table 2) [7]. Few studies have directly compared parasympathetic nervous system function in a pre-dialysis and hemodialysis-dependent chronic renal failure population. Heidbreder and colleagues assessed heart rate responses to respiration, orthostatic change and the Valsalva maneuver in 31 chronic renal failure and 35 hemodialysis patients. They demonstrated that both groups had abnormal heart rate responses when compared to a control population, though there were no significant differences between the two chronic renal failure groups [21]. Similarly, Campese and colleagues reported a significantly reduced Valsalva ratio in 21 chronic renal failure and 16 hemodialysis patients compared to 60 control subjects, though there were no differences between the two chronic renal failure groups [20]. Rockel and colleagues compared heart rate and blood pressure responses to the Valsalva maneuver and orthostasis in chronic renal failure with moderately (GFR 10 to 30 mL/min) and severely impaired (GFR 4 to 10 mL/min) renal function as well as in hemodialysis patients. In moderately impaired renal failure patients, 50% demonstrated abnormal heart rate responses to the Valsalva maneuver and 18% to orthostasis. This worsened in severe renal failure patients to 58% and 31%, respectively, and to 60% and 40% in hemodialysis patients [19].

Few studies have longitudinally assessed the parasympathetic nervous system function in chronic renal failure patients [26, 36, 37]. Solders, Persson and Gutierrez have reported worsening heart rate variability with increasing time on hemodialysis [26]. Vita and colleagues, who reported deterioration in heart rate responses to respiration 18 months after commencing hemodialysis in a series of 19 patients, confirmed this finding. Indeed, 33% of patients with normal tests of autonomic function at baseline had deteriorated by 18 months, and 62.5% by 56 months [36]. However, there were mixed messages from this study, as 43% of patients had an improvement in their autonomic score by 18 months, and 50% by 56 months [36]. Furthermore, 8 patients re-studied at 92 months after commencing hemodialysis demonstrated an improvement in heart rate responses to respiration when compared to 56 months. This improvement was attributed to a change to bicarbonate dialysis [37].

Age also may be an important factor in parasympathetic dysfunction. Jassal, Douglas and Stout found that 65.9% of their dialysis group over the age of 65 years had abnormal parasympathetic function tests, but only 33.3% of patients under the age of 65 years were affected. Nonetheless, chronic renal failure remained important in the cause of parasympathetic dysfunction, as only 11.8% and 0% of the comparator control groups were affected, respectively [34]. However, Agarwal and colleagues found evidence of parasympathetic dysfunction in their study population of mean age 28.5 years old [8]. Vita and colleagues also found evidence of parasympathetic dysfunction in young (35 to 53 years) hemodialysis patients (9%), but significantly higher levels in those aged 66 to 76 years (66%) [29]. Interestingly, in a later study, they reported no relationship between autonomic dysfunction and either age or dialysis duration [35].

Power spectral analysis techniques

In addition to the assessment of cardiac baroreceptor sensitivity, the technique of power spectral analysis with the use of fast Fourier Transform can be used to assess the integrity of the underlying sympathovagal balance of autonomic cardiovascular system control [11, 38, 39].

Table 2. Results of studies assessing parasympathetic nervous system function in chronic renal failure patients

Study	Population	Test	Findings
Ewing et al, 1975 [23]	26 HD	HR responses to respiration, VS	– 50% had abnormal/borderline HR response to VS – Abnormal VS ratio correlated with reduced respiratory HR variability
Campese et al, 1981 [20]	21 CRF 16 HD 60 Controls	HR responses to VS	– Impaired VS ratio in CRF (1.51) and HD patients (1.62) compared to Controls (2.10)
Naik et al, 1981 [24]	27 HD 15 Controls	HR responses to tilt, VS	– Reduced 30:15 HR ratio on standing in HD group
Zoccali et al, 1982 [25]	18 HD 12 Controls	HR responses to respiration, tilt, VS, atropine	– Impaired HR responses in HD vs. Controls (respiration, 12 vs. 23 bpm; tilt, 1.06 vs. 1.26; VS, 1.53 vs. 1.83) – Reduced tachycardia response to atropine in HD vs. Controls (34 vs. 41 bpm)
Heidbreder et al, 1985 [21]	31 CRF 35 HD 18 RT 37 Controls	HR responses to respiration, tilt, VS	– Impaired HR responses in CRF vs. Controls (respiration, 21 vs. 54 bpm; Tilt, 1.03 vs. 1.16; VS, 1.18 vs. 1.46) – Impaired HR responses in HD vs. Controls (respiration, 35 vs. 54 bpm; tilt, 1.06 vs. 1.16; VS, 1.27 vs. 1.46) – No significant differences between HR responses between RT vs. Controls (respiration, 57 vs. 54 bpm; tilt, 1.23 vs. 1.16; VS, 1.38 vs. 1.46)
Solders et al, 1985 [26]	44 HD 45 Controls	HR responses to respiration	– HR variability reduced in HD patients with (14) and without (30) hyperparathyroidism, i.e. unrelated to duration of uremia
Malik et al, 1986 [27]	19 CRF 40 HD 8 PD	HR responses to respiration, tilt, VS	– 32% of all patients had early PNS dysfunction – 39% of all patients had definite PNS dysfunction – No significant differences between groups in degree of PNS dysfunction
Mallamaci et al, 1986 [28]	12 HD 10 PD 11 RT 12 Controls	HR responses to respiration, tilt, VS	– Reduced HR responses in both HD and PD groups compared to Controls – No significant difference in HR responses between HD and PD groups – No significant differences between HR responses in RT and Control groups
Vita et al, 1987 [29]	20 HD	HR responses to respiration, tilt, VS	– PNS dysfunction (≥2 abnormal tests) more common in elderly (66–76 years) than young (35–53) group (66 vs. 9%)
Bondia et al, 1988 [6]	10 HD 8 Controls	HR responses to atropine	– Reduced tachycardic response to 0.015mg/kg atropine bolus in HD vs. Controls (29 vs. 59 bpm)
Heber et al, 1989 [7]	10 HD 5 Controls	HR responses to tilt	– No significant difference HD vs. Controls (1.13 vs. 1.26)
Heidebreder et al, 1989 [31]	27 HD 37 Controls	HR responses to respiration, tilt, VS	– Impaired responses in HD vs. Controls (respiration, 35 vs. 54 bpm; tilt, 1.04 vs. 1.16; VS, 1.24 vs. 1.46)
Vita et al, 1989 [32]	35 HD	HR responses to respiration, tilt, VS	– 14% of patients had ≥2 abnormal tests
Agarwal et al, 1991 [8]	25 CRF 8 Controls	HR responses to respiration, tilt, VS	– Impaired HR responses in CRF vs. Controls (respiration, 1.14 vs. 1.62; Tilt, 1.03 vs. 1.12; VS, 1.34 vs. 1.79) – Improvement in HR responses to respiration in 8 HD patients (1.14 vs. 1.19), though other parameters unchanged (tilt, 1.06 vs. 1.03; VS, 1.33 vs. 1.46) – Improvement in HR responses in 12 RT patients (respiration, 1.13 vs. 1.34; tilt, 1.05 vs. 1.08; VS, 1.37 vs. 1.65)
De Vecchis et al, 1994 [22]	7 CRF 8 LV dysfunction 8 Both	HR responses to respiration, tilt, VS atropine test	– PNS damage in 100% CRF, 62.5% LV dysfunction and 87.5% both patients
Jassal et al, 1997 [33]	71 HD	HR responses to respiration, tilt, VS	– 61% of patients had abnormal tests
Hathaway et al, 1998 [44]	43 CRF 168 HD 61 PD 67 Controls	HR responses to respiration, VS	– Reduced respiratory HR variability in CRF (14 bpm), HD (15) and PD (13) groups compared to Controls (25) – Reduced VS ratio in CRF (1.4), HD (1.3) and PD (1.3) groups compared to Controls (1.7)
Jassal et al, 1998 [34]	41 HD/PD (>65 yrs) 42 HD/PD (<65 yrs) 17 Controls (>65 yrs) 23 Controls (<65 yrs)	HR responses to respiration, tilt, VS	– Higher percentage of patients compared to Controls with impaired HR responses in both older (respiration, 73.2 vs. 35.3%; tilt, 58.5 vs. 17.6%; VS, 58.5 vs. 5.9%) and younger groups (respiration, 17.6 vs. 4.3%; tilt, 54.8 vs. 4.3%; VS, 19 vs. 4.3%)
Vita et al, 1999 [35]	30 HD	HR responses to respiration, tilt, VS	– 37% of patients had at least 1 abnormal test – 40% of patients had >1 abnormal test

Abbreviations are: CRF, chronic renal failure; HD, hemodialysis; PD, peritoneal dialysis; RT, renal transplant; BP, blood pressure; HR, heart rate; VS, Valsalva maneuver; bpm, beats per minute.

Table 3. Results of studies assessing autonomic nervous system function in chronic renal failure patients by spectral analysis techniques

Study	Population	Test	Findings
Axelrod et al, 1987 [45]	10 CRF 8 HD 7 PD 30 Controls	PI spectra (FFT)	– Reduced LF (0.1–0.2 Hz) power in all patients vs. Controls (0.27×10^{-4} vs. 0.95×10^{-4} msec^2), with non-significantly greater reductions in HD and PD vs. CRF – Reduced HF (0.2–0.3 Hz) power in all patients vs. controls (0.49×10^{-4} vs. 0.17×10^{-3})
Cloarec-Blanchard et al, 1992 [46]	6 HD 6 Controls	SBP spectra (FFT)	– Reduced LF (0.06–0.13 Hz) power on standing in HD vs. Controls (340 vs. 740 mm Hg^2) – No differences when supine (327 vs. 523 mm Hg^2)
Takahashi et al, 1996 [47]	11 HD 10 Controls	PI spectra (AR)	– Reduced LF (0.04–0.14 Hz) power HD vs. Controls supine (11 vs. 21 msec^2) and standing (12 vs. 26 msec^2) – Reduced HF (0.25 Hz) power HD vs. Controls supine (15 vs. 25 msec^2) and standing (11 vs. 15 msec^2) – Reduced LF/HF ratio HD vs. Controls supine (0.7 vs. 1.1) and standing (1.1 vs. 2.1)
Hathaway et al, 1998 [44]	43 CRF 168 HD 61 PD 48 Controls	PI spectra (FFT)	– Reduced LF (0.04–0.15 Hz) power in CRF (4.3 msec^2), HD (4.4) and PD patients (4.0) vs. Controls (6.4) – Reduced HF (0.15–0.4 Hz) power in CRF (3.6 msec^2), HD (3.6) and PD patients (3.2) vs. Controls (5.1)
Rubinger et al, 1999 [48]	14 HD 8 RT 14 Controls	PI spectra (AR)	– Reduced LF (0.05–0.15 Hz) and HF (0.15–0.4 Hz) powers in HD vs. Controls (LF, 1047 vs. 3515 msec^2; HF, 267 vs. 991) – No significant differences in LF and HF powers in RT vs. Controls (LF, 2832 vs. 3933 msec^2; HF, 810 vs. 1571)
Vita et al, 1999 [35]	30 HD (19 with AN) 20 Controls	PI spectra (AR)	– No significant differences in LF (0.03–0.15 Hz) and HF (0.15–0.33 Hz) powers HD vs. Controls supine (LF, 44 vs. 54 nu; HF, 26 vs. 23) – No significant differences in LF and HF powers HD patients with vs. without AN supine (LF, 39 vs. 53 nu; HF, 25 vs. 28) – Reduced LF but not HF power HD vs. Controls standing (LF, 52 vs. 72 nu; HF, 16 vs. 15) – Reduced LF but not HF power HD patients with vs. without AN standing (LF, 50 vs. 56 nu; HF, 16 vs.17)
Bald et al, 2001 (abstract)	20 HD 27 CRF 27 Controls	SBP spectra (AR) PI spectra (AR)	– Reduced LF (0.04–0.15 Hz)/HF (0.15–0.4 Hz) ratio for SBP spectra between HD but not CRF patients and Controls – No significant differences in LF/HF ratio for PI spectra between HD, CRF and Control groups
Carr et al, 2001 (abstract)	83 CRF (54 severe) 24 Controls	PI spectra (FFT) SBP spectra (FFT)	– PI: Reduced LF (0.05–0.15 Hz) power severe CRF (23 nu) compared to mild-to-moderate CRF (29) and Controls (29), but no differences in HF (0.2–0.35 Hz) power (19 vs. 16 vs. 19) – SBP: Reduced LF power severe CRF (15 nu) compared to mild-to-moderate CRF (24) and controls (31), but no differences in HF power (8 vs. 7 vs. 6)
Giordano et al, 2001[a] [49]	11 HD 10 Controls	PI spectra (AR)	– Increased LF (0.04–0.15 Hz) power HD vs. Controls (72.4 vs. 47.2 nu) – Reduced HF (0.16–0.45 Hz) power HD vs. Controls (18.7 vs. 54.5 nu) – Increased LF/HF ratio HD vs. Controls (5.6 vs. 0.8)

Abbreviations are: HD, hemodialysis; SBP, systolic blood pressure; FFT, fast Fourier Transform; LF, low frequency; PI, pulse interval; AR, autoregressive; HF, high frequency; AN, autonomic neuropathy; nu, normalized units; CRF, chronic renal failure. Only normotensive hemodialysis patients from these studies have been included in Table 3; see Table 5 for comparison of hypotension-prone and normotensive hemodialysis patients.

[a] Only non-diabetic hemodialysis-dependent chronic renal failure subjects were included

The high frequency power (0.20 to 0.35 Hz) of the decomposed spectrum of pulse interval variability is a reliable marker of vagal activity [11, 38, 40]. In particular, the use of physiological measures recognized to increase vagal drive, such as controlled respiration, cold facial stimulation and rotational stimuli, result in an increase in the high frequency peak [41, 42]. Conversely, the use of pharmacological vagal blockade with atropine practically abolishes pulse interval variability in the high frequency band [41, 43].

Using these techniques, there is a consistent reduction in high frequency power compatible with parasympathetic dysfunction in hemodialysis patients (Table 3) [44, 45, 47–49]. However, Vita and colleagues found no significant differences in high frequency power of the pulse interval spectra between 30 hemodialysis patients and 20 control subjects (Table 3) [35]. Again, there have been few studies of pre-dialysis chronic renal failure patients, though Axelrod and colleagues have compared the mid (vagal) and high (respiratory and vagal) frequency pulse interval powers in dialysis-dependent and dialysis-independent chronic renal failure. Greater reductions were seen in peritoneal and hemodialysis compared to dialysis-independent patients, all chronic renal failure patients have lower vagal powers than control subjects (Table 3) [45]. We further studied dialysis-independent patients with increasing degrees of chronic renal failure, and the data show no differences in high frequency power between patients with mild-to-moderate and severe chronic renal failure, and control subjects (unpublished data and Table 3).

SYMPATHETIC NERVOUS SYSTEM

Classical techniques

Standard assessments of the integrity of the sympathetic nervous system include the measurement of blood pressure responses to orthostatic change and pressor stimuli, including handgrip, mental arithmetic and cutaneous cold [18]. Unlike the results of studies assessing the parasympathetic nervous system, the conclusions vary. Some studies report abnormal sympathetic nervous system function in chronic renal failure patients [5, 19–21, 23, 27, 29, 30, 32–35], though others report normal function (Table 4) [6–8, 22, 24, 25, 28, 31]. Indeed, exaggerated hypertensive responses to mental arithmetic in predialysis [8] and to cold pressor in hemodialysis chronic renal failure patients [6] have been reported.

Interestingly, in those chronic renal failure patients with sympathetic dysfunction, there may be an improvement following hemodialysis [21]. However, continuing deteriorating blood pressure responses to orthostatic change and isometric handgrip have been found after 18 and 56 months, respectively, of hemodialysis [36]. As well as assessing the pressor response to isometric handgrip, Campese and colleagues also assessed the pressor responses to a norepinephrine infusion. They reported lower rises in dialysis-dependent and dialysis-independent chronic renal failure patients at all three-dose levels of norepinephrine. They concluded that there was evidence of end-organ responsiveness to catecholamine in addition to other sympathetic dysfunction [20].

Power spectral analysis techniques

In addition to the assessment of cardiac baroreceptor sensitivity, the technique of power spectral analysis with the use of fast Fourier Transform can be used to assess the integrity of the underlying sympathovagal balance of autonomic cardiovascular system control [11, 38, 39]. The low frequency power (0.05 to 0.15 Hz) of the decomposed spectrum of pulse interval variability may be significantly increased by measures that enhance sympathetic drive, including passive tilt or active standing [41, 42, 50, 51] and mental stress induced by arithmetic calculation [52, 53]. Pharmacological blockade with propranolol reduces low frequency power [54, 55]. However, low frequency power is not entirely abolished by beta-blockade, and atropine also may reduce low frequency power albeit under conditions of controlled respiration [41]. Furthermore, there are a number of other requirements in addition to intact sympathetic nervous system efferents for the generation of a low frequency peak, including a reactive vascular system and an intact baroreflex [56]. Therefore, low frequency power is not entirely a marker of the sympathetic nervous system, and results should be interpreted with caution.

Using these techniques, there are again different conclusions with only some research groups demonstrating reduced low frequency power of pulse interval [35, 48] and systolic blood pressure variability (Table 3) [46]. Interestingly, Cloarec-Blanchard and colleagues reported a significant difference in systolic blood pressure powers between hemodialysis patients and control subjects on standing, that is, when there should be sympathetic hyperactivity, and consistent with uremia-related sympathetic neuropathy [46]. However, other groups have reported increased low frequency powers (Table 3) [49]. Indeed, Giordano and colleagues have suggested that this increased sympathetic activity may predispose to sudden cardiac death in waiting list renal transplant patients [49].

However, the low-to-high frequency ratio is probably a more informative assessment of overall cardiovascular autonomic integrity. Concerning systolic blood pressure variability, Bald and colleagues reported a reduced low-to-high frequency ratio in 20 hemodialysis-dependent chronic renal failure children and adolescents compared to controls, indicating autonomic dysfunction. However, they did not find any differences compared to controls in the twenty-seven pre-dialysis patients studied (abstract; Bald at al, *ibid*). Concerning pulse interval variability, Giordano and colleagues reported an increased low-to-high frequency ratio reflecting increased sympathetic activity [49], in keeping with the findings of others [57]. Changes in the low-to-high frequency ratio have been specifically demonstrated in hemodialysis patients at risk of intra-dialytic hypotension [47, 58–60], which is discussed in a later section.

Alternative techniques of sympathetic nervous system assessment

Plasma norepinephrine levels reflect the rate of norepinephrine spillover from the synaptic cleft and its rate of removal from plasma, and have been measured also as an assessment of sympathetic nervous system function. Studies have generally reported increased levels of plasma norepinephrine in hemodialysis-dependent chronic renal failure patients compared to controls, suggesting either normal or increased sympathetic nervous system activity [24, 61–66], though others have found no significant differences compared to controls [20, 67]. However, Campese and colleagues investigated 16 hemodialysis-dependent and 21 pre-dialysis chronic renal failure patients compared to 60 control subjects, and identified increased plasma norepinephrine levels in the pre-dialysis patients only [20], confirming the findings of Atuk and colleagues [68].

The differences in these findings may relate to methodology, as well as the reproducibility of laboratory plasma norepinephrine estimations. However, the reduction toward control subject levels in hemodialysis-dependent patients may reflect the duration, type and efficiency of dialysis, and these factors may be important in explaining

Table 4. Results of studies assessing sympathetic nervous system function in chronic renal failure patients

Study	Population	Test	Findings
Ewing et al, 1975 [23]	26 HD	BP responses to handgrip	– Abnormal/borderline responses in 45% of patients
Campese et al, 1981 [20]	21 CRF 16 HD 60 Controls	BP responses to handgrip, tilt	– Reduced BP rise during handgrip in CRF (15 mm Hg) and HD (21) vs. Controls (28) – Significant orthostatic BP fall in Controls and CRF, but not HD patients
Naik et al, 1981 [24]	27 HD 15 Controls	BP responses to handgrip, tilt, cutaneous cold	– No significant differences in SBP increases HD vs. Controls (handgrip, 25 vs. 29 mm Hg; tilt, 4 vs. 0; cold, 17 vs. 21) – Significantly lower DBP increase HD vs. Controls for handgrip (18 vs. 30 mm Hg), though other responses not significantly different (tilt, 5 vs. 10; cold, 15 vs. 17)
Zoccali et al, 1982 [25]	18 HD 12 Controls	BP responses to tilt, handgrip, cutaneous cold	– No significant differences in BP increases HD vs. Controls (tilt, 13/10 vs. 4/8 mm Hg; handgrip, 30/24 vs. 29/27; cold, 23/16 vs. 21/17)
Heidbreder et al, 1985 [21]	31 CRF 35 HD 18 RT 37 Controls	BP responses to tilt, handgrip, cutaneous cold, mental stress	– Significant orthostatic SBP and DBP changes in CRF vs. Controls (−20/−2 vs. 3/4 mm Hg), though no significant differences in other tests (grip, 14 vs. 16; cold, 12/9 vs. 17/13; mental, 26/18 vs. 33/23) – No significant differences HD vs. Controls (tilt, −6/8 vs. 3/4 mm Hg; grip, 15 vs. 16; cold, 13/11 vs. 17/13; mental: 29/19 vs. 33/23). Orthostatic change significantly improves with HD vs. CRF groups (−6/8 vs. −20/−2) – No significant differences RT vs. Controls (tilt: −4/3 vs. 3/4 mm Hg; grip, 13 vs. 16; cold, 16/11 vs. 17/13; mental, 25/16 vs. 33/23). Orthostatic SBP change significantly improves with RT vs. CRF groups (−4 vs. −20)
Malik et al, 1986 [27]	19 CRF 40 HD 8 PD	BP responses to handgrip, tilt	– 21% had abnormal SNS tests (in addition to definite PNS dysfunction), with no difference between groups
Mallamaci et al, 1986 [28]	12 HD 10 PD 11 RT 12 Controls	BP responses to tilt	– No significant differences in MAP responses to tilt (HD, 9 mm Hg; PD, 11; RT, 9; Controls, 13)
Vita et al, 1987 [29]	20 HD	BP responses to tilt, handgrip	– Autonomic dysfunction (≥1 abnormal SNS test in association with ≥2 abnormal PNS tests) more common in elderly (66–76 years) than young (35–53) patients (55 vs. 9%)
Bondia et al, 1988 [6]	10 HD 8 Controls	BP responses to cutaneous cold	– Increased SBP rise in HD vs. Controls (42 vs. 24 mm Hg)
Heber et al, 1989 [7]	10 HD 5 Controls	BP responses to handgrip	– No significant differences HD vs. Controls
Heidbreder et al, 1989 [31]	27 HD 37 Controls	BP responses to handgrip, tilt, cutaneous cold, mental stress	– No significant differences HD vs. Controls (handgrip, 16 vs. 16 mm Hg; tilt, −5/8 vs. −3/4; cold, 14/12 vs. 17/13; mental, 28/19 vs. 33/23)
Vita et al, 1989 [32]	35 HD	BP responses to tilt, handgrip	– 26% ≥1 abnormal SNS test (in association with ≥2 abnormal PNS tests)
Agarwal et al, 1991 [8]	25 CRF 8 Controls	BP responses to tilt, noise, cutaneous cold, mental stress	– Increased BP responses to mental stress CRF vs. Controls (16/11 vs. 10/6 mm Hg), otherwise no significant differences (tilt, −6 vs. −5; noise, 12/7 vs. 18/4; cold, 19/10 vs. 18/10) – No significant changes in 8 HD patients: (tilt, 7 vs. 9 mm Hg; noise, 14/10 vs. 6/7; cold, 15/7 vs. 15/10; mental, 14/13 vs. 10/10) – No significant changes in 12 RT patients (noise, 12/6 vs. 10/8 mm Hg; cold, 19/10 vs. 13/9; mental, 12/10 vs. 10/9)
De Vecchis et al, 1994 [22]	7 CRF 8 LV dysfunction 8 Both	BP responses to tilt, handgrip, cutaneous cold	– No evidence of SNS damage
Jassal et al, 1997 [33]	71 HD	BP responses to handgrip, tilt	– 63% had abnormal tests
Jassal et al, 1998 [34]	41 HD/PD (>65 yrs) 42 HD/PD (<65 yrs) 17 Controls (>65 yrs) 23 Controls (<65 yrs)	BP responses to handgrip, tilt	– Higher percentage of patients compared to controls with impaired BP responses in both older (tilt, 31.7 vs. 0%; grip, 53.7 vs. 29.4%) and younger groups (tilt, 11.9 vs. 0%; grip, 14 vs. 0%)
Vita et al, 1999 [35]	30 HD	BP responses to tilt, handgrip	– 13% of patients had evidence of combined SNS and PNS dysfunction

Abbreviations are: CRF, chronic renal failure; HD, hemodialysis; PD, peritoneal dialysis; RT, renal transplant; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SNS, sympathetic nervous system; PNS, parasympathetic nervous system.

differences in dialysis studies. Furthermore, increased catecholamine levels may be related to co-morbid conditions, including congestive cardiac failure, and be associated with poorer prognosis [69, 70].

Sympathetic activity also can be directly and accurately measured by microneurographic techniques. Using these techniques, Converse and colleagues reported increased sympathetic nerve discharge in 23 hemodialysis-dependent patients compared to 11 control subjects, reflecting sympathetic hyperactivity [71]. Interestingly, they also reported evidence of higher sympathetic discharge in those 18 hemodialysis-dependent patients with native kidneys compared to 5 patients with bilateral nephrectomies, and suggested that chronic renal failure is associated with reversible sympathetic activation mediated by the failing kidney [71]. More recently, Ligtenberg and colleagues have reported increased muscle sympathetic activity using these techniques in dialysis-independent chronic renal failure patients, which is implicated in the associated hypertension and controlled by angiotensin-converting enzyme inhibitor therapy [72].

OTHER EFFECTS OF DIALYSIS ON CARDIOVASCULAR AUTONOMIC FUNCTION

Intra-dialytic hypotension

Acute hypotension is an important complication of hemodialysis treatment, occurring in up to one-third of dialysis sessions [73, 74]. Two clinical types of intra-dialytic hypotension have been recognized: a relatively asymptomatic gradual blood pressure reduction accompanied by a heart rate increase, and a more abrupt blood pressure fall accompanied by a bradycardia and symptoms of cramps, nausea and vomiting [75, 76]. While reduced cardiac performance secondary to left ventricular hypertrophy and myocardial interstitial fibrosis has been implicated in this condition [77, 78], the failure of cardiovascular autonomic regulatory mechanisms also is likely to be of importance.

In keeping with this premise, a number of groups have reported impairment in cardiac baroreceptor sensitivity in hemodialysis patients with intradialytic hypotension [7, 8, 20, 79–82]. Kersh and colleagues studied 8 patients with intradialytic hypotension, and identified two different patient groups. Two patients demonstrated a normal heart rate and blood pressure response to the Valsalva maneuver, and the hypotension responded to a fluid challenge. However, the other six patients had evidence of autonomic dysfunction, did not respond to a fluid challenge, but responded to norepinephrine [79]. Again, Lilley, Golden and Stone found evidence of impaired baroreceptor sensitivity in 10 patients with dialysis-induced hypotension, though baroreceptor sensitivity was normal in 10 patients without this complication. However, both groups demonstrated normal blood pressure responses to a cold pressor stimulus, suggesting that the defect was in the afferent limb of the baroreceptor reflex arc [80]. This hypothesis is further supported by the normal blood pressure responses to cold and mental arithmetic reported by Nies and colleagues in a group of five patients with intradialytic hypotension, who had significantly lower values for baroreceptor sensitivity than expected [81]. These findings were confirmed later in a non-invasive study of 12 patients (6 hypotension-prone) by Pelosi and colleagues. In addition, these authors reported a progressive reduction in the low frequency power of systolic blood pressure variability, which dramatically reduced at the time of vascular collapse, indicating sympathetic nervous system dysfunction (Table 5) [60]. Similar abnormalities with respect to sympathetic autonomic dysfunction also have been reported for pulse interval variability (Table 5) [47, 58, 59]. However, some researchers have found both combined parasympathetic and sympathetic dysfunction from reduced low and high frequency pulse interval spectral power [47] or isolated parasympathetic dysfunction from reduced heart rate variability [65].

Not all studies have reported evidence of autonomic dysfunction in patients with intradialytic hypotension [6, 25, 30, 83]. However, this may reflect methodological issues related to hemodynamic measures and subject selection. Straver and colleagues assessed autonomic function from heart rate variability to respiration, orthostasis and Valsalva maneuver in 10 hypotensive compared to 18 nonhypotensive hemodialysis patients and identified no differences in baseline autonomic function, though changes in autonomic parameters during dialysis were not studied [83]. Vita and colleagues identified 8 of a group of 22 hemodialysis patients with intradialytic hypotension, though 6 patients had normal autonomic function tests [30]. Similarly, studies estimating plasma norepinephrine as a measure of sympathetic activity have reported increased levels compared to control subjects in both hypotension-prone and non-hypotension–prone hemodialysis patients [24, 65]. However, Takahashi and colleagues found the highest plasma noradrenaline levels in 10 hypotensive compared to 11 non-hypotensive hemodialysis patients and 10 control subjects, probably reflecting poor end-organ catecholamine responsiveness [47].

Peritoneal dialysis

Low [84] and middle molecular weight [85] substances have been incriminated as factors in uremic neuropathy. Peritoneal dialysis leads to more effective clearance of these substances when compared to hemodialysis and, therefore, it has been suggested that peritoneal dialysis may be more effective than hemodialysis in reversing uremia-related autonomic nervous system dysfunction. This has only been formally assessed in a few studies [27, 28, 45]. One small study compared 12 hemodialysis and 10 peritoneal dialysis to 12 control subjects. Reduced

Table 5. Results of studies assessing autonomic nervous system function by spectral analysis techniques in stable (normotensive) and unstable (hypotension-prone) hemodialysis-dependent chronic renal failure patients

Study	Population	Test	Findings
Takahashi et al, 1996 [47]	11 Stable 10 Unstable	PI spectra (AR)	– Reduced LF (0.04–0.14 Hz) power in Unstable vs. Stable supine (4 vs 11 $msec^2$) and standing (5 vs. 12 $msec^2$) – Reduced HF (0.25 Hz) power in Unstable vs. Stable supine (7 vs. 15 $msec^2$) and standing (6 vs. 11 $msec^2$) – Reduced LF/HF ratio in Unstable vs. Stable supine (0.4 vs. 0.7) and standing (0.6 vs. 1.1)
Calvacanti et al, 1997 [58]	15 Stable 15 Unstable	PI spectra (AR)	– Stable patients exhibited predominantly LF (0.06–0.15 Hz) power during HD – Unstable patients exhibited predominantly HF (0.15–0.4 Hz) power during HD – LF/HF ratio was greater in Stable than Unstable patients throughout HD
Barnas et al, 1999 [59]	11 Stable 8 Unstable	PI spectra (FFT)	– No significant differences were seen in baseline LF (0.04–0.15 Hz)/HF (0.15–0.4 Hz) ratio between Unstable vs. Stable groups (1.12 vs. 1.65) – In Stable HD sessions, LF power increased (45.2 to 59.9 nu) and HF power reduced (54.8 to 40.2 nu) – In Unstable sessions, hypotension was associated with a sudden fall in LF power (62.8 to 40.0 nu) and rise in HF power (37.9 to 60.3 nu)
Pelosi et al, 1999 [60]	6 Stable 6 Unstable	PI spectra (AR) SBP spectra (AR)	– PI spectra: LF (0.03–0.15 Hz)/HF (0.15–0.4 Hz) ratio changes were significantly different at time of maximal BP decrease between Unstable and Stable patients (−2.9 vs. +3.7), predominantly reflecting increased LF power in Stable group – SBP spectra: LF power changes were significantly different at time of maximal BP decrease between Unstable and Stable patients (−8.6 vs. +13.3 mm Hg^2)

Abbreviations are: HD, hemodialysis; SBP, systolic blood pressure; FFT, fast Fourier Transform; LF, low frequency; PI, pulse interval; AR, autoregressive; HF, high frequency; nu, normalized units.

heart rate variability to respiration, orthostatic change and the Valsalva maneuver was observed in both dialysis groups, reflecting impaired parasympathetic nervous system activity. No significant differences were observed in blood pressure response to the orthostatic change between control and both dialysis groups, indicating an intact sympathetic nervous system function [28]. Similarly, Malik, Winney and Ewing did not identify any differences in autonomic score (reflecting the number of abnormal or borderline tests of parasympathetic and sympathetic function) between 40 hemodialysis and 8 peritoneal dialysis patients [27]. Similar results have been observed using power spectral analysis techniques. Axelrod and colleagues reported reduced low, middle and high frequency powers of pulse interval variability in all dialysis patients compared to controls, though there were no significant differences between hemodialysis and peritoneal dialysis patients [45].

EFFECTS OF RENAL TRANSPLANTATION ON CARDIOVASCULAR AUTONOMIC FUNCTION

Cardiovascular morbidity and mortality remains a significant problem within the renal transplant population, accounting for 15% of all deaths [86–88]. Therefore, it would be very interesting to establish the effects of renal transplantation on cardiovascular autonomic function. A number of studies have demonstrated no [31, 89–91] or only minimal [92] improvement in autonomic neuropathy following combined renal and islet cell transplantation for diabetic nephropathy. However, substantial improvement in peripheral neuropathy has been reported [89, 90]. These differences may relate to comorbid factors predisposing to autonomic neuropathy and the use of immunosuppressive medication, which may affect autonomic function.

Nonetheless, a number of studies have reported significant improvement in cardiovascular autonomic function. The reported improvements have been in parasympathetic nervous system function by the assessment of heart rate responses to respiration, orthostatic change and Valsalva maneuver [19, 21, 28, 93]. Improvements have been seen in sympathetic nervous system function by assessing blood pressure responses to orthostatic change and sustained handgrip [19, 21]. Rockel and colleagues studied 16 patients at 3 and 18 months post-renal transplantation, and reported an improvement in chronic renal failure-induced autonomic dysfunction with similar heart rate and blood pressure responses to the Valsalva maneuver and orthostatic change to those found in control subjects [19]. Reversal in baroreceptor sensitivity also was demonstrated following renal transplantation by newer time-domain [17] as well as frequency-domain techniques [48].

One main disadvantage to all these studies is that they compare dialysis-dependent chronic renal failure patient groups with different groups of post-renal transplant patients. However, longitudinal studies of chronic renal failure patients appear to confirm the observation that cardiovascular autonomic dysfunction is reversed by renal transplantation. Agarwal and colleagues reported a small subgroup of 12 patients who underwent renal transplantation. The baroreceptor sensitivity slope to bolus phenylephrine had improved when patients were further

studied a mean of 24 weeks following transplantation. Improvements were also seen in parasympathetic, but not sympathetic, cardiovascular autonomic function assessed by heart rate responses to respiration, orthostatic change and Valsalva maneuver and blood pressure changes to cold pressor, mental arithmetic and sudden loud noise stimuli, respectively [8]. In another study, Yildiz and colleagues studied 14 hemodialysis patients before and a mean of 4.6 months following renal transplantation. They reported an increase in low and high frequency spectral power of pulse interval variability, though no change in the low-to-high frequency ratio as a marker of sympathovagal balance [94].

PROGNOSTIC SIGNIFICANCE OF IMPAIRED CARDIOVASCULAR AUTONOMIC FUNCTION

Importantly, cardiovascular autonomic dysfunction may be of prognostic significance. As previously discussed, baroreceptor sensitivity is important in the short-term regulation of the cardiovascular system. Certainly, impaired cardiac baroreceptor sensitivity is associated with an increased risk of cardiovascular death following myocardial infarction, even allowing for other important prognostic factors, such as left ventricular dysfunction [95].

Interestingly, Jassal and colleagues have reported higher incidences of cardiac arrhythmias in hemodialysis patients with associated autonomic dysfunction on standard tests. These arrhythmias include: ventricular ectopics (24%), paroxysmal atrial fibrillation (11%), and ventricular tachycardia (8%) [33]. Furthermore, Hathaway and colleagues have reported abnormalities of 24-hour heart rate variability using power spectral analysis techniques in 278 dialysis-dependent and dialysis-independent diabetic and non-diabetic patients awaiting renal or combined renal-pancreatic transplantation. In particular, they noted a reduced standard deviation of mean RR intervals in successive five-minute blocks (reflecting circadian autonomic variability) and a reduced proportion of adjacent RR intervals with a difference of 50 msec (reflecting vagally-mediated alterations), compared to control subjects. During the six-month study period, there were five sudden cardiac deaths, none of whom had normal time or frequency domain measures of autonomic function [44].

Therefore, the prognostic significance of impaired cardiovascular autonomic function is increasingly being studied in chronic renal failure patients. Krivoshiev and colleagues found impaired heart rate responses to respiration and the Valsalva maneuver in 12 hemodialysis patients with a prolonged corrected QT compared to 8 patients with a normal corrected QT. They concluded that this reflected parasympathetic dysfunction and may predispose to sudden cardiac death. Indeed, they identified a group of 7 hemodialysis patients with sudden cardiac death who had a prolonged corrected QT interval [96]. In a study of 144 hemodialysis patients, Tozawa and colleagues reported that the hazard ratio for death from all causes increased 1.63 times per 1% increase in the coefficient of variation in systolic blood pressure (95% CI 1.05 to 2.53). The hazard ratio for death from cardiovascular causes increased by 1.78 times per 1% increase (95% CI 0.94 to 3.37) [97].

The use of power spectral analysis techniques also is yielding important prognostic information. Takahashi and colleagues have reported a significantly lower high frequency pulse interval power in 8 hemodialysis patients dying of sudden cardiac death, indicating reduced parasympathetic nervous system activity. These changes were in comparison with a group of 23 patients surviving for at least three years following cardiac catheterization (abstract; Takahashi et al, *J Am Soc Nephrol* 6:564, 1995).

CONCLUSIONS

In summary, chronic renal failure patients demonstrate evidence of autonomic dysfunction using both classical and newer non-invasive techniques of assessment. There is significant consensus regarding abnormalities of the parasympathetic nervous system, though conclusions are less clear-cut with respect to sympathetic nervous system function. Furthermore, there is evidence of impaired cardiac baroreceptor sensitivity, which is important in the overall integrity of cardiovascular autonomic control. These findings may be of clinical importance, and may be related to increased cardiovascular morbidity and mortality as well as intra-dialytic hypotension. The underlying mechanisms require further study before treatment strategies can be developed.

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