Autonomic Dysfunction In Uremia
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Autonomic nervous system dysfunction is a common feature in uremia and may have a number of clinical sequelae. Simple cardiovascular reflex screening can be performed in patients during conservative treatment, on periodic dialysis therapy, or after kidney transplantation to diagnose and follow up autonomic function impairment. Other approaches, such as heart-rate variability studies in the frequency domain by power spectral analysis, can provide a more accurate investigation of the disease.

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The autonomic nervous system (ANS) is involved in adaptation to environmental changes. The ANS is functionally distinguished in sympathetic and parasympathetic pathways, with both an afferent and efferent branch, under central control given by different structures in the brain stem, diencephalon, and telencephalon. Peripheral nerves regulating the autonomic control of heart rate and blood pressure show a histological structure of mainly small (2- to 6-μm) myelinated and unmyelinated fibers.

Autonomic involvement is common in metabolic disorders characterized by small-fiber damage, such as end-stage renal failure. The pathophysiological base of the axonal damage is most likely caused by the action of still unknown uremic toxins to nerve fibers. However, a different susceptibility of autonomic and somatic fibers is postulated because uremic autonomic and somatic neuropathies differ in incidence and response to dialysis treatment or kidney and combined kidney-pancreas transplantation.

Autonomic Function Investigation

The simplest way to noninvasively assess ANS function in the time domain is a battery of cardiovascular reflex tests that may show sympathetic or parasympathetic (afferent and/or efferent pathway) failure.

Tests of Predominantly Parasympathetic Function

R-R interval variability. Electrocardiogram recording during quiet breathing can evaluate heart-rate variation. This analysis examines beat-to-beat R-R interval variability, considering its SD. Interbeat variability seems to be predictive in identifying patients at increased risk for cardiac sudden death.

Valsalva’s maneuver. This test is used most frequently because it allows evaluation of the entire autonomic reflex arc. Although the Valsalva ratio is usually considered, calculated by dividing the longest R-R interval in phase IV by the shortest R-R interval in phase II, continued monitoring of heart rate and blood pressure permits one to obtain valuable information on the baroreflex arc.

Deep breathing. During the inspiration/expiration cycle, heart-rate changes are an expression of the efferent parasympathetic pathway.

Heart-rate response to standing. Recording the heart rate while standing, the 30/15 ratio is calculated as the ratio of the R-R interval at beat 30 to that at beat 15 after standing. It examines the integrity of the efferent parasympathetic branch.

Tests of Predominantly Sympathetic Function

Blood-pressure response to standing. Blood pressure is recorded after a convenient period of supine rest. In 1996, an international consensus committee established that orthostatic hypotension is diagnosed when standing is followed by a reduction in systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg within 3 minutes.
**Sustained handgrip.** This test studies the blood-pressure response to an isometric handgrip exercise.

Several studies showed an age-dependent derangement of cardiovascular reflexes in healthy subjects. Therefore, a critical approach to these tests should be considered using age-adjusted confidence intervals of normal values. In addition, old-aged uremic patients on intermittent hemodialysis therapy have more extensive parasympathetic and sympathetic damage than middle-aged patients, indicating that ANS in the elderly is more susceptible to uremic noxae. Other tests can be performed to evaluate sympathetic function, such as blood-pressure changes to cold stimulus, mental arithmetic exercise, or loud noise; the sympathetic skin response, and measurements of plasma catecholamine levels. There are also invasive tests evaluating the ANS, such as baroreceptor sensitivity studied by recording R-R interval variation and blood-pressure changes after the intravenous administration of phenylephrine, as a marker of end-organ responsiveness, and heart-rate response to intravenous atropine injection to assess the integrity of the efferent parasympathetic pathway. Recently, ANS function in uremic patients has been studied by single-photon emission computed tomography, using iodine 123–metaiodobenzylguanidine (MIBG) to evaluate its uptake in the cardiovascular and respiratory systems as an expression of autonomic sympathetic function.

A complementary approach to evaluate sympathetic-parasympathetic balance can be performed by considering power spectral analysis of heart-rate variability. Commonly, two different spectral regions can be distinguished: a high-frequency (HF) band in the range of 0.15 to 0.4 Hz and a low-frequency (LF) band in the range of 0.04 to 0.15 Hz. HF and LF components are regarded, but not invariably, as specific markers of parasympathetic and sympathetic activities, respectively. Finally, the LF-HF ratio can be considered a good indicator of sympathovagal balance.

**AUTONOMIC DYSFUNCTION**

An autonomic derangement was recognized since the early studies in uremic patients. Impotence, postural dizziness, gastric fullness or delay in emptying, bowel dysfunction, and reduced sweating are the most common symptoms. Neurophysiological investigation showed a reduction in heart-rate variability and baroreceptor control impairment. Afferent parasympathetic pathway damage was shown by means of the atropine test. It is noteworthy that parasympathetic influence is considered to have a protective role in avoiding dangerous arrhythmias.

Results of sympathetic activity investigation are contradictory. An impairment in reflex blood-pressure control has been found to be less common than parasympathetic damage in several studies. Recently, power spectral analysis of heart-rate variability allowed better insight into cardiovascular autonomic involvement in uremia, showing that the current opinion of major parasympathetic damage in hemodialysis patients has to be modified in favor of more widespread autonomic dysfunction involving both the sympathetic and parasympathetic pathways. However, Kurata et al. using MIBG as a sympathetic activity marker, found cardiac overactivity and a possible pulmonary abnormality in uremic patients on dialysis treatment.

In early studies, hemodialysis treatment seemed to improve autonomic function in uremic patients. Following reports did not confirm those results. A longitudinal study of chronic uremic patients on hemodialysis treatment suggested that ANS derangement is somewhat unavoidable and irreversible. Conversely, in a retrospective study, Laaksonen et al. found evidence that the adequacy of hemodialysis or peritoneal dialysis is a predictor of improvement in ANS function.

A wide assessment of autonomic function also was performed during a regular hemodialysis session, showing no acute autonomic dysfunction. This study also confirmed that hypotension during hemodialysis is not clearly caused by an autonomic derangement.

The relationship between autonomic dysfunction and renal transplantation is still not clearly definite. Several studies showed improvement in or normalization of autonomic parameters after kidney transplantation. In diabetic nephropathy, autonomic neuropathy was found to be unchanged up to 4 years after simultaneous transplantation of kidney and pancreas. It is noteworthy that the Swedish Huddinge group, despite a clear improvement in somatic polyneu-
ropathy, found no significant change in autonomic dysfunction 6 and 12 months after renal transplantation, as well as 6, 12, and 24 months after combined kidney-pancreas transplantation. However, they documented a slight improvement in parasympathetic function 48 months after either kidney or combined transplantation. The latter findings suggest that uremic autonomic neuropathy needs a long time to be repaired in transplant recipients. This is in accordance with a study from our group showing that ANS dysfunction can recover after long-term (8 years) bicarbonate dialysis.

REFERENCES


