REVIEW

Baroreflex failure: a neglected type of secondary hypertension

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ABSTRACT

The arterial baroreflex buffers abrupt transients of blood pressure and prevents pressure from rising or falling excessively. In experimental animals, baroreceptor denervation results in temporary or permanent increases in blood pressure level and variability, depending on the extent of denervation. In humans, the clinical syndrome of baroreflex failure may arise from denervation of carotid baroreceptors following carotid body tumour resection, carotid artery surgery, neck irradiation and neck trauma. The syndrome is characterised by acute malignant hypertension and tachycardia followed by labile hypertension and hypotension. Baroreflex failure can be a cause of hypertension and should also be considered in the differential diagnosis of pheochromocytoma. Patients with suspected baroreflex failure should be referred to specialised centres for diagnostic testing and treatment.

BARORECEPTORS

In the late 1920s, Hering and Koch were the first to recognise the reflex nature of changes in heart rate and blood pressure evoked by external massage of the neck. The afferents were tracked as nerve endings at the carotid bifurcation.[1,2] The arterial baroreflex buffers abrupt transients of blood pressure and originates from stretch sensitive receptors in the arterial wall of the carotid sinus and the aortic arch and large vessels of the thorax.[3,4] Afferent fibres from carotid sinus baroreceptors join the glossopharyngeal nerve (ninth cranial nerve) and project to the nucleus tractus solitarii in the dorsal medulla, which in turn projects

to efferent cardiovascular neurones in the medulla. In addition to carotid baroreceptors, stretch-sensitive baroreceptors are also located in the aortic arch, heart and large pulmonary vessels. The extra-carotid baroreceptors transmit their afferent information along with the vagal nerves to the same brain stem nuclei. The efferent limbs of the baroreflex loop consist of sympathetic and parasympathetic fibres to the heart as well as to blood vessels.

EXPERIMENTAL AND IATROGENIC DENERVATION OF BARORECEPTORS

Arterial baroreceptors provide a tonic inhibitory influence on sympathetic tone, thus controlling peripheral vasoconstriction and cardiac output.[1,2] Therefore, baroreceptor denervation would be expected to result in a sustained increase in sympathetic tone and, as a consequence, a sustained increase in blood pressure. Indeed, experimental denervation of carotid, aortic and cardiopulmonary baroreceptors in dogs produces a persistent increase in blood pressure level and variability.[5] Following selective carotid and/or aortic baroreceptor denervation, the increase in blood pressure and heart rate is usually temporary.[5-8] The first report on baroreceptor denervation in humans appeared in the 1930s.[9] Unilateral section of the glossopharyngeal nerve in five patients with glossopharyngeal neuralgia produced a prompt and pronounced rise in blood pressure, which lasted 5 to 12 days. In 1956, a patient died from a fatal hypertensive crisis following unilateral carotid sinus denervation, which had been performed for the relief of recurrent syncope due to a

hypersensitive carotid sinus syndrome.[10] In 1985, Fagius and Wallin reported the effects of experimental chemical blockade of carotid baroreceptors in humans.[11] These authors performed bilateral anaesthetic blockade of vagal and glossopharyngeal nerves upon each other, which resulted in an elevation of blood pressure and tachycardia, accompanied by a strong increase in muscle sympathetic nerve activity.

Apart from these experimental studies, inadvertent baroreceptor denervation may occur as a complication of bilateral carotid body tumour resection,[12-14] radiotherapy and surgery for laryngeal/pharyngeal carcinoma,[12,15,16] bilateral[17,18] and unilateral[19,20] carotid endarterectomy and trauma of the neck.[12] Disruption of the baroreflex has also been reported in the event of ischaemic or neurodegenerative lesion of the nucleus tractus solitarii.[21] The clinical syndrome of baroreflex failure has now been characterised as a separate clinical entity.[12,22]

BAROREFLEX FAILURE SYNDROME

The acute form of baroreflex failure is encountered following loss of glossopharyngeal or carotid sinus nerve function due to surgical intervention or accidental injury.[17-20] It is characterised by severe, unremitting hypertension, tachycardia, and headache (*table 1*). The systolic blood pressure typically exceeds 250 mmHg,[22] which may lead to hypertensive encephalopathy[17,19] and (fatal) cerebral haemorrhage.[10,20] Hypertensive crisis may evolve over days and weeks into the more chronic volatile hypertension phase.[12,14,18,23,24] In addition, votatile hypertension may result from a gradual decline in baroreflex function due to neck irradiation.[12,16] Irradiation may affect the stretch-induced afferent baroreceptor activity due to direct trauma of baroreceptors or by inducing atherosclerosis and fibrosis of the carotid sinus arterial wall.[25-27] Volatile hypertension due to baroreflex failure is characterised by paroxysms of abrupt sympathetic activation, including excessive increments in plasma catecholamine levels.[12,22] Surges of blood pressure and tachycardia may occur spontaneously or are elicited by mental stress or physical stimuli such as exercise, cold and sexual arousal.[28] These bouts of sympathetic activation may be accompanied by severe headache, palpitations, diaphoresis, light-headedness and anxiety.[12] Intraocular pressure may be increased.[29] In addition, emotional instability appears to be a prominent feature in this phase of baroreflex failure. Apart from hypertensive surges, hypotensive valleys may occur during sleep.[16] In rare cases, inadequate baroreflex buffering of cardiovagal efference is the most prominent feature, resulting in malignant vagotonia with hypotension, bradycardia, and asystole.[30] Accompanying symptoms of this so-called 'selective baroreflex failure' include fatigue and dizziness, with possible progression to frank syncope.

Table 1
Symptoms and signs of baroreflex failure

ACUTE PHASE FOLLOWING BARORECEPTOR DENERVATION (DAYS-WEEKS)	
Severe sustained elevation of blood pressure (systolic pressure typically >250 mmHg)	
Tachycardia	
Elevation of plasma catecholamines	
Headache	
Complications of hypertension	Encephalopathy
	Cerebral haemorrhage

CHRONIC PHASE (WEEKS-YEARS)	
Common	
Volatile hypertension and tachycardia	
Paroxysm of	Palpitations
	Headache
	Diaphoresis
	Light headedness
	Anxiety
	Emotional instability
	Increased intraocular pressure
Rare	
Hypotension (during sleep)	
Bradycardia, asystole	
Fatigue	
(Orthostatic) dizziness	
Syncope	

WHEN SHOULD BAROREFLEX FAILURE BE CONSIDERED?

A history of prior (iatrogenic) trauma of the neck is the most important clue in suspecting the diagnosis of baroreflex failure. The diagnosis of baroreflex failure should be considered in patients with a negative work-up for pheochromocytoma, since this carries a strong clinical resemblance to baroreflex failure. Apart from pheochromocytoma, which should be ruled out by the proper biochemical and radiographic investigations, the differential diagnosis of baroreflex failure includes paroxysmal tachycardia, migraine, hyperthyroidism, renovascular hypertension, alcohol withdrawal, drug use (e.g. amphetamines or cocaine), mastocytosis, carcinoid syndrome, intracranial lesions and psychological disorders (panic attack, generalised anxiety disorder).[22]

Labile hypertension and hypotension can be demonstrated by a 24-hour ambulatory blood pressure recording.[17] Patients with a suspicion of baroreflex failure should be referred

to a specialised centre for the evaluation of autonomic cardiovascular function. Disruption of the baroreflex arch is demonstrated by absence of reflex bradycardia and tachycardia in response to intravenous injection of pressor drugs such as phenylephrine and depressor drugs as nitroprusside, respectively.[12,31] The baroreflex modulation of muscle sympathetic nerve activity can be assessed by microneurography of sympathetic fibres within the peroneal nerve (*figure 1*).[32,33] Additional cardiovascular reflex tests such as Valsalva's manoeuvre, standing up, forced breathing, cold face test, cold pressor test and mental arithmetic[34] can be used to tease out the localisation of the baroreflex lesion.[34] Baroreflex failure is essentially different from autonomic neuropathy, which is either primary (pure autonomic failure, multiple system atrophy) or secondary (e.g. diabetes mellitus). In contrast to baroreflex failure which is caused by lesions of the afferent innervation of baroreceptors, autonomic neuropathy is characterised by abnormal efferent innervation to the heart and resistance vessels. The key feature of autonomic neuropathy is (severe) orthostatic hypotension.[35] Syncope due to the hypersensitive carotid sinus syndrome is caused by excessive afferent nerve impulses towards the brainstem, causing cardioinhibition and/ or vasodepression resulting in syncope.[36]

TREATMENT AND PROGNOSIS

Information on the treatment of acute, postsurgical baroreflex failure is scarce and relies on observational case studies. As in any form of hypertensive crisis, antihypertensive treatment in baroreflex failure is aimed at the prevention of hypertensive encephalopathy, (cerebral) haemorrhage, myocardial infarction, heart failure and hypertensive retinopathy. Haemodynamic monitoring of these patients in a medium or intensive care unit is warranted in the acute phase. Theoretically, intravenous administration of drugs with a short half-life is preferred in view of the strong blood pressure lability. Drugs that have been used in this setting include nitroprusside, phentolamine and labetalol.[37,38] Apart from antihypertensive treatment, adequate analgesic and sedative therapy for relief of postsurgical discomfort and baroreflex failure related symptoms such as headache and palpitations are indicated.

In the phase of labile hypertension, the primary goal of therapy is to reduce the frequency and magnitude of surges in blood pressure and heart rate. Clonidine, a centrally and peripherally acting α-adrenoreceptor and imidazoline
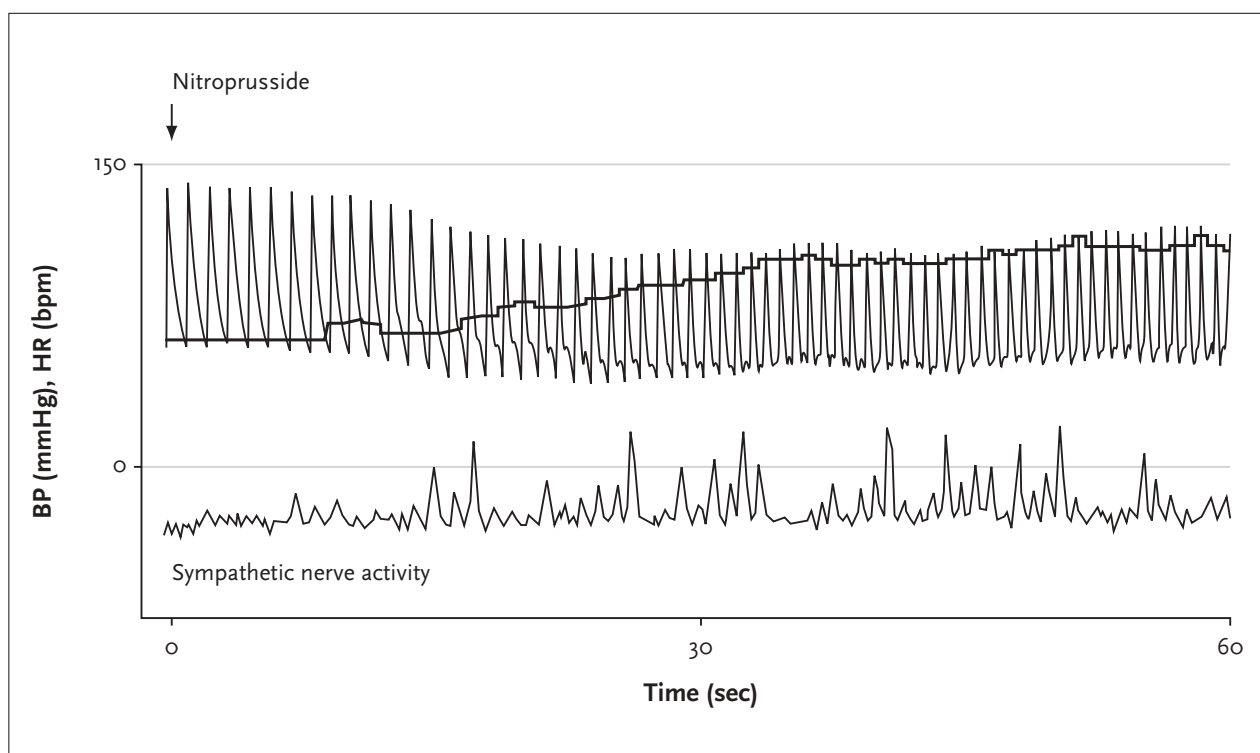
Figure 1

Assessment of baroreflex control of heart rate (upper panel) and muscle sympathetic nerve activity (lower panel) in a normal subject. Nitroprusside-induced hypotension elicits a baroreflex mediated increase in heart rate and muscle sympathetic nerve activity. BP = blood pressure, HR = heart rate.

agonist, has been shown to reduce both frequency and severity of pressor surges.[12,20-22] Both central inhibition of noradrenergic neurotransmission and sedative effects may contribute to the beneficial effect of clonidine in baroreflex failure. If tolerated by the patient, daily doses as high as 1.2 to 2.4 mg may be required. The α-adreno-receptor blocker phenoxybenzamine has also been shown to reduce the magnitude of blood pressure surges.[12] In patients who have been well controlled for months to years, clonidine may be tapered off and replaced by high doses of benzodiazepines, such as diazepam.[22] Apart from these agents, experimental treatment of baroreflex failure includes (non-registered) inhibitors of norepinephrine release. Agents that increase synaptic norepinephrine concentra-tions and may thereby elicit profound pressor responses are probably better avoided in baroreflex failure.[22] These include tricyclic antidepressants, amphetamines, mono amino oxidase A inhibitors, cocaine, and tyramine-contain-ing food and beverages. Additional nonpharmacological strategies include avoidance of individual factors that evoke sympathetic surges and (relaxation) biofeedback training.[39-41] In the rare patients with malignant vagotonia due to selective baroreflex failure, insertion of a pacemaker may be necessary.[30] In the rare patients with predominant hypotension, low doses of fludrocortisone and increased dietary salt may be indicated.[22] Regarding the polar shifts in blood pressure, treatment of baroreflex failure can be challenging and frequent follow-up of patients is warranted. The clinical expression of baroreflex failure varies consid-erably among patients, probably depending on the extent of denervation of baroreceptors. In addition, the natural cause of baroreflex failure is unpredictable. In most cases, the pressor surges attenuate over time, but in some cases, volatile hypertension is permanent.[12]

CONCLUSION

Baroreceptors are essential for buffering acute changes in blood pressure and prevent it from rising or declining excessively. The syndrome of baroreflex failure results from denervation of arterial and/or cardiopulmonary barorecep-tors and is characterised by labile hypertension and rarely hypotension. Baroreflex failure is particularly likely to develop following carotid body tumour surgery, carotid artery surgery, neck irradiation and injury. Baroreflex failure should be considered in the differential diagnosis both of the cases with (severe) hypertension with a striking blood pressure variability and in patients with suspected pheochromocytoma. Referral to a specialised centre for correct diagnosis and specific therapy is warranted.

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