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EDITORIAL

The arterial baroreflex in neurogenic orthostatic hypotension

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Reflex control of blood pressure (BP) is under primary control of the arterial baroreflex. The afferent limb of the baroreflex is mediated by vagal and glossopharyngeal fibers, providing information about changes in BP detected by carotid and aortic pressor sensors to the brainstem. The efferent output includes a vagal limb, regulating heart rate; and an adrenergic limb, regulating vasomotor tone/total peripheral resistance, as well as cardiac output. Traditionally, evaluation of baroreflex function in humans was done using the modified Oxford technique, which relates heart period change to a pharmacologically induced BP change [4, 5]. This method, which of course solely evaluates the vagal limb of the baroreflex, involves intravenous injection of a depressor agent (sodium nitroprusside) followed by a pressor agent (phenylephrine), resulting in large changes in BP. With development of non-invasive standardized autonomic function testing, we modified the approach to be applicable to routine autonomic testing, relating heart period change to the fall and rise in BP that occurs during and immediately following the Valsalva maneuver, and generated normative values [3, 7, 10].

While the importance of evaluating the adrenergic limb of the baroreflex was appreciated, its application has been limited by technically challenging methodology. The modified Oxford technique can be modified to evaluate the adrenergic limb by microneurographically recorded muscle sympathetic nerve activity to the induced BP change [8], but this technique is too technically and time demanding for use in the clinical autonomic laboratory, and its use remained limited to research applications in dedicated laboratories. Adrenergic failure can be recognized as a loss of BP recovery during (late phase II) and BP overshoot following the Valsalva maneuver (phase IV). Limitations of this approach are that (a) BP overshoot can be absent in some normal subjects, and (b) quantitation of increasing severity of adrenergic failure is not possible once those phases have disappeared. Recognizing that the function of the adrenergic limb of the baroreflex is expressed as response to the BP drop during early phase II and manifest starting with BP recovery during late phase II and later BP recovery and overshoot during phase IV, we surmised that indices that quantify this recovery in BP allow for better quantitative assessment of the adrenergic limb of the baroreflex than conventionally used parameters. These parameters were shown to correlate with adrenergic baroreflex measures derived from microneurographic approaches, and the simplest and most intuitive of these parameters, BP recovery time (PRT), defined as the time it takes from the lowest BP point of phase III of the maneuver to BP reaching baseline, in response to an adequate stimulus, has since been widely used in autonomic laboratories [9]. Normative data are available [10] with mild, moderate and severe adrenergic failure is reflected as PRT of 6–10 seconds, 11–20 seconds and >20 seconds, respectively [1].

Impaired adrenergic baroreflex function of sufficient degree leads to OH, which underlies the concept of "neurogenic OH". Since autonomic function testing is not readily available everywhere, a simple surrogate measure of neurogenic OH has been recommended [6]. In contrast to non-neurogenic causes of OH, patients with neurogenic OH commonly have a decreased HR response to head-up tilt considering the drop in BP, which can be quantified as delta HR/delta BP ratio, which represents an easy to derive index that has naturally been embraced for clinical trials due to its simplicity. The low delta HR is primarily a manifestation of impairment of the vagal baroreflex limb. It is, therefore, a good index when the vagal and adrenergic limbs are both severely affected, as in generalized autonomic failure. Its limitation is that in partial autonomic failure, the adrenergic limb can be selectively or disproportionately affected.

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There is a whole spectrum of orthostatic hypotension and partial autonomic failure that far exceeds the prevalence of generalized autonomic failure. In partial autonomic failure, the ratio is often normal or can even be increased, as in cases of hyperadrenergic OH or OH with tachycardia. This is also true in situations when a structural lesion selectively damages the adrenergic pathway, as in the excellent example in the report by Goldstein et al [2]. The ratio is often increased in postural tachycardia syndrome (POTS); neuropathic POTS can, therefore, be considered to represent one end of the spectrum from mild to complete adrenergic failure. With more severe adrenergic failure, OH occurs while still retaining orthostatic tachycardia resulting in neurogenic OH with tachycardia. The ratio can be spuriously low when cardiovagal function is selectively impaired by medication effect or disease. This is common in diabetic neuropathy where cardiovagal failure may precede adrenergic failure by years. Such a patient who develops non-neurogenic OH will have a spuriously low ratio.

So what is the take-home message? First, patients with OH and a reduced ratio likely have neurogenic OH; however, the ratio could be spuriously low because of selective cardiovagal neuropathy, medication effect or cardiac factors. Second, OH with a normal ratio does not rule out neurogenic OH. Third, an increased ratio represents a red flag for baroreflex impairment, since it is a signal of compensatory tachycardia and could be an early indication of adrenergic stress/failure. Finally, autonomic laboratory evaluation remains the gold standard in determining a neurogenic etiology of OH, as it is much superior to quantify the severity and distribution of adrenergic as well as cardiovagal impairment.

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Declarations

Competing interests The authors declare that they have no competing interests.

References

1. Cheshire WPFR, Gibbons CH, Cortelli P, Wenning GK, Hilz MJ, Spies JM, Lipp A, Sandroni P, Wada N, Mano T, Ah Kim H, Kimpinski K, Iodice V, Idiaquez J, Thaisetthawatkul P, Coon EA, Low PA, Singer W (2021) Electrodiagnostic assessment of the autonomic nervous system: a consensus statement endorsed by the American Autonomic Society, American academy of neurology, and the international federation of clinical neurophysiology. Clin Neurophysiol 132:666–682
2. Goldstein DS, Sullivan P, Grabov E, Chittiboina P (2023) Baroreflex-sympathoneural without baroreflex-cardiovagal failure in neurogenic orthostatic hypotension. Clin Auton Res. https://doi.org/10.1007/s10286-023-00935-z
3. Huang CC, Sandroni P, Sletten D, Weigand S, Low PA (2007) Effect of age on adrenergic and vagal baroreflex sensitivity in normal subjects. Muscle Nerve 36:637–642
4. Korner PI, West MJ, Shaw J, Uther JB (1974) "Steady-state" properties of the baroreceptor-heart rate reflex in essential hypertension in man. Clin Exp Pharmacol Physiol 1:65–76
5. Low PA, Walsh JC, Huang CY, McLeod JG (1975) The sympathetic nervous system in alcoholic neuropathy a clinical and pathological study. Brain 98:357–364
6. Norcliffe-Kaufmann Lucy, Kaufmann Horacio, Palma Jose-Alberto, Shibao Cyndya A, Biaggioni Italo, Peltier Amanda C, Singer Wolfgang, Low Phillip A, Goldstein David S, Gibbons Christopher H, Freeman Roy, Robertson David, Autonomic Disorders Consortium (2018) Orthostatic heart rate changes in patients with autonomic failure caused by neurodegenerative synucleinopathies. Ann Neurol 83:522–531
7. Schrezenmaier C, Singer W, Muenter Swift N, Sletten D, Tanabe J, Low PA (2007) Adrenergic and vagal baroreflex sensitivity in autonomic failure. Arch Neurol 64:381–386
8. Vallbo ABHK, Wallin BG (2004) Microneurography: how the technique developed its role in the investigation of the sympathetic nervous system. J Appl Physiol 96:1262–1269
9. Vogel ER, Sandroni P, Low PA (2005) Blood pressure recovery from Valsalva maneuver in patients with autonomic failure. Neurology 65:1533–1537
10. Wada N, Singer W, Gehrking TL, Sletten DM, Schmelzer JD, Kihara M, Low PA (2014) Determination of vagal baroreflex sensitivity in normal subjects. Muscle Nerve 50:535–540