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Blood pressure instability in head and neck cancer survivors

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Of the 51,000 Americans that survive head and neck cancer, around 4% develop lower cranial nerve deficits after radiotherapy [1], and in those with persistent disease who require rescue salvage surgery, the rate of cranial nerve complications rises substantially to 40% [12]. In this issue of *Clinical Autonomic Research*, Barboi and Pocica report 23 patients referred to their autonomic clinic because of wide fluctuations in blood pressure and a history of treatment for skull base tumors [2]. They were subsequently diagnosed with afferent baroreflex failure. Their experience mirrors ours [7] and together reveal some new insights about this underdiagnosed and poorly understood disorder.

Most of the cardiovascular autonomic control happens in the brainstem with inputs arising from mechano-sensing baroreceptors expressed on afferent nerve endings that innervate the aortic arch and the carotid sinus [6]. Radiation to the neck or rescue dissection surgery frequently injures the glossopharyngeal (IX) and vagus (X) cranial nerves, which enter the brainstem at the base of the skull and carry baroreceptive signals. Without this mechanosensory signaling from the vasculature, blood pressure becomes erratic and hard to control [7, 11]. Patients with afferent baroreflex failure can present with symptoms of both extreme highs and lows in blood pressure occurring with different situations. Like Barboi and Pocica, we had a similar referral base for our cohort that included surgeons, oncologists, neurologists, cardiologists, and ICU attendings, which suggests that these patients see multiple specialists. A number of our patients were self-referred. So, any outreach to find them needs to cast a wide net.

The incidence of afferent baroreflex failure appears to be increasing. What emerges from both cohorts [2, 7] is that the syndrome appears to strike with a high prevalence middle-aged white men, who make up 60-85% of the cases. The reasons are unclear. It could be that this is a selected group who had access to care and, therefore, higher survival rate. It could also

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be that this is a consequence of the increasing incidence of human papilloma virus (HPV)-related oropharyngeal cancer in this particular demographic [7, 8, 13]. It is unclear exactly how many patients develop afferent baroreflex failure after neck radiation or dissection. It is also unclear how soon after surgery or radiotherapy the blood pressure instability begins. A small minority of patients develop severe hypertension immediately after surgery, but in most the autonomic complications occur within 1-year of surgery, and in rare instances may be an indicator of tumor reoccurrence [7]. It is worth noting that 85% of head and neck cancer patients develop hypertension within 5 years of treatment [5], and these patients have a higher cardiovascular mortality compared to the age-matched population [4]. It is most likely that afferent baroreflex failure is still underdiagnosed.

Another interesting observation from our cohorts is the coexistence of afferent baroreflex failure with signs of additional cranial nerves involvement. For instance, many patients have a distinctive appearance having undergone massive surgeries which deform the face and the neck, require a tracheostomy, and leave the patient unable to speak beyond a whisper. In both series, up to 90% of patients had other cranial nerve deficits. These are well recognized complications. Informative websites and brochures complied by support groups for survivors of head and neck cancers include dysarthria, dysphagia, dry mouth, and ageusia as possible side effects of radiation/surgery, but surprisingly, none list blood pressure instability.

There is still much to be learned about afferent baroreflex failure. From a physiological perspective it is difficult to tease out whether there is afferent or efferent involvement using classic autonomic function tests. Around two-thirds of patients have orthostatic hypotension on tilt, which is due to a failure of the afferent baroreceptor neurons to elicit an increase in sympathetic nerve activity on standing, rather than a deficit in the efferent nerves themselves. Perhaps the most characteristic feature of afferent baroreflex failure is the sharp rise in blood pressure and heart rate with arousal. Asking the patient to recall events that make them happy, excited, fearful or angry while measuring blood pressure and R-R intervals provokes hypertension and tachycardia.

In spite of the fact that no other autonomic disorder causes this type of extremely labile hemodynamic responses, there is little evidence to guide treatment and, so far, there have been no placebo-controlled studies. Recently, general guidelines for blood pressure management in patients with afferent baroreflex failure were published by Biaggioni and colleagues [3]. This is a good starting point although much work remains to be done. These expert opinion guidelines recommend accepting the fact it is not possible to normalize blood pressure, educating the patient, avoiding chasing the blood pressure, and treating breakthrough hypertension with short-acting sympatholytic medications. The problem is, α- and beta-blockade are usually ineffective, calcium channel blockers or ACE-inhibitors increase the risk of symptomatic hypotension and syncope, and centrally-acting α-adrenergic agonists, like clonidine, tizanidine and α-methyldopa have significant CNS side effects [7]. This leaves few options and a true unmet need for safe, effective, approaches to target the excessive sympathetic surges without worsening the lows.

As an added challenge, many of these patients have abnormal ventilatory responses to hypoxia, a stimulus that also arrives to the brainstem in cranial nerves IX and X. Patients

have a higher frequency of sleep disordered breathing, day time hypoventilation, and sudden death during sleep is common, presumably because there is no arousal response to hypoxia. Drugs with CNS depressant effects can result in respiratory arrest.

In the long-term, unstable blood pressure produces target organ injury. Patients appear to develop heart failure due to repeated takotsubo-like events and renal insufficiency [7]. In congenital forms of afferent baroreflex failure, renal biopsies are consistent with hypertensive nephropathy and there is evidence of catecholaminergic toxicity causing necrosis of the myocardium [9, 10]. A long-acting background peripheral sympatholytic drug with no CNS effects, if effective, would transform the care of patients with afferent baroreflex failure.

Last but not least, as the report of Barboi & Pocica reveals, the nomenclature is also a tangled web of archaic syndromes describing rare cancers of different pathologies that all impact the skull base. From an autonomic perspective it is not much clearer either. The terms *baroreflex failure* and *autonomic failure* are often used interchangeably, when in reality each describes different neurological causes of cardiovascular disarray, which demand very different approaches to treatment. In autonomic failure (i.e., efferent baroreflex failure), there is a primary deficit in the sympathetic nervous system, the blood pressure and pulse remain unchanged with emotions, and these patients do not have paradoxical hypertensive crises with hypertension, tachycardia, agitation and diaphoresis, which are the characteristic feature of patients with afferent baroreflex failure.

In summary, we would like to applaud Barboi & Pocica for raising awareness about the increasing number of cases of afferent baroreflex failure that they are encountering in their clinic. There is an unmet need to improve the awareness about this disorder and find better treatments for these patients. Identifying effective ways to manage their hypertensive surges could potentially be applicable to other, more common forms of dysautonomia involving excessive sympathetic activity.

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