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A sluice to normotension?

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The current issue of the *Journal of Hypertension* features an article on the long-term effects of the ROX coupler (ROX Medical, San Clemente, California, USA) in a patient with alleged treatment-resistant hypertension [1]. The authors describe how blood pressure (BP) changed with the opening and closure, like a sluice, of the arteriovenous fistula which was created by this device, with results that are just as what one would expect. Undoubtedly, treatment-resistant hypertension is 'hot'. Ever since Calhoun *et al.* [2] published their statement on resistant hypertension a decade ago, many research groups have focused on this particular problem in hypertension. It is a bit unfortunate, though, that the condition was called 'treatment-resistant hypertension', in which 'difficult-to-treat hypertension' would have been a more appropriate term. Although at first sight, it seems relatively easy to make a diagnosis of treatment resistance, in reality it is not. When one systematically and carefully examines a group of patients who are supposed to be resistant, the diagnosis cannot be confirmed in a substantial portion of these patients [3]. Among the factors that could lead to a false diagnosis of resistance are undetected secondary hypertension, white-coat effects and, perhaps the most important of all, inadequate adherence to treatment. The latter, in particular, has probably clouded much of the literature in this area as it is extremely difficult to rule out nonadherence with absolute certainty.

One of the reasons why it has become so popular to engage in research on treatment resistance has been the emerging availability of devices with which BP can be lowered. Starting with renal denervation [4] and baropacing [5], we now have several other modalities among which the so-called ROX coupler device. With this self-expanding stent-like device one creates a fistula between the external iliac artery and vein which results in a markedly reduced peripheral vascular resistance [6]. This, by the way, is not unlike the situation in patients with end-stage renal disease who have an arterial–venous fistula for facilitating hemodialysis.

Remarkably enough, the ROX coupler was not primarily invented for the treatment of patients with hypertension but rather as a means to increase the mixed venous oxygen content (CvO_2) in patients with chronic obstructive pulmonary disease (COPD). The theoretical background to justify the creation of an arterial–venous fistula in COPD patients is that oxygenated arterial blood will be shunted from the arterial to the venous circulation whereby the CvO_2 in the left atrium will increase, thus limiting the degree of systemic hypoxemia [7]. Indeed, when the ROX device was tested in a small group of patients with severe hypoxemic COPD, it significantly improved exercise capacity to a degree that was comparable with that achieved by supplemental oxygen [8]. Based on the reasonable assumption that an arterial–venous fistula would lower BP through a sluice-like reduction in systemic vascular resistance, Faul *et al.* [9] assessed the effect of the ROX device on office BP in 24 patients with COPD and hypertension. They found a significant reduction in both systolic and diastolic pressure but did not specify how pressure was measured. Importantly, this study was uncontrolled and did not utilize ambulatory BP monitoring. Moreover, patients continued to take their antihypertensive medication. Although the hypotensive effect was greater in those with the highest pressure at baseline, this result can simply be due to regression toward the mean. These data, and these only, formed the very limited piece of evidence, if it deserves that term at all, which led to a randomized clinical trial in which the efficacy of the device was tested in 42 treatment-resistant hypertensive patients [10]. If it were a drug, we would probably have required much more solid data before exposing patients to the new treatment. Nevertheless, the device did lower both office and ambulatory pressures, albeit at the expense of 25 adverse events. Efficacy and safety data after 1 year of follow-up confirmed a sustained reduction in BP, even in patients who had failed to respond to prior renal denervation [11]. However, one-third of the patients had developed ipsilateral venous stenosis so the procedure is not without complications.

On theoretical grounds, one can expect a variety of complications and adverse events following insertion of

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the ROX coupler device [12]. It diverts approximately 800 ml/min blood from the arterial to the venous circulation and this hemodynamic challenge may have serious consequences such as enhanced sodium retention (due to, e.g. renal hypoperfusion) with edema formation and right ventricular volume overload due to an augmented venous return. High-output cardiac failure is another classical sequela of an arterial–venous fistula [13]. The case report in the current issue of the *Journal of Hypertension* clearly illustrates how pathophysiological and clinical thinking should come together when we are dealing with patients who have been treated with the ROX coupler. The case describes the fate of a 57-year-old man who was followed for 3.5 years after placement of the device. The patient is a typical example of what many of us will encounter in daily practice. Despite the use of six antihypertensive agents and prior renal denervation he remained hypertensive. Although he was considered to be treatment-resistant, it is questionable whether this was truly the case. Indeed, during follow-up his BP turned out to be very fluctuant which the authors thought was due to poor medication adherence. One could argue, therefore, whether this patient should have been treated with renal denervation and the arterial–venous fistula in the first place, although we have to realize that such clinical decisions are notoriously difficult. One year after the procedure the patient presented with ipsilateral venous stenosis, apparently the most significant complication [11]. However, several years later, the typical signs of high-output heart failure developed, a complication that can be expected on pathophysiological grounds. This case illustrates that it may take a long time before the clinical signs of heart failure become manifest. We must, therefore, be very cautious before embracing this new modality as the Columbus' egg. In addition, it is important to keep a registry of all patients, not only of a selected subgroup, who have been treated with the device. Finally, a thorough cost–benefit analysis is necessary not only with respect to economic costs but also, and primarily, in terms of patient burden. Finally, the present report once again shows that even in an era in which big data, epidemiological surveys and large trials dominate the medical literature, there is room and even a need for case reports such as the one by the German investigators.

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Conflicts of interest

There are no conflicts of interest.

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