

Haemodynamic assessment in hypertension: the soloists and the orchestra

Eleanor Murray^a, Giacomo Rossitto^{a,b}, and Christian Delles^a

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The circulatory system regulates perfusion of organs and tissues according to varying physiological conditions. In this context, maintaining and adapting blood pressure (BP) to meet the organism's needs is of utmost importance. Unsurprisingly, a large number of systems regulate BP, ranging from vasoactive mediators such as nitric oxide, endothelin and angiotensin II; to neurohumoral systems including the sympathetic nervous system; and the complex interplay between salt, volume status and renal function. Inflammation, oxidative stress and other pathophysiological conditions can interfere with BP regulation and cause hypotension or hypertension.

Hypertension is broadly categorized into primary and secondary forms. In the latter, a single pathophysiological factor, for example excess aldosterone production in primary aldosteronism, explains most if not all of a patient's high BP. In primary hypertension we see a combination of many but more subtle disturbances in regulatory systems aggregating to increase BP. Accordingly, patients with secondary hypertension can be treated and even cured by addressing the major cause of their high BP, whereas those with primary hypertension, in theory, benefit from tackling more than one system.

On the contrary our pharmacologic tools to treat hypertension are relatively blunt. The most commonly prescribed drugs act as vasodilators [e.g. dihydropyridine-type calcium channel blockers and renin–angiotensin–aldosterone system (RAAS) inhibitors], reduce body salt and volume (e.g. diuretics) or reduce cardiac output (CO) (e.g. beta blockers). We do not currently have clinically approved agents that counteract primary pathophysiology such as increased production of reactive oxygen species, endothelial dysfunction and inflammation. The good news, however, is that from a purely mechanical perspective, BP is

determined by the product of vascular resistance and CO, with the latter depending on cardiac function *per se* and volume status. As such our seemingly blunt tools may not target the original pathophysiology but they all address the major downstream corollary of hypertension. In fact, they are not blunt at all. They are so powerful that even in patients with primary hypertension where multiple pathophysiological mechanisms would be expected, a single agent can often normalize BP. Traditionally, guidelines have therefore recommended to start treatment with a single agent, uptitrate to the maximum tolerated dose and only then add a second (third, fourth etc.) agent if BP targets are not reached.

There have been endless discussions about the rational choice of the first antihypertensive agent in a patient with newly diagnosed hypertension. If we disregard compelling indications for specific drugs in some patients (e.g. beta blockers in hypertensive patients who also have ischaemic heart disease), the majority of patients with primary hypertension could be treated with any antihypertensive agent. Such liberal recommendation has been the cornerstone of previous European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines [1] and gave physicians a wide range of choices for initial treatment and in case a second agent was required. In contrast, some guidelines, including the National Institute for Health and Care Excellence (NICE) guidelines in the United Kingdom [2], are more prescriptive and recommend RAAS inhibitors in younger and calcium channel blockers in older patients and patients with Afro-Caribbean background because of the more active RAAS in the former group [3]; in a next step, the drug class that has not been prescribed in the first step will then be added. Evidence from clinical trials and genome-wide association studies suggest that biomarkers and genotype can predict the response to certain drugs [4,5] but these data have not yet been implemented in guidelines.

There is very limited evidence that the choice of antihypertensive agents really matters. What matters, however, is the achieved BP as highlighted by meta-analyses [6] and specific clinical trials such as HOT [7] and SPRINT [8]. Generally, lower achieved BP is associated with more favourable outcomes and even small differences in BP can effect changes at the population level [9] and in clinical trials (as experienced in the VALUE Trial [10]). In this

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^aInstitute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK and ^bDepartment of Medicine DIMED, University of Padua, Italy

Correspondence to Christian Delles, MD, Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow G12 8TA, UK. Tel: +44 141 330 2749; fax: +44 141 330 3360; e-mail: Christian.Delles@glasgow.ac.uk

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context one can argue that the choice of first-line antihypertensive agents does matter. A drug that is well tolerated and most effective in an individual patient, may more rapidly control their hypertension and beget long-term benefits.

But how should the ideal first-line treatment be determined if in fact primary hypertension is a multifactorial condition? This question is the principal obstacle to precision medicine in hypertension, as it is in many other common diseases. A reductionist approach, basing the decision on simple parameters such as age (as recommended by NICE), could therefore provide reasonable clinical guidance. Another approach is to focus on the two main drivers of BP: vascular resistance, and volume/CO; addressing the part of the equation that is dysregulated most.

In this issue of the *Journal of Hypertension*, Glinz *et al.* [11] present data of a study that used the HOTMAN system (Hemo Sapiens Medical Inc., Sedona, Arizona, USA) to evaluate a patient's haemodynamic status. This device assesses a range of haemodynamic parameters by bioimpedance, and has been validated against invasive techniques. There is little doubt that the device produces accurate data, providing information about vascular resistance and volume/CO. The authors hypothesized that such data can guide pharmacotherapy, particularly a choice between vasodilators (AT1 blocker: olmesartan; angiotensin-converting enzyme inhibitor: perindopril; calcium channel blocker: amlodipine) and diuretic (hydrochlorothiazide). They conducted a study in newly diagnosed hypertensive patients who were randomized in a 1:1:1:1 ratio to one out of four drugs mentioned above; an untreated normotensive control group was also included. Treatment duration was 4 weeks. The study showed similar BP control across groups, independent of haemodynamic profile at baseline and treatment allocation.

The study by Glinz *et al.* has some design flaws and has been affected by issues that happen to many clinical trials. One can argue about the choice of antihypertensive drugs, their dosage and treatment duration. One could have asked for a cross-over rather than parallel design, and allocation based on haemodynamic profiling, rather than retrospective assessment of treatment concordance with phenotype. And one would have liked to see data that the haemodynamic measurements are reproducible in the authors' hands – the lack of follow-up data in the control groups is a missed opportunity. The study also experienced the usual drop-out and some under-recruitment of participants that may raise questions regarding power, and some imbalance in randomization to treatment arms which is due to the play of chance but can still affect interpretation of the data. However, the neutral result of the present data is broadly in keeping with previous attempts to use haemodynamic data to guide personalized treatment and particularly with the BEAUTY trial [12].

Despite the limitations of the study by Glinz *et al.* [11] it comes with clear messages. First, there is no readily detectable difference in response to treatment based on haemodynamic profiles. It may well be that in larger cohorts with longer follow-up such differences could be demonstrated but the immediate benefit of haemodynamic assessment to

inform treatment choice for an individual patient remains disputable. Second, the study comes with a treasure chest of data on haemodynamic profiles in newly diagnosed patients with essential hypertension. And third, based on the baseline profiles, it may still inform therapeutic choices but maybe not in the originally anticipated form. We will comment on the second and third points in more detail.

What were the haemodynamic profiles at baseline? Here, the authors found hypervolaemia with vasoconstriction in 48% of hypertensive patients and hypervolaemia without vasoconstriction in 45%. However, classification into these groups was based on '%-deviations of volaemia, inotropy, vasoactivity and chronotropy', and even where 'hypervolaemia' was predominant there may also have been a degree of vasoconstriction in some patients. And for those with 'hypervolaemia with vasoconstriction' not all will have had the same degree of hypervolaemia and vasoconstriction. While the authors' approach to categorize patients into three major groups (the third being 'vasoconstriction without hypervolaemia') is pragmatic and clinically relevant, a fair amount of overlap between the groups is likely. Essentially, the authors elegantly demonstrate the key feature of primary hypertension, that is that it is driven by more than one pathophysiological principle, and therefore also affects all relevant components of BP including CO, volume and vascular resistance, albeit to varying degree between patients. It should be noted though that also the apparently healthy controls had haemodynamic 'abnormalities', a finding that requires some thought when interpreting abnormal results in patients.

So how can the present data inform more precise treatment? They can't – despite the limitations of the study, a neutral outcome has clearly been demonstrated by Glinz *et al.* [11]. But with no difference at least in the BP response within 4 weeks, and a range of haemodynamic profiles with overlapping features at baseline; the pragmatic approach is to go for combination therapy right from the beginning. In fact, the most recent edition of the ESC/ESH guidelines [13] much more strongly recommends initial combination therapy compared with previous editions and the current study by Glinz *et al.* [11] provides further support for this strategy. Can any antihypertensive agents be combined for treatment initiation? Probably yes (with the exception of the combination of angiotensin-converting enzyme inhibitors and AT1 blockers) but it would be wise to combine different mechanisms of action to address both factors that contribute to BP: increased vascular resistance and increased volume and CO. The finding by Glinz *et al.* [11] that the vast majority of their patients had hypervolaemia in some shape or form reminds us of the need to address volume status. In fact, it reminds us to address sodium status as in most cases hypervolaemia is paralleled by increased total body sodium [14,15]. Diuretics could more frequently be used as part of initial combination therapy and even more importantly, we should never forget to recommend reductions in salt intake to our patients [13].

Is the study by Glinz *et al.* the final nail in the haemodynamic assessment coffin? Certainly not. Devices such as the HOTMAN device provide accurate data and combined with other assessments of volume status and vascular structure and function these are important research tools. They can

help us to understand pathophysiology and the effects of therapeutic interventions. If widely implemented in clinical trials such data can provide important information. For example, the assessment of central BP in the CAFE Study [16] helped to understand some of the reasons for the favourable outcome of patients in the amlodipine-based arm compared with those in the atenolol-based arm of the ASCOT Trial [17] despite similar peripheral BP control.

Detailed haemodynamic phenotyping plays a role in clinical studies and therefore in our understanding of the disease but does not, at least not in isolation, inform therapeutic decisions in the clinic. This is not a failure of the device; it is because of the complexity of primary hypertension, that correspondingly requires more than just a single intervention. In this sense, successful treatment of primary hypertension often requires an orchestra rather than a soloist approach.

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Conflicts of interest

There are no conflicts of interest.

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