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Individualizing Antihypertensive Combination Therapies: Clinical and Hemodynamic Considerations

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Abstract While there are strong trial data to guide the selection of initial hypertension treatment choice and limited data to support second agent choice, beyond the first two agents, subsequent steps are empiric. As medications are added, the resulting polypharmacy may be complex, inefficient and poorly tolerated, resulting in low treatment adherence rates. The selection of antihypertensive drug therapy based on hemodynamic mechanisms is not new but became practical with the availability of noninvasive hemodynamic parameters using impedance cardiography. Individualized therapy based on hormonal or hemodynamic measurements can effectively control hypertension as shown in several small clinical trials. Hemodynamic measurements are obtained quickly, painlessly and can be used in a serial fashion to guide treatment adjustments. Current limitations relate to availability of the measurement device and personnel trained in its use, reimbursement for the measurements, expertise in interpretation of the measurements and systems to adjust medication and repeat measurements in a serial fashion until targets are attained. The potential utility of this approach increases with greater complexity of the medication regimen. Further studies are indicated and may advance options for individualized treatment of hypertensive patients.

Keywords Hypertension treatment · Hemodynamics · Bioimpedance · Protocol-based therapy · Resistant hypertension

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Introduction

Methods for initial drug selection for hypertension treatment, as specified in current clinical guidelines[1, 2], are based on randomized controlled trials combined with provider and patient preferences. The intention is to maximize efficacy and convenience, while minimizing side effects and cost. While there are trial data to support first agent selection and limited data to support second agent choice, beyond the first two agents, subsequent steps are generally empiric. Here the provider is advised to choose an additional agent from one of the remaining drug classes not already used, and repeat this stepped care approach until all classes are prescribed. A decision to stop a prescribed agent is usually based on side effects rather than evidence for lack of efficacy. The resulting polypharmacy may be complex, inefficient and poorly tolerated, resulting in low treatment adherence rates.

Hypertension treatment and control rates are positively associated with protocol-based evaluation and care using multidisciplinary teams [3••]. Under protocol-based care, each team member serves at the top of their skill set to provide cost effective care with back-up expertise available when needed. Protocols reduce variability of practice, increase adherence to evidence based treatment selection and titration practices, allow incorporation of electronic tools including algorithms and tracking of blood pressure measurements, direct referral timing when goals are not achieved and improve provision of efficient and cost effective care. Such protocol-based treatment can be highly effective in counteracting therapeutic inertia and accelerating progress to achieve high population rates for blood pressure control.

A counter argument to protocol-based care is the concern that application of a formulaic approach promotes a less personalized selection of drug treatment without consideration for the individual patient's needs and concerns. It is at this interface that individualized measurements may bridge the gap

between process and patient experience to optimize success. This review discusses the use of hemodynamic measurements to guide antihypertensive drug selection and adjustment, particularly when faced with the need for multi-agent regimens.

Rationale for a Hemodynamic Approach

Methods for add-on drug selection proposed by us and others rest on use of protocols that utilize hormonal or hemodynamic measurements, based on the concept that mechanisms of hypertension may differ between individuals, and these differences may be hidden by attention to group means. Use of patient clinical characteristics, laboratory data and hemodynamic measurements can effectively guide add-on therapy for the individual using a protocolized process. This approach has been tested in small prospective clinical hypertension treatment trials with promising results [4, 5, 6••].

The prescription of antihypertensive drug therapy based on hemodynamic mechanisms dates back to the principles of Tarazi [7]. Agents were classified primarily by their effects on the systems that modify blood pressure levels in health and disease. The classification of antihypertensive agents by mechanism of action and biochemical structure is the foundation for hypertension treatment, generally based on selection of one agent from each of several classes to be used in combination in order to achieve blood pressure control. Each agent has a primary effect on the circulation but also triggers compensatory mechanisms that attempt to correct the primary effect back to baseline [8, 9]. For example, a diuretic may reduce intravascular volume leading to reduced renal perfusion, which triggers renin release, vasoconstriction and a muted BP response. In another setting, the addition of a direct vasodilator will lower BP via arterial dilatation leading to avid sodium and volume retention by the kidneys, which reduces the net BP lowering outcome. Use of agents from different classes in combination, each having different effects on cardiac output, systemic vascular resistance and volume, can effectively reduce BP while blocking such compensatory actions.

In essence the basis for individualized hormonal or hemodynamic based treatment is to utilize this principle to adjust drug selection based on single or serial noninvasive measurements. Variations include the use of algorithms based on circulating vasoactive mediators (plasma renin activity, ANP/BNP) or patient classification based on demographic variables to guide drug selections.

Individualized Therapy Based on Hormonal or Vasoactive Mediators

Using the Renin Test-Guided Therapeutic (RTGT) algorithm, patients are designated by a peripheral venous plasma renin activity (PRA) level as having "V" sodium-volume excess (PRA <0.65 ng/ml/h, low renin) or "R" renin-angiotensin vasoconstrictor excess (PRA ≥0.65 ng/ml/h, normal or elevated renin) hypertension [10, 11]. Drug treatment is assigned based on "V" or "R" type, using drugs with specific effects on PRA: for "V" patients natriuretic anti-"V" drugs (diuretics, spironolactone, calcium channel blockers or α1-blockers) are added while withdrawing antirennin "R" drugs (ACE inhibitors, angiotensin receptor antagonists or β-blockers) and the converse approach is used for "R" patients. Egan et al., tested this algorithm prospectively on 84 adult patients with treated (mean of three agents) uncontrolled hypertension in a randomized open label trial compared to clinical hypertension specialist care [12]. Patients were seen every 2-4 weeks for redirection of therapy over a 6 to 12 week timeframe. For the 77 patients who completed the protocol, analyzed by intention to treat, SBP was comparable and DBP was lower at the final visit for RTGT treated patients with both groups taking similar numbers of agents (a mean of 3). What differed between the groups was the removal of agents and reductions in dosage of some medications, seen more commonly in the RTGT treatment arm. There were more RTGT patients reaching BP target (74 % RTGT vs. 59 % for specialist care) but this was not statistically different (p=0.17). The authors suggest RTGT as an effective alternative approach when hypertension specialist care is not available.

The RTGT concept was adopted in modified form by the British Hypertension Society as the modified Cambridge AB/CD rule using age (<55 or ≥ 55 years) and ethnic group (black or non-black) as surrogates for PRA to guide selection of "R" and "V" drugs without requiring a plasma renin measurement [13, 14]. This approach was based on the assumption that non-black and younger patients are more likely to have elevated PRA based hypertension while black and elderly patients are more likely to have low renin, high volume mediated hypertension. The A/C + D rule, a further modification which excluded beta blockers as first line therapy, was incorporated into the NICE guidelines released in 2011 [2]. ACE inhibitors or ARBs – the "A" drugs – are selected for those of Caucasian race or younger than age 55 years; calcium channel blockers – the "C" drugs or diuretics – the "D" drugs – are selected for those age 55 and older or of black race. While this approach has been increasingly embraced, it remains primarily empiric and has not been tested in a large prospective clinical trial. Beyond selection of the first two agents, there is little data to support specific multi-agent regimens or guide selection of the third agent.

The availability of renin and aldosterone measurements and increasing use of the aldosterone to renin ratio have facilitated earlier detection of relative aldosterone excess states prior to progression to the full-blown disease of primary aldosteronism. Aldosterone-induced sodium retention may be a causal mechanism for low-renin hypertension, which may

evolve to classic primary aldosteronism [15]. Beginning with autonomous aldosterone production in a low-renin normotensive individual, progressive sodium retention, suppression of plasma renin activity, autoregulatory vasoconstriction and increased blood pressure lead first to low renin essential hypertension then to normokalemic hyperaldosteronism then to classic hypokalemic primary aldosteronism. This continuum is supported by prevalence data for primary aldosteronism in a large unselected primary care population diagnosed using ARR, plasma aldosterone level and blood pressure response to spironolactone [16]. Primary aldosteronism was rare (2 %) yet 8 % had an elevated ARR and a significant blood pressure response to aldosterone blocker therapy. The best indicator for blood pressure response was a low plasma renin activity level, off beta-blockers. In a subgroup enrolled in a prospective placebo-controlled cross-over trial of amiloride/hydrochlorothiazide (as an aldosterone inhibitor), 89 % demonstrated a substantial blood pressure response [17]. The efficacy of add-on empiric aldosterone antagonist therapy even without regard for plasma aldosterone levels supports a role for aldosterone in drug resistant hypertension [18, 19]. The exact mechanism of blood pressure reduction is not clear and appears to be comparable in those with and without demonstrated aldosterone excess. Further, aldosterone antagonists produce additional blood pressure reduction beyond the effects of angiotensin converting enzyme or angiotensin receptor blocking agents already on board.

The Role of Volume Expansion in Drug Resistance

Whether resistance is mediated by low-renin status, inappropriate aldosterone excess or avid sodium retention, the resulting volume expansion plays a key contributing role [20, 21]. The mechanism of treatment resistance is an insensitivity to standard diuretic therapy and the counter regulatory sodium retention response to reduction of blood pressure by non-diuretic antihypertensive medications, regardless of the patient's level of renal function. Classic studies measuring plasma volume in resistant hypertensive patients support a positive correlation between measured blood volume and systolic and diastolic blood pressure in patients treated with sympatholytic agents or vasodilators [20, 22]. Intensified diuretic treatment improved blood pressure control via a measurable reduction in plasma volume [20–24]. Assessment of effective cardiopulmonary volume by clinical exam can be difficult as the presence of peripheral edema as seen with calcium channel blocking agents, may not accurately reflect intravascular volume [25]. Markers of volume status such as plasma renin activity may be affected by numerous drugs or concurrent renal artery disease. Increased fluid volume occurs commonly as a compensatory response to antihypertensive therapy and may manifest as fluid retention (weight gain, edema) or as a poor response to increased doses of antihypertensive agents. Direct measurements of plasma volume may be helpful but are often impractical due to scheduling challenges and cost [24]. In a proof of principle study of nine patients with resistant hypertension, Graves et al., used measurements of plasma volume to adjust therapy. Plasma volume was increased in eight of the nine patients, all of whom responded to aggressive diuretic therapy allowing simplification of their regimens. For the one patient with contracted plasma volume, vasodilation was effective in controlling blood pressure. None of the patients had clinical evidence of volume overload and those with expanded plasma volume were already taking diuretic agents, either thiazide or loop diuretics at conventional dosages.

Individualized Therapy Based on Hemodynamic Measurements

Thoracic bioimpedance, also known as impedance cardiography, provides noninvasive hemodynamic measurements that may be used to adjust complex antihypertensive treatment [26]. As with hormonal approaches, the premise is to direct treatment to the hemodynamic profile and to control the compensatory responses to treatment by adjusting antihypertensive agents with different hemodynamic actions. While it is recognized that achievement of blood pressure control requires a reduction in systemic vascular resistance, the effects of specific drugs can be heterogeneous and may lead to volume retention (weight gain, edema) and a poor response to increased dosage of medication [8, 20, 27]. An alternative explanation for resistance may relate to the interaction of antihypertensive agents used in combination leading to activation of the sympathetic nervous system or the renin angiotensin aldosterone system (RAA system). Thoracic bioimpedance measures changes in thoracic fluid volume during electrical systole using skin electrodes and a low voltage current to derive stroke volume. Using concurrent heart rate and blood pressure measurements, the instrument derives real-time measurements of cardiac output and systemic vascular resistance. Absolute impedance measurements and changes in impedance with posture change from a supine to a standing position reflect cardiopulmonary volume, based on comparative data from normal subjects studied on controlled sodium intakes.

We, and subsequently others, studied the use of serial noninvasive hemodynamic measurements to guide drug selection and dosing compared to standard drug adjustment techniques in patients with resistant or refractory hypertension (Fig. 1, Table 1) [4-6]. In a series of 104 patients with resistant hypertension randomized to hemodynamic guided treatment or specialist care, blood pressure levels were lower and control rates higher in those treated according to their hemodynamic parameters [4]. While nearly all subjects were taking a diuretic

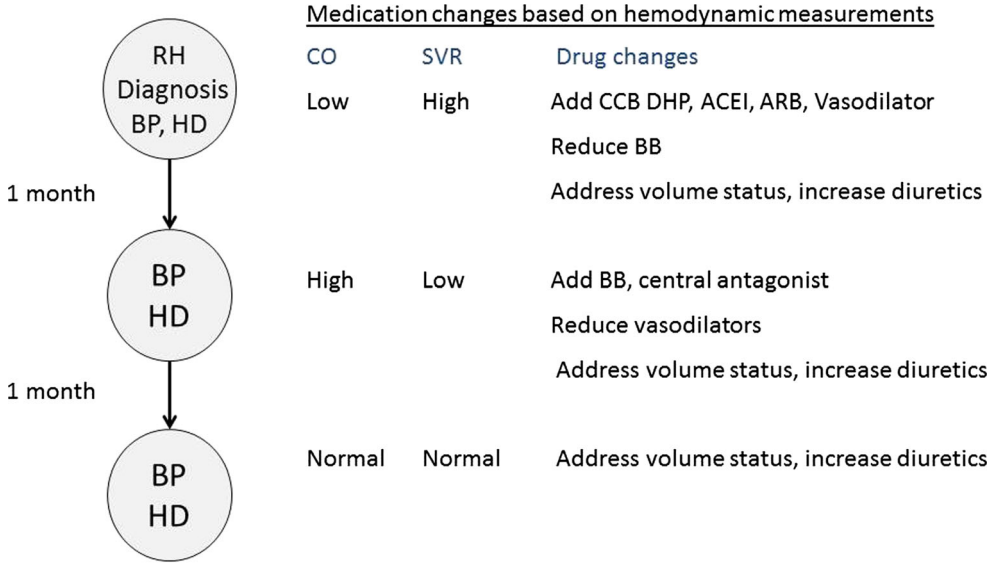

Fig. 1 Use of hemodynamic measurements in the titration of antihypertensive therapy based on methodology used in the clinical studies. Hemodynamic measurements are taken at entry and repeated monthly with drug titration based on the measurements. (BP blood pressure, HD hemodynamic measurements, CO cardiac output, SVR systemic vascular resistance, CCB calcium channel blocker, DHP dihydropyridine, ACEI angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker, BB beta blocker)

at entry (91 %), diuretic therapy was intensified more often in the hemodynamic treatment group than in the specialist care group. Improved blood pressure control correlated with greater reduction in systemic vascular resistance in those treated according to hemodynamic values. Therapy based on hemodynamic and volume measurements achieved superior blood pressure control to that attained by empiric selection of drugs, even by clinical experts. The contribution of volume excess as a mechanism for resistance is consistent with other models of low renin or autonomous aldosterone mediated hypertension.

A similar approach was tested in cohorts of patients with moderate hypertension uncontrolled on 1-2 agents. Smith et al., randomized 164 patients with uncontrolled hypertension while taking 1-3 antihypertensive agents [5]. At the end of three months, patients randomized to the hemodynamic care treatment had higher controls rates (77 % vs. 57 % <140/90 mm Hg, $p<0.01$) and lower systolic and diastolic blood pressure measurements mediated by lower systemic vascular resistance while cardiac output did not change or differ between treatment groups. The number of medications did not differ between groups although higher ARB use was noted in the hemodynamic group. Krzesinski et al., randomized 128 patients (age 18-65 years) with uncontrolled hypertension taking 0-2 agents to hemodynamic or empiric therapy based on a single hemodynamic profile measured after a 2 week drug washout period [6]. The algorithm was somewhat different from the other two studies and did not require serial measurements. Even with this limitation, office systolic and diastolic BP and nocturnal ambulatory diastolic BP were lower in the hemodynamic group with greater use of beta-blockers and calcium channel blockers, and there was greater use of more than one agent in the hemodynamic group. In a meta-analysis of five published trials using impedance

Table 1 Trials using hemodynamic measurements

Trial	Intervention	Results
Taler SJ et al.[4]	Hemodynamic vs Specialist medication titration in resistant hypertension N=104, 1:1 randomization Study duration: 3 months	Greater BP reduction, higher control rates, similar numbers of medications but higher diuretic doses in the hemodynamic group
Smith RD et al.[5]	Hemodynamic vs standard medication titration by published guidelines in essential hypertension uncontrolled on 1-3 agents N=164, 3:2 randomization Study duration 3 months	Greater BP reduction, higher control rates in the hemodynamic group, similar numbers of medications but higher thiazide diuretic doses in the standard treatment group
Krzesinski P et al.[6]	Hemodynamic vs empiric medication titration in arterial hypertension untreated or uncontrolled on 1-2 agents N=128, 1:1 randomization Study duration 3 months	Greater BP reduction including day and night readings in hemodynamic group, higher night-time DBP, more hemodynamic group patients likely to be taking more than 1 agent

BP blood pressure, DBP diastolic blood pressure

cardiography, Ferrario et al., noted a benefit for ICG-guided treatment with combined odds ratio of 2.41 and 67 % successful goal attainment for the two RCTs and comparable success rates of 68 % in three single-arm prospective trials [28].

Beyond these small single center trials, the optimal application of hemodynamic measurements to guide hypertension care remains unknown. Use is presently limited by availability of the measurement device and personnel trained in its use, limited reimbursement for the measurements, the need for expertise in interpretation of the measurements and systems to adjust medication and perform repeated measurements in a serial fashion until targets are attained. Randomized controlled trials provide adequate guidance for first and to some degree second agent selection, thus, the adoption of a hemodynamic approach for all hypertensive patients is impractical. Clearly the potential utility increases with greater complexity of the medication regimen.

Additional Applications of Individualized Hemodynamic Measurements

Non-adherence to therapy is often difficult to detect. The differential includes biological variability in response to specific drug classes or specific agents. In such settings, we have used hemodynamic measurements taken at baseline before medication ingestion and again after observed drug dosing to discriminate non-adherence from non-response. It is important to use caution in deciding how many of the prescribed medications to administer by observed dosing as we have seen dramatic falls in blood pressure when a patient is truly nonadherent.

Product Availability Challenges

The Taler and Smith trials described here used Cardiodynamics BioZ devices [4, 5]. Subsequently, the company was sold with indications that the buyer (Sonosite) will not support these devices beginning in January 2015. The Krzesinski trial used an Niccomo device (Medis, Germany) [6]. Other products are available that may fill this gap, however, these devices have not been tested for the titration of antihypertensive medications.

Conclusions

Hypertension control rates remain a challenge and a national priority [29]. Current guidelines offer limited guidance beyond selection of the first and second treatment agents. Hemodynamic measurements can be obtained efficiently, non-invasively and in a serial fashion. Limited clinical trial data supports the utility of this approach for patients with uncontrolled hypertension taking two or more agents. While the field has been challenged by changes in the devices currently available, this approach merits further study as a useful tool in the treatment armamentarium. Further, it offers additional options for individualized treatment of complex hypertensive patients.

Compliance with Ethics Guidelines

Conflict of Interest Sandra J. Taler declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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