Hypertension is a major public health concern and represents the most common medical reason for an adult to visit his physician. More than 25% of the world’s population is affected. It is associated with an increased risk of coronary artery disease, heart failure (49% of all causes of heart disease are secondary to hypertension), stroke (62% of all strokes are determined by hypertension), or renal disease and death (an estimated 7.1 million deaths a year; equivalent to 13% of total worldwide deaths) [1]. The pathogenesis of hypertension is complex, involving increased systemic vascular resistance, arterial stiffening, increased cardiac output, fluid retention, or a combination of all of these factors. Despite the diversity of aetiology/pathogenesis for raised blood pressure (BP), and the impressive range of different pharmacological actions possessed by antihypertensives, there has been little systematic research undertaken to try to match these two parallel sets of information. Thus, we have diuretics, blockers of central sympathetic drive, blockers of renin-angiotensin-aldosterone, and numerous drugs with vasodilatory actions, used apparently at random and without clear reference to the potential reasons for the elevated BP in affected patients (which are mostly neither considered nor investigated). Most importantly, the BP control rate is still surprisingly and unacceptably low. In the United States, only 34% of hypertensives patients achieve BP
values <140/90 mm Hg [2]; in the recent Health Survey for England, 20% of hypertensive patients had uncontrolled BP, despite administration of at least three drugs [3]. In Eastern European countries, only 27% of patients achieved adequate BP control [4].

This is by no means explained simply the failure to detect and to treat elevated BP – this does play a part – but actually most likely represents a failure to match BP elevation pathomechanisms with BP drug action. In fact, only the British Hypertension Society guidance from 2011–2013 (with NICE) suggest an age and race algorithm – below age 55, ACE and ARBs are recommended first, whereas for those >55 years of age, or in black patients, CCBs and diuretics are suggested as first-line interventions [5].

The Role of the Kidney in the Pathogenesis of Hypertension

Although the pathophysiology of hypertension is complex, involving a combination of both environmental and genetic factors, the central role of the kidney in this multifaceted mechanism is well established. Short-term changes in BP are produced by a multitude of mechanisms that affect cardiac output, total peripheral resistance, and cardiovascular capacitance [6]. In the long term, the kidney plays an essential role, by appropriate renal adjustments of sodium balance and blood volume. Normal BP can be sustained as long as the mechanisms regulating sodium excretion can maintain sodium balance by proper modulation of the pressure-natriuresis relationship. An increase in BP stimulates the kidneys to excrete more salt and water, thereby decreasing the extracellular and plasma volume. Alteration of the ability of the kidney to maintain sodium and water balance can determine increased BP [7]. It is now recognized that unidentified, clinically unapparent volume expansion is an important cause for resistance to antihypertensive treatment [8]. In reality, unaccounted increase in volume is probably present in a large proportion of all hypertensive patients.

Methods for Volume Assessment

These generally accepted statements are hampered in clinical practice by a lack of a simple, standardized, objective measure of volume changes from normalcy. Detection of both hypovemia and hypervolemia is an inaccurate clinical science that poses a specific challenge. Several methods are currently in use to determine the hydration status, such as clinical examination, measurement of inferior cave vein diameter using ecocardiography, or the evaluation of cardiac biomarkers – mainly N-terminal prohormone brain natriuretic peptide (NT-proBNP). Last but not the least, bioimpedance appears to be one of the most promising and increasingly used techniques to objectively determine fluid status.

The clinical examination provides a useful, but imprecise picture of fluid status. Changes in body mass following changes in nutrition and dietary Na+ and water intake may complicate the process of dry weight assessment and achievement. Inadequate attainment of dry weight ultimately results in higher levels of blood pressure. Often, more antihypertensive medication is added as a consequence [9]. Echocardiography can provide relevant information related to hydration status, besides assessment of end-organ damage, but is cumbersome, time-consuming, and requires specialized equipment and personnel. Furthermore, diastolic dysfunction and/or the low venous compliance may determine an expansion of the inferior cave vein diameter and thus are important confounders [10]. Other markers of volume expansion, such as plasma renin activity, can be modified by numerous drugs and other conditions. BNP and NT-proBNP are vasopeptide hormones secreted from the left ventricle in response to myocardial wall stress. Theoretically, overhydration increases parietal stress and secretion of BNP and NT-proBNP; therefore, BNP and NT-proBNP could be used as ideal markers for volume status evaluation [11]. However, their diagnostic value has been considered to be limited, since both renal dysfunction and associated cardiovascular diseases may affect BNP levels.

The Role of the Bioimpedance in Volume Assessment

Bioimpedance provides a noninvasive and a reliable and a simple – bedside technology for diagnosing subclinical fluid accumulation, utilizing the electrical properties of body tissues – i.e. specifically relying on conductance (ionic) and reactance (tissue properties) to measure water. This technique has been introduced in different forms during the last 15 years (single/multiple frequency, segmental/whole-body bioimpedance) but recently gained momentum on the basis of new solid evidence from clinical studies on fluid status assessment. It has been validated in both healthy persons and patients with
chronic kidney disease (CKD) by isotope dilution methods, by accepted reference body composition methods, and by techniques that measure relative changes in fluid volumes [12]. The technique descriptions, the advantages, and also the limitations and errors for each form of bioimpedance are described in table 1.

<table>
<thead>
<tr>
<th>Technique description</th>
<th>Advantages</th>
<th>Errors and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole body BIA</td>
<td>Easy, relative minor costs for device and operation. Estimation is simple and fast.</td>
<td>Accuracy is not sufficient for clinical use due to inter- and intra-individual variation in body composition.</td>
</tr>
<tr>
<td>MF-BIA</td>
<td>Simple technique. Calculation is easy and fast. Provide a stable and relative precise intracellular, extracellular, muscle mass estimation.</td>
<td>Accuracy can be affected by the amount of subcutaneous fat (extreme obesity).</td>
</tr>
<tr>
<td>Vector BIA</td>
<td>Relatively simple technique.</td>
<td>Accuracy limited by the lack of independence of R and Xc.</td>
</tr>
<tr>
<td>SF-BIA</td>
<td>Same advantages as the whole-body techniques.</td>
<td>Less validates. Requires a previous standardization, with the need to standardize both the types of electrodes used and their placement.</td>
</tr>
<tr>
<td>MF-BIA</td>
<td>Underestimates lean body mass and overestimates fat mass. Requires more electrodes, and cautious positioning of electrodes. Requires a previous standardization, with the need to standardize both the type of electrodes used and their placement.</td>
<td></td>
</tr>
<tr>
<td>Calf BIS</td>
<td>Less validated, lacks prognostic data.</td>
<td></td>
</tr>
</tbody>
</table>

SF-BIA = Single frequency bioimpedance; MF-BIA = multifrequency bioimpedance; vector BIA = bioelectric impedance vector analysis; calf BIS = calf bioimpedance.

The Role of Bioimpedance in Hypertensive’s Population

Utilization of impedance measurements to guide optimal antihypertensive treatment is widespread in renal patients and is now considered for a minor pro-
portion of the non-renal hypertensive population. There are a few studies in the nonrenal population assessing bioimpedance to guide diuretic therapy in resistant hypertension, with very promising results. The first randomized controlled trial was reported by Taler et al. [13]: patients treated according to hemodynamic measurements had an improved BP control rate (56% vs. 33% in the control group, \( p < 0.05 \)) and incremental reduction in systemic vascular resistance measurements compared with the group of patients treated as per clinical judgment alone. Higher doses of diuretics (not a greater prevalence of use) were prescribed for the hemodynamically management group that greatly reduced the BP. Smith et al. analyzed the role of hypertension therapy guided by impedance-derived noninvasive hemodynamics in 164 patients with uncontrolled hypertension and no significant accompanying diseases [14]. Study patients were randomized to either standard care with empiric selection of antihypertensive medication or to a hemodynamic arm that used impedance cardiology to guide treatment. After three months of treatment, therapy based on hemodynamic evaluation was associated with considerably better BP control, including a significant decrease in average systolic and diastolic BP values. The hemodynamic arm achieved the BP goal (<140/90 mm Hg) more frequently (77% vs. 57%; \( p < 0.01 \), and 55% vs. 27% for a more aggressive BP control – at <130/85 mm Hg; \( p < 0.0001 \)) compared with the control group. Similar results were obtained in a third RCT that included 128 patients [15].

Therapy based on impedance cardiography significantly increased the reduction in office systolic BP (11.0 vs. 17.3 mm Hg; \( p = 0.008 \)) and diastolic BP (7.7 vs. 12.2 mm Hg; \( p = 0.0008 \)) as well as 24-h mean systolic BP (9.8 vs. 14.2 mm Hg; \( p = 0.026 \)), daytime systolic BP (10.5 vs. 14.8 mm Hg; \( p = 0.040 \)), and night-time systolic BP (7.7 vs. 12.2 mm Hg; \( p = 0.032 \)). A recent published meta-analysis, involving five studies comprising a total population of 759 patients confirmed the better BP control in the bioimpedance-treated patients [16]. However, it is important to note that the studies used in this meta-analysis generally had small sample sizes and most were single-arm trials; only a few details of the populations and study characteristics were reported. Additionally, the authors did not report whether any language and publication restrictions were applied. It appeared that the review only included published data, which raised the possibility of publication bias. Risks of reviewer error and bias were unclear, as the authors did not report how many reviewers were involved in study selection and data extraction. Given these limitations, the conclusions of the review may not be wholly reliable.

**Bioimpedance in CKD and ESRD Patients**

Volume overload is an important determinant of hypertension in CKD 3–5/dialysis patients, alongside other contributors, such as sympathetic overactivity and increased arterial stiffness. Correct estimation of dry weight is thus essential for CKD patients. Inadequate estimation of dry weight can lead to chronic volume overload, which increases cardiovascular morbidity and mortality. An increasing number of studies, both in predialysis and dialysis patients have investigated bioimpedance as a fluid management tool. Hung et al. recently showed, in 338 patients with stages 3–5 CKD, that 20% of them presented with volume overload (≥7%) in the absence of clinically detectable edema [17]. Verdalles et al. [18] used bioimpedance to assess fluid status in CKD patients and to guide diuretic therapy for treating hypertension in these patients. Thirty patients with extracellular volume (ECV) expansion and a diuretic were compared to 20 patients without ECV expansion who instead received another additional antihypertensive medication. At 6 months of follow-up, SBP decreased by 21 mm Hg in patients with ECV expansion compared to 9 mm Hg in patients with normal ECV (\( p < 0.01 \)). In addition, more patients achieved the target BP of less than 140/90 mm Hg at 6 months in the group with ECV expansion (nine of 30 patients with ECV expansion cf. two of 20 without ECV expansion).

In hemodialysis patients, based on bioimpedance and cuff BP measurements, Wabel et al. [19] described four distinct categories of individuals: (i) normotensive–normovolemic; (ii) hypertensive–normovolemic; (iii) normotensive–hypervolemic; (iv) hypertensive–hypervolemic. It is clear that BP management by different classes of drugs could be tailored in an easier manner and related to prevailing underlying pathophysiological mechanisms. Furthermore, bioimpedance-guided fluid management was associated with an improvement in BP control, intradialytic symptoms, left ventricular mass index, or arterial stiffness. Moissl et al. optimized the fluid status of 55 HD patients using a bioimpedance device over the course of 3 months. This active fluid management improved significantly the BP control; every 1 1 change in fluid overload was accompanied by a 9.9 mm Hg change in predialysis systolic BP [20]. Most impor-
tantly, we now have two RCT directly comparing standard clinical assessment [21]. Recently an RCT-performed bioimpedance spectroscopy was performed in 156 patients; in half of them, fluid removal during dialysis was adjusted based on bioimpedance measurements. After 1 year of follow-up, a substantial regression of the left ventricular mass index was reported in the interventional group (mean difference between groups –10.2 g/m²; p = 0.04); additionally, values for blood pressure and arterial stiffness decreased in the intervention group, but not in the control group. We [22] showed in a randomized controlled parallel group trial including 136 HD patients follow-up for 2.5 years that strict volume control guide by bioimpedance is associated with a better survival rate (p = 0.03). After 2.5 years, there was a greater decline in arterial stiffness (PWV −2.78 m/s; (95% CI, −3.75 to 1.80) m/s; p < 0.001); and systolic BP (−2.43 mm Hg; (95% CI, −7.70 to 2.84) p = 0.4) in the bioimpedance group than the clinical-methods group.

**Bioimpedance – Limitations and Errors**

Although extensively used in the recent past, bioimpedance as the bedside technique used in the assessment of body composition has some potential limitations [23]: (1) it is contraindicated in pregnant women, children, and subjects wearing a pacemaker; (2) measurements may be affected by eating, intense physical activity, and alcohol and fluid intake before evaluation. Moreover, extreme obesity and acute body mass changes following protein malnutrition are also significant limitation of the use of bioimpedance. Patients should be prepared: avoidance of alcohol for at least 8 h before the test and no water for 4 to 6 h; if the test is applied within a 2–4 h interval after a meal, the reading may yield a higher value of 4–15 Ohms, contributing to an erroneous interpretation; in clinical practice sometimes to follow these preparation initiatives could be difficult.

The basic limitation of the model derives from the assumption that the human body is regarded as a cylinder with uniform conductivity. This limitation affects measurements accuracy. The cross-sectional area of the trunk is relatively much larger compared to that of the limbs. Consequently, the whole body resistance is largely (90%) provided by the resistance in the arms and legs (parts containing a relatively lower fluid volume than the trunk). In this context, some users prefer to apply segmental bioimpedance to eliminate the impact of higher resistance in the extremities. Although combining several segmental measurements may possibly give a more accurate description of body composition, there is no clear evidence that this translates into better hard clinical outcomes [24].

Finally, it is important to remember that the validation studies have commonly implicated healthy individuals. The elderly, adolescents, children, or ethnic minorities provided far more limited data. Individuals who differ substantially from the reference population will limit validity and the accuracy of the measurements.

Recently, a very informative study evaluating the intrinsic error of various bioimpedance methods used for estimating body fluid volume in renal patients has been published [25]. The authors compared the precision and accuracy of single and multifrequency-BIA with direct estimation methods (DEM, dilutometry, and isotopic reference methods) for total body water (TBW) (deuterium oxide dilution), extracellular fluid (ECF) (bromide dilution), and intracellular fluid (ICF) (total-body-potassium count). Although none of the analyzed methods could serve as a true ‘gold standard,’ there is slightly better accuracy for ECF assessment with multi-over, single-frequency-BIA. In conclusion, bioimpedance is very close to gold standard methods for hydration estimation and can be of great help in clinical medicine for close monitoring of body fluid volumes and nutritional markers such as muscle mass and intracellular volume.

**A New Paradigm for Hypertension Management: Bioimpedance and Office BP**

After so many years from the introduction of sphygmomanometer we propose a new paradigm. Specifically, we propose that it is now time to implement a combined office BP and bioimpedance volume assessment in all patients, for the routine management of hypertension. Historically, sphygmomanometers were difficult to be accepted over intraarterial BP measurements and for all patients, but because of easiness to use in the office and relevance of obtained measurements they prevailed and became the only norm. It is time to consider a new revolution in BP measurements, by combining two very easy-to-use, affordable, and relevant evaluations/measurements: BP and volume – sphygmomanometers and bioimpedance portable devices. Four different categories of patients should be obtained; these categories and the proposal for their optimal management are described in figure 1.
By using individualized hemodynamic measures and individualized antihypertensive treatment in all patients, it seems probable to improve BP control and possibly end organ damage. Although we have numerous drugs to lower BP, we have never aligned how we think they work with any phenotyping (or genotyping). So we have a ‘one size fits all’ approach to raised BP. In CKD, we can see the folly of this all too clearly. Volume matters. Salt and water could make the difference. Given that we can now measure volume expansion reliably and noninvasively, and titrate BP treatment, why do we not bother, in all patients?

Disclosure Statement

None.

References


