Journal of Cardiovascular Translational Research
https://doi.org/10.1007/s12265-019-09910-4

CORRESPONDENCE

Correlation of Quantitated Intravascular Volume with Blood Pressure in Patients with Systemic Hypertension

Marat Fudim[1,2] · Vanessa L. Blumer[1] · Renato D. Lopes[2] · Patrick Rossignol[3] · Michael Feldschuh[4] · Wayne L. Miller[5] · Paul A. Sobotka[6]

Received: 12 July 2019 / Accepted: 23 August 2019

Abstract

Volume management is an essential component of anti-hypertensive therapy. Different volume phenotypes have been proposed. We sought to study the total blood volume (TBV), plasma volume (PV), and red blood cell volume (RBV) in hypertensive patients. We included patients followed in an outpatient cardiology clinic from 1998 to 2003. Blood volume (BV) parameters were measured using radioisotope iodine-131-labeled albumin dilution technique. Values were expressed as percentage (%) deviation from ideal volumes. A total of 95 patients were included. The intravascular volume distribution as percent deviation from normal volume ranged from −23 to +28% for TBV, −22 to +36% for PV and −29 to +37% for RBV. There was no significant correlation between systolic BP and any of the BV parameters (TBV and SBP, $r = -0.03$; PV and SBP, $r = -0.12$; RBV and SBP, $r = -0.08$). Patients with hypertension have a wide variation in BV parameters. BV does not correlate with SBP.

Keywords Blood volume analysis · Hypertension · Race · Gender

Introduction

Uncontrolled blood pressure (BP) is a leading cause for cardiac and renal-related morbidity and mortality. Evidence-based guidelines focus on the simplification of hypertension management, moving away from personalized treatment approaches. Blood volume (BV) and vascular tone are well-established determinants of BP [1–3], making them central targets in the management of hypertension. The presence of several hypertension phenotypes based on the combination of volume status and vascular tone have been reported [4] but findings have been inconsistent. Studies investigating the significance of volume phenotypes in hypertension date back to the 1970s and were mostly performed in experimental settings. The present study was undertaken to provide a contemporary analysis of the three main components of total BV in adults with hypertension (total blood volume (TBV), plasma volume (PV), and red blood cell volume (RBV)), and determine whether there is a relationship between BV parameters and systemic BP in hypertensive patients encountered in clinical practice.

Associate Editor Ana Barac oversaw the review of this article

✉ Marat Fudim
marat.fudim@dm.duke.edu

[1] Department of Medicine, Division of Cardiology, Duke University Medical Center, Durham, NC, USA

[2] Duke Clinical Research Institute, Durham, NC, USA

[3] CIC-Inserm 1433, Inserm U1116, Nancy University hospital, and FCRIN INI-CRCT, University of Lorraine, Nancy, France

[4] Daxor, New York, NY, USA

[5] Department of Medicine, Mayo Clinic, Rochester, MN, USA

[6] Department of Medicine, Ohio State University, Columbus, OH, USA

Methods

Retrospective analysis of patients with chronic stable hypertension followed in a US urban cardiology outpatient clinic from 1998 to 2003. BV was measured during early evaluation of hypertension using the indicator-dilution-technique of radiolabeled iodine-131 albumin. The clinic used an FDA-approved and commercially marketed technology indicated for blood volume determinations (Daxor Volumex HSA I-131, NY). There was no specific timing as to when a BV was obtained in the course of an evaluation of HTN. The science behind blood volume analysis is based upon the indicator dilution technique. A

Published online: 28 August 2019

known amount of tracer is introduced into an unknown volume, and after it has fully mixed within that volume, the dilution of the tracer is measured. The lower the concentration of tracer, the larger the volume of the substance the tracer was introduced into. Labeled albumin was injected over 1 min with serial blood draws at 12, 18, 24, 30, and 36 min post-injection. Activity values were extrapolated back to time zero to provide a measure of PV (BVA—100, Daxor, NY). Values are expressed as percentage (%) deviation (±) from normal expected volumes. Normal reference values were determined from previously established gender-adjusted reference curves using the deviation from ideal body weight method [2, 5]. BP was obtained in a seated position with single timepoint measurements. The deidentified dataset was obtained from Daxor, NY, for all patients with available BV analysis and clinical data. Analysis was performed using the Student *t* test and interaction testing. A p value < 0.05 was considered statistically significant.

Results

A total of 95 consecutive patients were included in our analysis. The mean office systolic BP (standard deviation (± SD)) was 148 (± 48) mmHg and mean diastolic pressure (± SD) was 91 (± 7) mmHg. There was a predominance of women (56.8%), with an overall mean age of 60 years. The self-identified racial background of our patients varied, with 40% White, 35.8% Black, 8.4% Hispanic, and 2.1% Asian. Twenty-nine patients (30.5%) had diabetes, 5 (5.3%) had diagnosed renal disease (eGFR < 60 mg/dl/min), and 11 (11.6%) had heart failure. The majority of the patients were receiving at least one anti-hypertensive medication (70.6%); 21.2% were on a beta-blocker, 27.1% on ACE-inhibitor or ARB, 22.3% were on a diuretic, 17.6% received calcium channel blockers, and 8.2% alpha-blockers. Diuretic therapy was equally distributed between Blacks and non-Blacks (15% vs 17%).

The intravascular volume distribution as percent deviation from normal volume ranged from − 23 to + 28% for TBV, − 22 to + 36% for PV, and − 29 to + 37% for RBCV (Fig. 1a). There was no significant correlation between systolic BP and any of the BV parameters (TBV and systolic BP, $r = -0.03$; PV and systolic BP, $r = -0.12$; TBV and systolic BP, $r = -0.08$) (Fig. 1b). There was a significant interaction for gender and the relationship between gender and systolic BP (women: coefficient 0.35 vs. men: coefficient − 0.65; $p = 0.022$). Blacks had significantly lower BV compared with non-Blacks

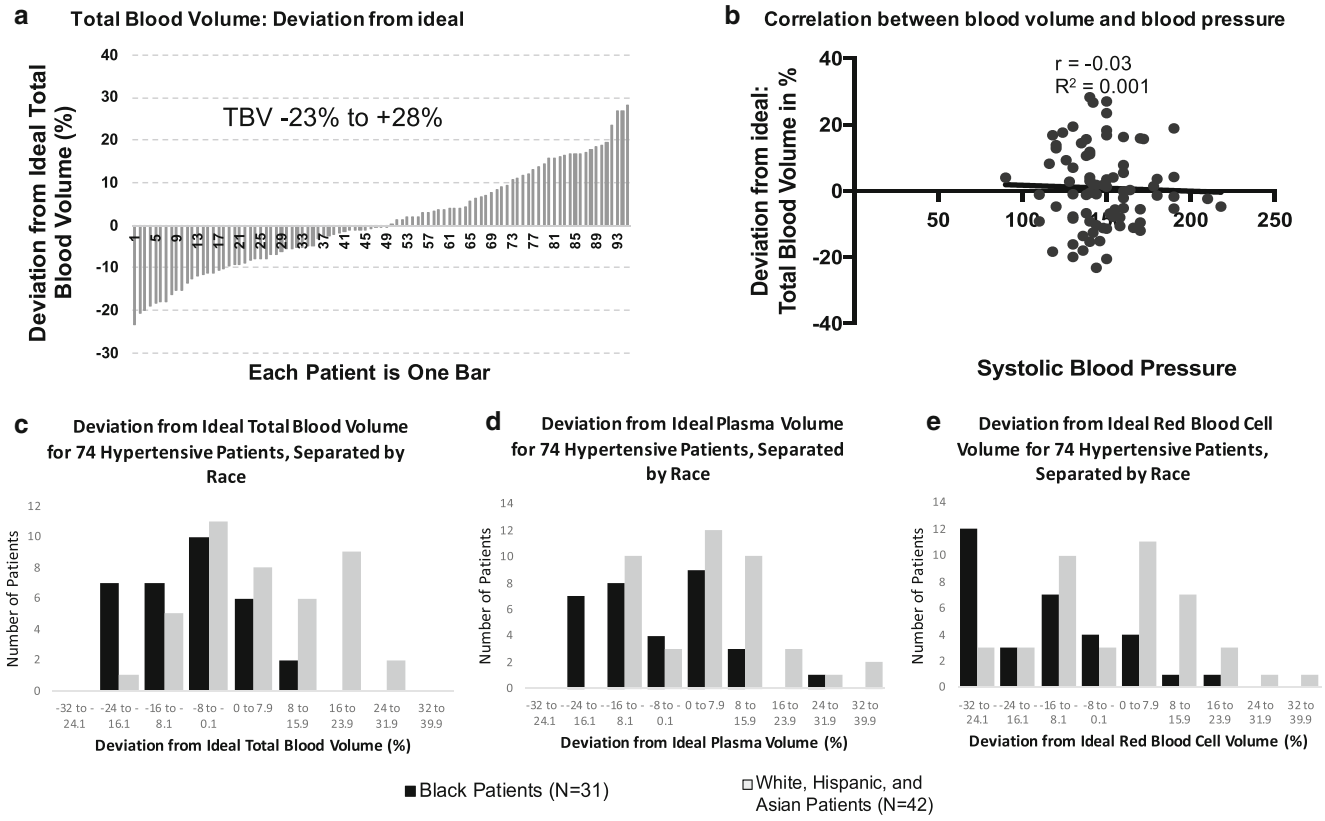

Fig. 1 Blood volume analysis in patients with hypertension. **a** Deviation of total blood volume from ideal. **b** Correlation between blood volume and systolic blood pressure. Race-based blood volume analysis. Deviation from ideal **c** total blood volume, **d** plasma volume, and **e** red blood cell volume, stratified by race (Blacks vs. White/Hispanic/Asian)

($p < 0.001$), despite comparable SBP (152 ± 25 mmHg vs. 145 ± 20 mmHg, (mean ± SD), $p > 0.05$) (Fig. 1c–e). There was no difference in TBV, PV, or RBV when comparing patients with or without anti-hypertensive treatment ($p > 0.05$); patients on diuretics had overall lower BV parameters, but this difference was not statistically significant.

Discussion

Our findings reveal a large variability in measured BV among patients with chronic stable hypertension. There does not appear to be a significant association between volume status and BP regardless of treatment, gender, or race. The present findings are unique as we report from a contemporary clinical cohort, and the results suggest the presence of diverse volume phenotypes among patients with hypertension. The findings highlight that hypervolemia should not be regarded as ubiquitous in hypertension or necessarily the prime target in the management of hypertension for every patient.

While the relationship between BV and plasma renin-activity was reported to differ among racial subgroups [6], it has been suggested that Blacks with hypertension are likely to be in the low-renin profile, and hence, the BP-lowering efficacy of renin-angiotensin-aldosterone-system (RAAS) inhibitors to be attenuated in this patient population. Although limited by the lack of RAAS measurements in our study, BV parameters shown to be lower in Blacks despite similar BP. This provides uncertainty toward any long-held conclusion of predominant volume expansion as a sole basis for hypertension in Black patients.

Some limitations are worth mentioning. The clinical diagnostic use of BV analysis using radiolabeled dilution technique was not protocolized/standardized. Thus, it is likely that not all patients with the diagnosis of hypertension underwent this test which introduced an unmeasured bias. Further, the therapeutic actions by the clinician and the outcomes of the patients were not measured and included in the analysis.

Volume management is essential to anti-hypertensive therapy as described in current guidelines. Our findings suggest that volume assessment could provide unique insight during the workup of hypertension. Thus, future work needs to determine whether quantitated volume analysis might help guide the most appropriate therapy in hypertensive adults.

Compliance with Ethical Standards

Human and Animal Studies No human or animal studies were carried out by the authors for this article.

Conflict of Interest Marat Fudim is supported by an American Heart Association grant 17MCPRP33460225 and NIH T32 grant 5T32HL007101; he consults for Coridea, AxonTherapies, and Galvani. Renato D. Lopes research grants: Amgen, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, Medtronic PLC, Sanofi-Aventis; consulting/advisory board fees: Bristol-Myers Squibb/Pfizer, Bayer, Boehringer Ingelheim. Michael Feldschuh is an employee of Daxor. All other authors declare that they have no conflict of interest.

Clinical Relevance Hypertension is one of the major health risk factors, and uncontrolled hypertension is highly prevalent. The physiology of hypertension is complex and knowledge of volume phenotypes might be relevant to clinical management.

References

1. Weidmann, P., Hirsch, D., Beretta-Piccoli, C., Reubi, F. C., & Ziegler, W. H. (1977). Interrelations among blood pressure, blood volume, plasma renin activity and urinary catecholamines in benign essential hypertension. *The American Journal of Medicine, 62*, 209–218.
2. Feldschuh, J., & Katz, S. (2007). The importance of correct norms in blood volume measurement. *The American Journal of the Medical Sciences, 334*, 41–46.
3. Mayet, J., & Hughes, A. (2003). Cardiac and vascular pathophysiology in hypertension. *Heart, 89*, 1104–1109.
4. Laragh, J. H., Sealey, J. E., Niarchos, A. P., & Pickering, T. G. (1982). The vasoconstriction-volume spectrum in normotension and in the pathogenesis of hypertension. *Federation Proceedings, 41*, 2415–2423.
5. Feldschuh, J., & Enson, Y. (1977). Prediction of the normal blood volume. Relation of blood volume to body habitus. *Circulation, 56*, 605–612.
6. Chrysant, S. G., Danisa, K., Kem, D. C., Dillard, B. L., Smith, W. J., & Frohlich, E. D. (1979). Racial differences in pressure, volume and renin interrelationships in essential hypertension. *Hypertension (Dallas, Tex : 1979), 1*, 136–141.