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TECHNICAL NOTE

Pulse Waveform Analysis of Chinese Pulse Images and Its Association with Disability in Hypertension

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Abstract
Hypertension affects functional capacity and quality of life. Pulse wave analysis (PWA) quantifies the pulse waveform's propagation and its changes resulting from arterial remodeling. Pulse image analysis (PIA) in traditional Chinese medicine contributes to pattern differentiation and therapeutic intervention. This protocol study evaluates the relationships between the parameters of both PWA and PIA to identify patterns in patients with hypertension and the associations of those patterns with functional capacity. In this observational, cross-sectional study protocol 40 patients were subjected to clinical and laboratorial examinations to assess the risk factors for cardiovascular disease and pattern differentiation. PWA was noninvasively performed at the radial artery to estimate the pulse wave's velocity, arterial compliance, and reflection index. PIA using the "simultaneous pressing" method was performed to assess nine indicators. Handgrip strength and physical activity was assessed as functional outcomes. We hypothesized that interactions between patterns and pulse images affect the PWA parameters and that the functional outcomes are weakly associated with personal, hemodynamic and risk factors for cardiovascular disease. Performing a PIA in patients with hypertension might allow the identification of early target-organ damage, standardization of the PIA based on the PWA, and unification of the pulse diagnosis.

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1. Introduction

Hypertension is a major public health problem worldwide, and is the cardiovascular disease (CVD) with the highest prevalence in developed countries [1]. Chronic hypertension affects functional capacity [2,3] and impacts the quality of life of patients [4], often subjecting them to cardiac rehabilitation. High blood pressure acts silently through arterial remodeling [5] until signs or symptoms secondary to target—organ damage (TOD) [1] or skeletal muscles [6] occur. Clinical history, physical examination, and complementary exams are needed to monitor the disease's progress and the effects of therapeutic interventions [1]. In this sense, pulse waveform analysis (PWA) is a noninvasive and reliable method for assessing the cardiovascular system based on the phenomenon of waveform propagation and reflection throughout the arterial system [7]. PWA can be performed at both central and peripheral arteries, such as the aorta and radial arteries, respectively, and evidence shows that variables obtained from PWA of proximal arteries are similar to those obtained from peripheral arteries [8].

Traditional Chinese medicine (TCM) is a traditional health practice with systematic-philosophic reasoning based on the relationships between humanity and nature. TCM experts do not diagnose diseases, but they identify patterns as their morbid counterparts. Currently, the paradigm of pattern/disease is advocated for research [9]; i.e., patterns are studied within the context of a given disease. Contemporary literature relates five patterns to patients with hypertension, and these are identifiable by using inspection, auscultation-olfaction, inquiry, and palpation [10—15]. Even nowadays, pulse image analysis (PIA) is an important diagnostic procedure in TCM [16,17] and is performed on the radial artery bilaterally at three different positions and depths, setting the so-called nine indicators [18—20].

Previous studies achieved important findings due to advances in biomedical instrumentation, albeit with major limitations from the perspectives of either traditional or conventional medicines. Theories developed in animal models were not tested in humans and showed no theoretical correspondence with TCM [21,22]. Findings from healthy participants could not be extrapolated to other populations without proper evidence [23—25], and incomplete descriptions of the diagnostic criteria for hypertension, as well as traditional descriptions of PIA, were also found [24,26]. Finally, a lack of comparison among patterns of hypertension was found [26]. Most importantly, the relationship between PWA and PIA among TCM patterns of hypertension, as well as the relationship between those patterns and functional capacity, remains unknown.

Because structural and functional changes in hypertension primarily impact the arteries and, thus, determine the waveform's morphology, patients with hypertension present with different phenotypes due to gene—environment interactions; in addition, the radial artery can be used for both PWA and PIA. Thus, we hypothesized that variables related to PWA might have sufficient information to describe PIA. Therefore, this study protocol aims to describe the PIA by using PWA variables in patients with hypertension, to compare the variables from PWA and PIA with the hypertension-related patterns, and to quantify the association of PWA and PIA variables with the clinical and functional characteristics of the sample.

2. Materials and methods

A printed case report form was developed to collect data from each participant regarding all procedures (Supplementary file 1). Primary data obtained from the paper case report form was typed in an electronic worksheet developed in Excel for Mac (Microsoft Corp., Redmond, WA, USA) with data formatting and data validation of entries. Secondary data was calculated by using equations inserted in the spreadsheet. Statistical analysis was performed by using SPSS version 22 (IBM Corp., Armonk, NY, USA) after data importing.

The arterial function analysis system [27—29] was used to acquire noninvasive blood pressure signals. The software was developed in LabVIEW 8.0 (National Instruments, Austin, TX, USA) and controls a preamplifier circuit connected to a 14-bit acquisition board (USB 6009, National Instruments). Noninvasive piezoelectric transducers (PT-102, iWorx System Inc., Dover, NH, USA) was attached to the upper arm with Velcro straps.

The pattern differentiation algorithm (PDA) was used for pattern differentiation and was also developed in LabVIEW 8.0 (National Instruments). Data from the electronic worksheet was imported into the PDA for automated pattern differentiation. The accuracy of the PDA for pattern differentiation was 94.7% (sensitivity = 89.8%; specificity = 99.5%) [30].

2.1. Timing and study design

This is an observational, cross-sectional protocol study with prospective admission of cases. Fig. 1 exhibits the study's flowchart with the respective timing of each procedure. The same examiner (N.G.R.M.), a certified TCM expert who has had a 2-year training period and 6 years of TCM clinical practice, performed all procedures and measurements.

2.2. Ethics

This study protocol was approved by the Institutional Ethics Committee (Centro Universitário Augusto Motta (Rio de Janeiro, RJ, Brazil)) prior to its execution (CAAE 34723714.2.0000.5235). Participants, after having received an explanation of the study's aims and potential risks and of the benefits associated with their participation, signed a written informed consent form to participate in this study.

2.3. Participant recruitment: Inclusion and exclusion criteria

Data were collected at the Division of Arterial Hypertension at the National Institute of Cardiology (Rio de Janeiro, RJ, Brazil) between 08:00 AM and 11:00 AM, as recommended for PWA [7] and PIA [18,19], from September 2014 to June 2015. Patients enrolled for antihypertensive drug treatment were addressed for eligibility by checking the inclusion and the exclusion criteria discussed below. Medications used

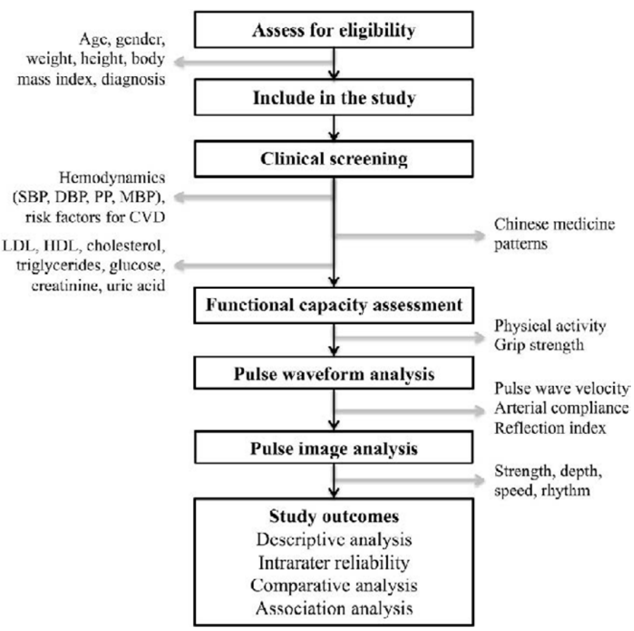

Figure 1 Study flowchart. CVD = cardiovascular disease; DBP = *diastolic* blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MBP = *mean blood pressure;* PP = pulse pressure; SBP = systolic blood pressure.

were annotated for possible analysis of their effects on the studied variables.

Participants who simultaneously met the following criteria were included in the study: age $\geq$ 18 years; clinical diagnosis of primary systemic arterial hypertension confirmed with complementary exams; absence of valvular disease, ventricular dysfunction, or severe cardiac arrhythmias; and signature on the written informed consent form. Participants were excluded if they lacked complete data related to control or outcome variables. Participants using pharmacological antihypertensive treatment were not excluded, and their treatments were not suspended, as they may characterize patients with resistant hypertension.

2.4. Clinical and laboratory examinations

A disease-specific questionnaire was used for the collection of manifestations corresponding to the following five patterns: liver-fire blazing upwards; kidney-*yin* deficiency and Liver-*yang* rising; obstruction of phlegm and dampness of heart/liver/gallbladder; *Qi* and blood deficiency leading to liver-*yang* rising; and kidney-*yin*/*yang* deficiency [31]. The functional outcomes evaluated in this study comprise physical activity and grip strength. Physical activity was assessed by using the self-administered, short form of the International Physical Activity Questionnaire. Physical activity levels were categorized as very active, active, irregularly active, or sedentary [32]. Grip strength was measured by using the self-reported dominant hand. The participant was asked to sit comfortably with the shoulders in the anatomical position, the elbow of the dominant upper extremity flexed at 90° at the chair's arm, and the nondominant hand relaxed over the thigh. The handgrip was adjusted in the dynamometer individually before measurement such that the proximal haste was located closer to the body above the phalanges of fingers II-III-IV. Three maximal voluntary contractions lasting 5 seconds each was performed with a 60-second interval between contractions, with the largest value being used as the representative grip strength [33].

Other personal variables included [1]: weight and height as measured by using an analog scale (0.1 kg) and a stadiometer (0.01 m); the Quetelet index (body mass index: weight/height^2); self-reported duration of hypertension; systolic blood pressure, diastolic blood pressure (DBP), and heart rate (BP3AF1-3 model, G-TECH, China) after a 10-minute rest in the sitting position; pulse pressure (pulse pressure = systolic blood pressure − DBP) and mean arterial pressure (mean arterial pressure = DBP + pulse pressure/3]); current medications; left ventricular hypertrophy as assessed from the electrocardiogram; and laboratory analysis of blood. Control variables were used to classify the hypertension grade and the obesity grade [34]. Additionally, the following risk factors for CVD were assessed: cigarette smoking; smoking history; obesity; sedentary life style; dyslipidemia, and diabetes mellitus [35]; history of premature CVD; TOD to the heart, kidney, brain, and eyes.

2.5. PIA

PIA was performed using the "simultaneous pressing" technique from the deepest level to the surface in both wrists according to traditional methods [18–20]. Briefly, the patient was sitting for 10 minutes before examination and was instructed to calm his breathing. The examiner was facing the patient to take the pulse; the middle finger was placed on the skin over the styloid process of the radius bone (i.e., *guan* position), and the index and annular fingers rested naturally proximal and distal to the *guan* position (i.e., *cun* and *chi* positions, respectively). The radial artery was be pressed until complete obliteration is felt (i.e., "bone level"); then, the pressure was relieved in three stages to account for the pulse depth. Pulse speed was reported based on the number of the patient's heartbeats felt during a complete respiratory cycle (i.e., inhalation followed by exhalation) of the examiner. The fundamental aspects of the PIA was annotated as the following factor: strength (strong or weak), depth (superficial or deep), speed (slow, moderate, or fast), and rhythm (regular or intermittent).

2.6. PWA

PWA was performed after a 10-minute rest with the patient in the lying position. The participant was instructed to remain still during data collection to reduce motion artifacts in the signal. Piezoelectric transducers were placed, by using adjustable Velcro straps, on the wrist over the radial artery (*guan* position) and on the elbow over the brachial artery, both on the right side of the body. The linear distance between transducers (Δx) were used for further calculations. Pressure-pulse waveform signals were captured at a sampling rate of 1.0 kHz for 60 seconds.

The pulse wave's velocity (PWV) was automatically calculated by using the ratio between Δx and time taken to travel between sites [27]. Arterial compliance (AC) was estimated by using the three-section transmission-line model and an optimization algorithm [28]. The morphology of the pulse was quantified by using the reflection index ($IR_{1,2}$) estimated with an optimization algorithm [29]. All above-cited parameters were averaged over the same sequence of 10 heartbeats. Those parameters have been selected because they are related to changes in arterial stiffness (PWV, AC) and total peripheral resistance ($IR_{1,2}$) due to arterial remodeling in hypertension [27—29]. Other parameters (e.g., the amplitude of the waveform and the area under the pressure-pulse's waveform) are available for PWA, but are not included in the study protocol because the system for data acquisition obtains blood-pressure signals in raw, relative units (i.e., Volts) rather than absolute pressure (i.e., mmHg). Worthy of note is the fact that PWV, AC, and $IR_{1,2}$ do not require absolute values of blood pressure, but only scaled waveform morphologies [27] (Fig. 2).

2.7. Statistical analysis

Considering the association of PWA and PIA with functional capacity as the main outcome, a minimum sample of 36 patients was required to observe at least a weak association of $\pm$ 0.41 ($\alpha = 5\%$, $\beta = 20\%$). Considering further the reliability for PIA, a minimum sample of 30 patients was required to observe at least a poor reliability of $\kappa_1 = 0.40$ ($\kappa_0 = 0.00$, $\alpha = 5\%$, $\beta = 20\%$) for two measurements with binary variables. Therefore, to achieve a representative result, the highest estimated sample size required to complete the study was 36. Adjusting for potential data loss, the sample size was increased by 10% to 40 patients. Because of the subjective nature of PIA, a subsample of 15 participants was assessed twice (30-minute interval) to estimate of the intra-rater reliability for each fundamental aspect of the pulse images and hemodynamics.

Descriptive statistics was displayed as mean $\pm$ standard deviation, median (minimum; maximum), or absolute frequency (%) accordingly to the variable type. The *F*-test in two-way classifications with different numbers of observations per cell was used to test the null hypothesis of no main or interaction effects for the pulse image factors, i.e., strength, depth, and speed, on the PWA parameters and functional capacity. Associative statistical analyses was performed by using the Cramer's *V* coefficient to test the null hypothesis of no association ($p < 0.40$) between variables. The intrarater reliability for PIA and hemodynamics was assessed by using the Kappa (κ) coefficient and intraclass correlation coefficient ($ICC_{2,1}$), respectively, both with respective 95% confidence intervals. The value of statistical significance was $p < 0.05$.

3. Discussion

Because patterns related to hypertension are described by distinct pulse images, we hypothesized an interaction effect of the factors strength, depth, and speed on the PWA

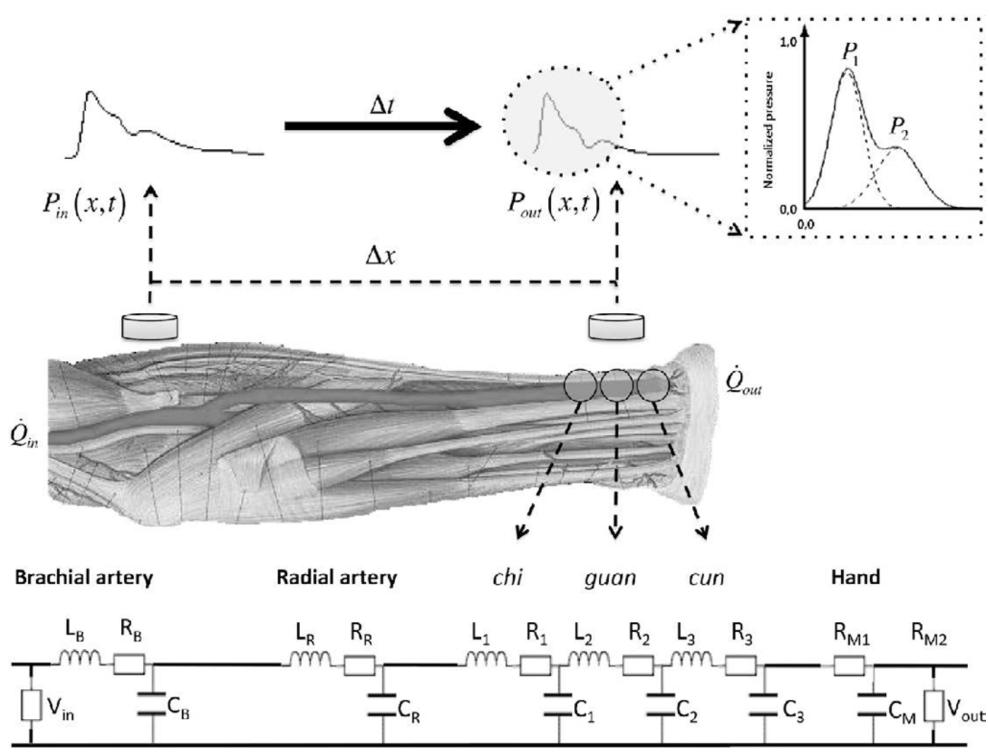

Figure 2 Scheme representing the assessment of the pulse wave's velocity, arterial compliance, and reflection index ($IR_{1,2}$) by using the same pressure pulse signals. The pressure pulse's waveform travels a fixed distance (Δx) from the brachial (P_{in}) to the radial (P_{out}) arteries during a time interval (Δt), thus determining its pulse wave's velocity. During its course, the pulse's waveform is modified according to the inertances (*L*), resistances (*R*), and compliances (*C*) of these vessels passing through the three positions for pulse image analysis (*chi*, *guan*, *cun*). The relative amplitude of the first two peaks (P_2/P_1) of the pulse's waveform at the radial artery determines the $IR_{1,2}$.

parameters. Additionally, due to the chronic disabling nature of hypertension, personal, hemodynamic, and risk factors for CVD were expected to be at least weakly associated ($\rho = 0.40$) with the functional outcome variables. Finally, considering the subjective aspect of palpating pulse images and the training of the TCM rater, at least a slight ($\kappa = 0.00-0.20$) or fair intrarater reliability was expected ($\kappa = 0.21-0.40$), depending on the fundamental aspect under consideration, and at least a fair reliability was expected for the hemodynamic variables ($ICC_{2,1} > 0.41$).

The Chinese pulse diagnosis is essentially a subjective analysis. Thus, a quantification and standardization of the pulse diagnosis for TCM experts is an urgent need that requires the transformation of qualitative descriptions into physical quantities. Parameters such as the PWV, AC, and $IR_{1,2}$ are markers for the diagnosis and the prognosis of CVD. Use of the PWA to understand the PIA might improve the objectivity of pulse palpation in TCM, allowing even less experienced practitioners to achieve a more accurate diagnosis. Collectively, establishing a PIA in patients with hypertension might allow the early identification of TOD and a unification of pulse diagnosis.

Disclosure statement

The authors declare that they have no conflicts of interest and no financial interests related to the material of this manuscript.

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Appendix A. Supplementary file

Supplementary file related to this article can be found online at http://dx.doi.org/10.1016/j.jams.2015.06.012.

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