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ESTIMATING ARTERIAL AND VENOUS DYNAMICS THROUGH A VENOUS OCCLUSION PLETHYSMOGRAPHY-BASED WINDKESSEL MODEL: PRELIMINARY RESULTS

DINÂMICA ARTERIAL E VENOSA ESTIMADA POR MEIO DE UM MODELO WINDKESSEL BASEADO EM PLETISMOGRAFIA POR OCLUSÃO VENOSA: RESULTADOS PRELIMINARES

DINÁMICA ARTERIAL Y VENOSA ESTIMADA MEDIANTE UN MODELO WINDKESSEL BASADO EN PLETISMOGRAFÍA POR OCLOSIÓN VENOSA: RESULTADOS PRELIMINARES

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ABSTRACT
This study presents preliminary findings from a pilot investigation involving five healthy subjects to evaluate a vascular mechanics model applied to venous occlusion plethysmography. The proposed model characterizes arterial and venous mechanical properties at baseline and enables dynamic parameter estimation during post-occlusion recovery. Reactive hyperemia induced by forearm venous occlusion was assessed under baseline conditions and after physiological interventions (ibuprofen administration and exercise). The model quantified transient hemodynamic responses, consistently showing decreases in arterial and venous resistances and increases in venous compliance, followed by gradual recovery toward baseline values. Condition-dependent differences were identified: resistance reductions were more pronounced after ibuprofen administration, whereas venous compliance exhibited greater enhancement following exercise. These results demonstrate the model's sensitivity to pharmacological and physiological modulation of vascular function. The proposed framework offers a noninvasive approach for the simultaneous assessment of arterial and venous dynamics and may contribute to opening new paths for cardiovascular function assessment.

KEYWORDS: Reactive hyperemia. Vascular dynamics. Vascular mechanics. Windkessel model.

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RESUMO
Este estudo apresenta resultados preliminares de um estudo piloto envolvendo cinco indivíduos saudáveis para avaliar um modelo de mecânica vascular aplicado à pletismografia por oclusão venosa. O modelo proposto caracteriza as propriedades mecânicas arteriais e venosas em condições basais e permite a estimativa de parâmetros dinâmicos durante a recuperação pós-oclusão. A hiperemia reativa induzida pela oclusão venosa do antebraço foi avaliada em condições basais e após intervenções fisiológicas (administração de ibuprofeno e exercício). O modelo quantificou as respostas hemodinâmicas transitórias, mostrando consistentemente reduções nas resistências arterial e venosa e aumentos na complacência venosa, seguidos por uma recuperação gradual em direção aos valores basais. Foram identificadas diferenças relacionadas à condição: as reduções de resistência foram mais pronunciadas após a administração de ibuprofeno, enquanto a complacência venosa apresentou maior aumento após o exercício. Esses resultados demonstram a sensibilidade do modelo à modulação farmacológica e fisiológica da função vascular. O modelo proposto consiste numa abordagem não invasiva para a avaliação simultânea da dinâmica arterial e venosa que pode contribuir para a abrir novos caminhos para a avaliação da função cardiovascular.

PALAVRAS-CHAVE: Hiperemia reativa. Dinâmica vascular. Mecânica vascular. Modelo Windkessel.

RESUMEN
Este estudio presenta resultados preliminares de una investigación piloto con cinco sujetos sanos, orientada a evaluar un modelo de mecánica vascular aplicado a la pletismografía por oclusión venosa. El modelo propuesto caracteriza las propiedades mecánicas arteriales y venosas en condiciones basales y permite la estimación dinámica de parámetros durante la fase de recuperación posterior a la oclusión. La hiperemia reactiva inducida por la oclusión venosa del antebrazo fue evaluada en condiciones basales y tras intervenciones fisiológicas (administración de ibuprofeno y ejercicio). El modelo cuantificó las respuestas hemodinámicas transitorias, mostrando de manera consistente disminuciones en las resistencias arterial y venosa, así como incrementos en la complacencia venosa, seguidos de una recuperación gradual hacia los valores basales. Se identificaron diferencias dependientes de la condición: las reducciones de resistencia fueron más pronunciadas tras la administración de ibuprofeno, mientras que la complacencia venosa mostró un mayor aumento después del ejercicio. Estos resultados demuestran la sensibilidad del modelo a la modulación farmacológica y fisiológica de la función vascular. El modelo propuesto consiste en un enfoque no invasivo para la evaluación simultánea de la dinámica arterial y venosa que puede contribuir a abrir nuevos caminos para la evaluación de la función cardiovascular.

PALABRAS CLAVE: Hiperemia reactiva. Dinámica vascular. Mecánica vascular. Modelo Windkessel.

INTRODUCTION

Vascular mechanical dysfunction may represent an early marker of endothelial impairment. Conversely, functional alterations can contribute to the development and progression of atherosclerosis and other cardiovascular diseases. The endothelium plays a central role in regulating vascular tone and vessel diameter, as well as in modulating blood cell adhesion, proliferation, and inflammatory processes (Ajoolabady; Pratico; Ren, 2025; Wang; He, 2024; Ray *et al.,* 2023; Neubauer; Zieger, 2022).

Importantly, endothelial dysfunction often precedes clinically detectable structural changes in the vascular wall (Ajoolabady, Pratico and Ren, 2025). Therefore, early detection is essential for effective prevention, and the analysis of vascular mechanics may contribute significantly to this objective.

The Windkessel model simplifies the complex cardiovascular system into an equivalent hydraulic circuit composed of resistive and compliant elements, facilitating the understanding of blood flow and pressure dynamics (Damag, 2025). Methods capable of detecting endothelial dysfunction prior to structural vessel alterations are highly desirable for cardiovascular risk prevention.

Macedo *et al.,* (2008; 2013; 2020) proposed innovative approaches emphasizing the importance of modeling the dynamic behavior of cardiovascular parameters rather than relying solely on absolute or relative values obtained at isolated time points. Static measurements frequently exhibit substantial variability, complicating comparisons across experiments and allowing biological variation to obscure meaningful physiological differences.

In this context, Macedo *et al.,* (2020) introduced a Windkessel-based model applied to Venous Occlusion Plethysmography (VOP) to estimate arterial and venous compliance and resistance, as well as blood pressure, simultaneously. Although post–reactive hyperemia flow behavior was previously modeled using VOP waveforms (Macedo *et al.,* 2008; 2013), the temporal dynamics of compliance and resistance during the post-occlusion recovery phase have not been fully investigated.

Reactive hyperemia protocols are typically performed by occluding limb blood flow for approximately five minutes. Upon release, increased shear stress stimulates endothelial nitric oxide production, leading to vasodilation. The vascular system subsequently regulates this response to restore homeostasis and return to baseline conditions (Rosemberry; Nelson, 2020; Tremblay; Pyke, 2017). Prolonged ischemia thus provides a controlled perturbation that enables observation of the system’s recovery dynamics. Venous occlusion plethysmography is a noninvasive technique that allows implementation of reactive hyperemia protocols with continuous signal acquisition, making it particularly suitable for vascular behavior analysis.

Accordingly, the aim of this pilot study was to investigate time-dependent vascular mechanics using the VOP-based model proposed by Macedo *et al.,* (2020), focusing on the restoration of vascular equilibrium following marked vasodilation induced by reactive hyperemia. The principal contribution of this work lies in addressing the recurring challenge of biological variability by shifting the analytical emphasis toward dynamic physiological behavior. This perspective may provide novel insights into the early detection of endothelial dysfunction through the simultaneous assessment of arterial and venous mechanical properties.

2. MATERIALS AND METHODS

The VOP model developed by Macedo *et al.,* (2020) to evaluate vascular mechanics under basal conditions was applied in this study. The proposed model was used to analyze post–reactive hyperemia data obtained under placebo, ibuprofen (a nonsteroidal anti-inflammatory drug that inhibits prostaglandin synthesis), and post-exercise conditions.

The results of this pilot study indicate that important adjustments in the plethysmographic signal acquisition method are necessary. The approach employed—commonly reported in the literature—led to the loss of the most critical component of the signal, namely the first plethysmographic cycle, and reduced the sample size from 10 to 5 subjects. These issues and suggestions will be presented throughout the paper.

2.1. Induced vascular conditions

The database analyzed in this study was originally compiled for a separate experiment focused exclusively on flow measurements derived from the plethysmography signal. The data were collected using a randomized, double-blind, paired design. The experimental protocol was conducted over two separate days.

On the first day, each volunteer ingested a capsule containing either a placebo or 1200 mg of ibuprofen, according to a random allocation. Two hours later, venous occlusion plethysmography (VOP) was performed. Subsequently, participants completed a maximal, progressive, individualized treadmill exercise test, followed by a second VOP recording. On the second day, the same protocol was repeated, with each volunteer receiving the alternate capsule.

Inclusion criteria comprised young males with normal fasting glucose levels, normal oral glucose tolerance, and normal triglyceride and cholesterol levels. The exclusion criteria included smoking and the presence of cardiovascular, renal, or other chronic diseases. The Ethics Committee approved the protocol, and volunteers provided their informed consent prior to enrollment.

VOP signals collected after placebo and ibuprofen administration, as well as post-exercise under placebo condition were analyzed considering three experimental conditions: normal vascular condition (Placebo group), post-ibuprofen administration (Ibuprofen group), and post-exercise (Post-exercise group).

2.2. Experimental data acquisition

Volunteers rested in supine position in a temperature- and noise-controlled room for 30 minutes to allow physiological stabilization. Two pneumatic cuffs and a strain gauge were placed in the right upper limb, which was maintained above heart level (Salisbury *et al.,* 2018).

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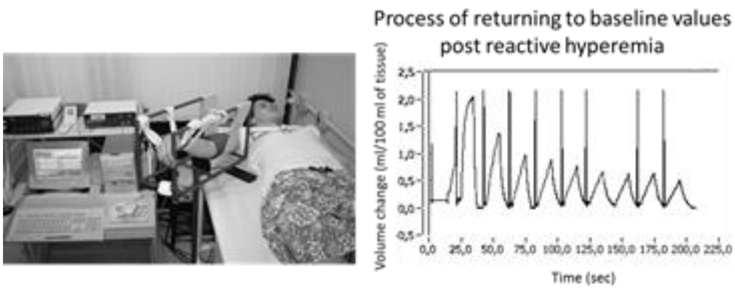
Forearm ischemia was induced by inflating the upper arm cuff to 200 mmHg for five minutes (Betik *et al.,* 2004), with the aim of perturbing vascular homeostasis and enabling the analysis of vasomotor dynamics during recovery. During the fourth minute of ischemia, the wrist cuff was inflated to 200 mmHg to prevent hand blood flow from interfering with the venous occlusion plethysmography (VOP) signal (Alomari *et al.,* 2004).

After five minutes of ischemia, arm circulation was restored, and 10 seconds later, the upper arm cuff pressure was set at 50 mmHg (Alomari *et al.,* 2004). This pressure is higher than venous pressure but remains lower than diastolic arterial pressure, resulting in a selective occluding venous return while allowing arterial inflow. As a result, forearm volume increases due to continued arterial perfusion (Hokanson, 1998). The 50-mmHg pressure was maintained for 10 seconds and quickly released, allowing equivalent period for venous emptying, and thereby completing a plethysmographic cycle. This alternation sequence of venous occlusion and release, each lasting 10 seconds, was repeated for 3 minutes, resulting in nine plethysmographic cycles (Figure 1b). The temporal variation in forearm volume provides insights into vascular system behavior as it progressively reestablishes local homeostasis.

Signal acquisition was controlled by a plethysmography system (Hokanson, Bellevue, USA). Data were digitized, acquired, monitored, and processed using an AT-MIO-16 acquisition board (National Instruments, Austin, TX, USA) interfaced with a custom program developed in LabVIEW® (National Instruments, Austin, TX, USA).

Figure 1. Venous occlusion plethysmography acquisition (a) and the nine plethysmographic cycles of a signal obtained after five minutes ischemia before the treadmill exercise (b)



(a) (b)

2.3. The VOP Model proposed by Macedo *et al.* (2020)

The venous occlusion plethysmography (VOP) protocol employs pneumatic cuffs to control blood flow in the forearm. A distal cuff positioned at the wrist was inflated to 200 mmHg (suprasystolic pressure) to isolate the hand, thereby preventing both arterial inflow and venous outflow throughout the data acquisition period. The proximal cuff placed on the upper arm was

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intermittently inflated to 50 mmHg and deflated to 0 mmHg, enabling controlled interruption of venous return. Arterial inflow was allowed whenever the cuff pressure remained below the arterial pressure. The resulting changes in forearm volume, caused by arterial inflow during venous occlusion, were detected using the mercury-in-silastic strain gauge placed around the largest circumference of the forearm (Macedo *et al.,* 2020; Salisbury *et al.,* 2018).

The VOP model assumes that the observed volume changes occur within a single vascular compartment (the forearm), incorporating the dominant arterial and venous contributions, as described in Equation 1 (Macedo *et al.,* 2020).

(1)

$$\begin{bmatrix} \dot{P}_B \\ \dot{P}_V \end{bmatrix} = \begin{bmatrix} -\frac{1}{R_a C_B} & \frac{1}{R_a C_B} \\ \frac{1}{R_a C_V} & -\frac{1}{C_V}\left(\frac{1}{R_a}+\frac{1}{R}\right) \end{bmatrix} \begin{bmatrix} P_B \\ P_V \end{bmatrix} + \begin{bmatrix} \frac{Q}{C_B} \\ 0 \end{bmatrix}$$

The parameters are: blood flow input (Q); brachial compliance (C_B); arteriolar resistance (R_a); venous compliance (C_V); resistance to venous outflow (R_{cuff}), correlated with cuff pressure around the arm; venous resistance (R_V); arterial (brachial) blood pressure (P_B); venous blood pressures (P_V); blood flow in C_B (Q_B); blood flow in C_V (Q_V); blood flow in R_a (Q_{Ra}) and blood flow in the series R_V + R_{cuff} (Q_R). For details, see Macedo *et al.*, (2020).

The brachial mean flow for each volunteer was calculated using Equations 2 (Macedo *et al.,* 2020) and 3 (Ruchti *et al.,* 1989):

$$\bar{F}(t) = F_{Plethys} * 14.84 \text{ ml/min}$$

(2)

(3)

$$Q(t) = \begin{cases} F(t), & \text{if } F(t) \geq 0 \\ 0, & \text{if } F(t) < 0 \end{cases}$$

$$F(t) = A\sin(\omega t) - \frac{A}{2} \quad ml/s$$

where $Q(t)$ is a pulsed flow source, $\omega = 2\pi\frac{HR}{60}$, HR is the heart rate in beats per minute, and A is a constant determined to mimic the volunteer mean brachial artery blood flow in order to simulate VOP data. Forearm volume changes were calculated in ml/100 ml of tissue per unit of time, unit of measurement commonly used in plethysmography. Thus, $\bar{F}$ (t) is the brachial artery flow and $F_{Plethys}$ is the forearm flow in ml/100 ml of tissue/min (Macedo *et al.,* 2020).

Based on experimental data in the literature, Macedo *et al.,* (2020) suggested the following initial values used: C_V = 0.66 ml/mmHg; R_V = 1.5 mmHg.s/ml; R_a = 16 R_V.

The following relations in Equations 4 (Guyton and Hall, 2016) and 5 were considered:

$$C_B = \frac{C_V}{24} \quad (4)$$

$$\frac{\Delta P_a}{R_a} = \frac{\Delta P_V}{R_V} \quad (5)$$

Where P_a is the arterial pressure and P_V is the venous pressure (Macedo *et al.,* 2020). R_{cuff} = 0 when plethysmography cuff pressure is zero and R_{cuff} = 20 R_V when plethysmography cuff pressure is activated. Venous outflow restriction was implemented by increasing the R_{cuff} value. The relationship between R_{cuff} and R_V was obtained from the experimental data itself. The volume change values (estimated by $\Delta P_V \times C_V$) were divided by forearm volume initial estimate (V_0) obtained for each volunteer from forearm dimensions. The result was then multiplied by 100% to use the same units (ml/100 ml of tissue per unit of time) of the experimental plethysmography signal (Equation 6, Macedo et al., 2020).

$$\Delta V = \frac{\Delta P_v * C_V}{V_0} * 100\% \quad (6)$$

For VOP data collected under baseline conditions, Macedo *et al.,* (2020) reported that the compliance and resistance parameters estimated by the model were consistent with values reported in the literature. Additionally, the pressure waveforms generated by the model remained within physiologically expected ranges (Macedo *et al.,* 2020).

However, certain methodological limitations identified in previous studies—and retained in the present pilot investigation—should be acknowledged. These include the use of linear equations, the simplification of the vascular system as a single compartment, and the fixation of arterial compliance, a parameter that proved more difficult to estimate reliably.

2.4. Fitting the experimental data

Plethysmographic signals were processed offline using a program developed in MATLAB® (version 5.3). Each plethysmographic cycle was individually identified and segmented. This procedure enabled: (A) definition of the time intervals corresponding to R_{cuff} = 20 R_V (arterial inflow phase, with venous occlusion) or R_{cuff} = 0 (venous outflow phase, when the arm cuff is deactivated); (B) determining mean arterial flow. Whenever necessary, the onset of volume change in each plethysmographic cycle was adjusted to zero by baseline correction, as described by Macedo *et al.,* (2020).

The inflow function *Q(t)* was calculated considering the volunteer's heart rate under *Placebo*, *Ibuprofen* or *Post-exercise* conditions. Blood flow was estimated using VOP signal at the inflow phase by considering the rate of volume change over time (Hokanson, 1998; Macedo *et al.,* 2020). Venous compliance (C_V), venous resistance (R_V), and arteriolar resistance (R_a) were estimated using the *fmincon* function in MATLAB®. Arterial compliance was fixed. The iterative parameter estimation procedure followed the methodology described by Macedo *et al.,* (2020).

Given the small sample size, Friedman's one-way analysis of variance for paired nonparametric data was applied to compare mechanical parameters across the three experimental conditions (Placebo, Ibuprofen, and Post-exercise), followed by Dunn's post hoc test when appropriate. Statistical significance was set at 5%. In addition, the physiological plausibility of the estimated parameters was evaluated.

3. RESULTS

The database comprised ten young male participants (mean age: 30.3 ± 6.0 years, height: 1.8 ± 0.07 m, weight: 74.7 ± 8.1 kg, and body mass index: 24.1 ± 2.5 kg/m^2). The data were originally collected for flow analysis, which relies only on the initial portion of the plethysmographic signal of each cycle. However, for the purposes of vascular mechanics modeling, complete waveform acquisition was required. Therefore, volunteers whose recordings exhibited saturation in more than one plethysmographic cycle were excluded from the analysis.

The first plethysmographic cycle of all signals was removed because it was saturated in nine out of ten volunteers in the exercise group, three volunteers in the ibuprofen group, and three in the placebo group, leading to fitting errors (Figure 2). Volunteers whose signals presented saturation in additional cycles beyond the first were excluded, resulting in a sample of five subjects. For each subject, signals collected under placebo, ibuprofen and post-exercise conditions were analyzed, with the first plethysmographic cycle consistently excluded from all conditions.

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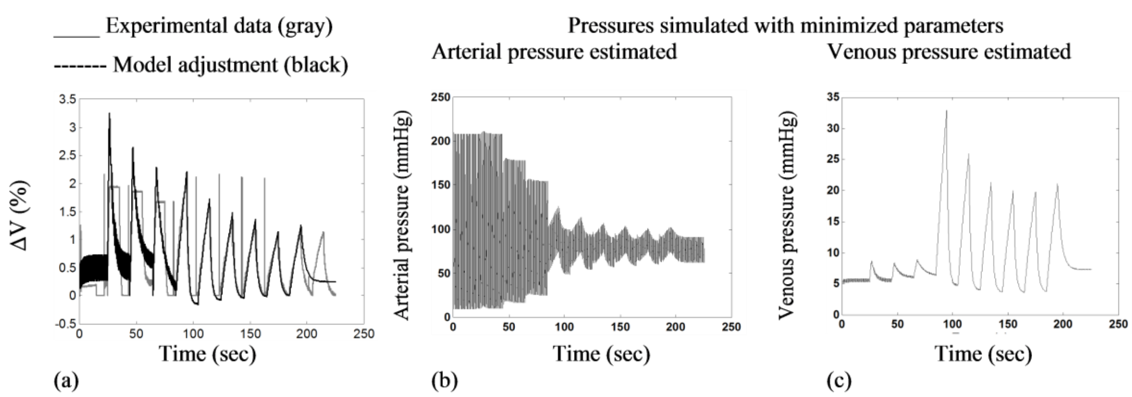
Figure 2. Signal of a subject excluded by having the first three cycles saturated and the model fit for this signal (a). Arterial (b) and venous (c) pressures estimated by the model



3.1. Behavior of the parameters over time

Figure 3 presents the model fitting for post-ischemia recordings from the only volunteer whose signal showed no saturation under any experimental condition: placebo (Figure 3a), ibuprofen (Figure 3b) and post-exercise (Figure 3c). The second and third lines display the arterial and venous pressure waveforms estimated by the model, respectively. A greater variation in forearm volume is observed in the initial plethysmographic cycles, reflecting higher blood flow immediately after ischemia release and a progressive return toward baseline conditions. Notably, even during reactive hyperemia, the estimated blood pressure values remained within physiologically plausible ranges.

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Figure 3. Parametric VOP model of vascular mechanics adjusted to the experimental data (1st line). Arterial (2nd line) and venous pressure (3rd line). Behavior simulation in the system for placebo (a) ibuprofen (b) and post-exercise (c) conditions over time post-ischemia

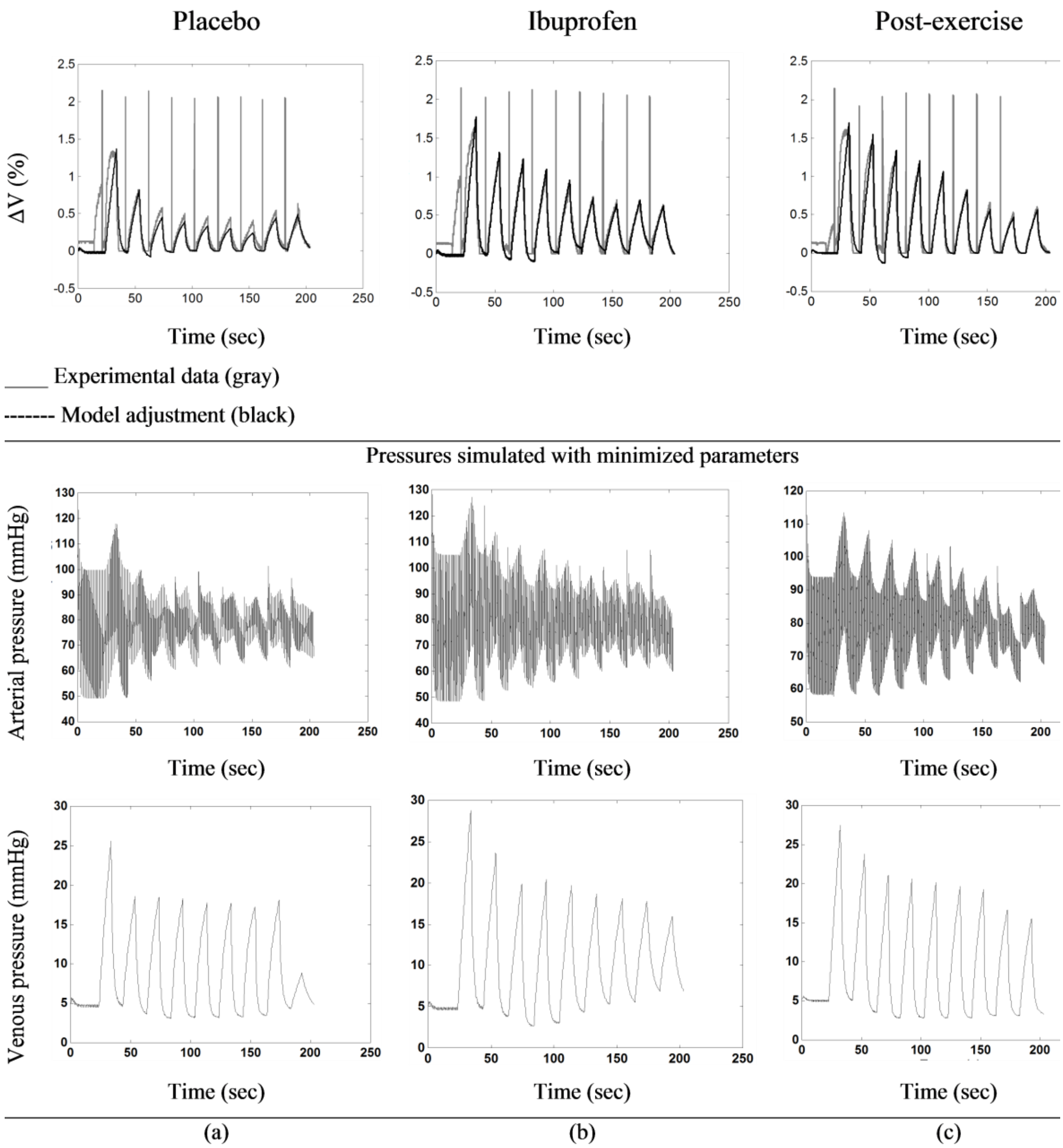
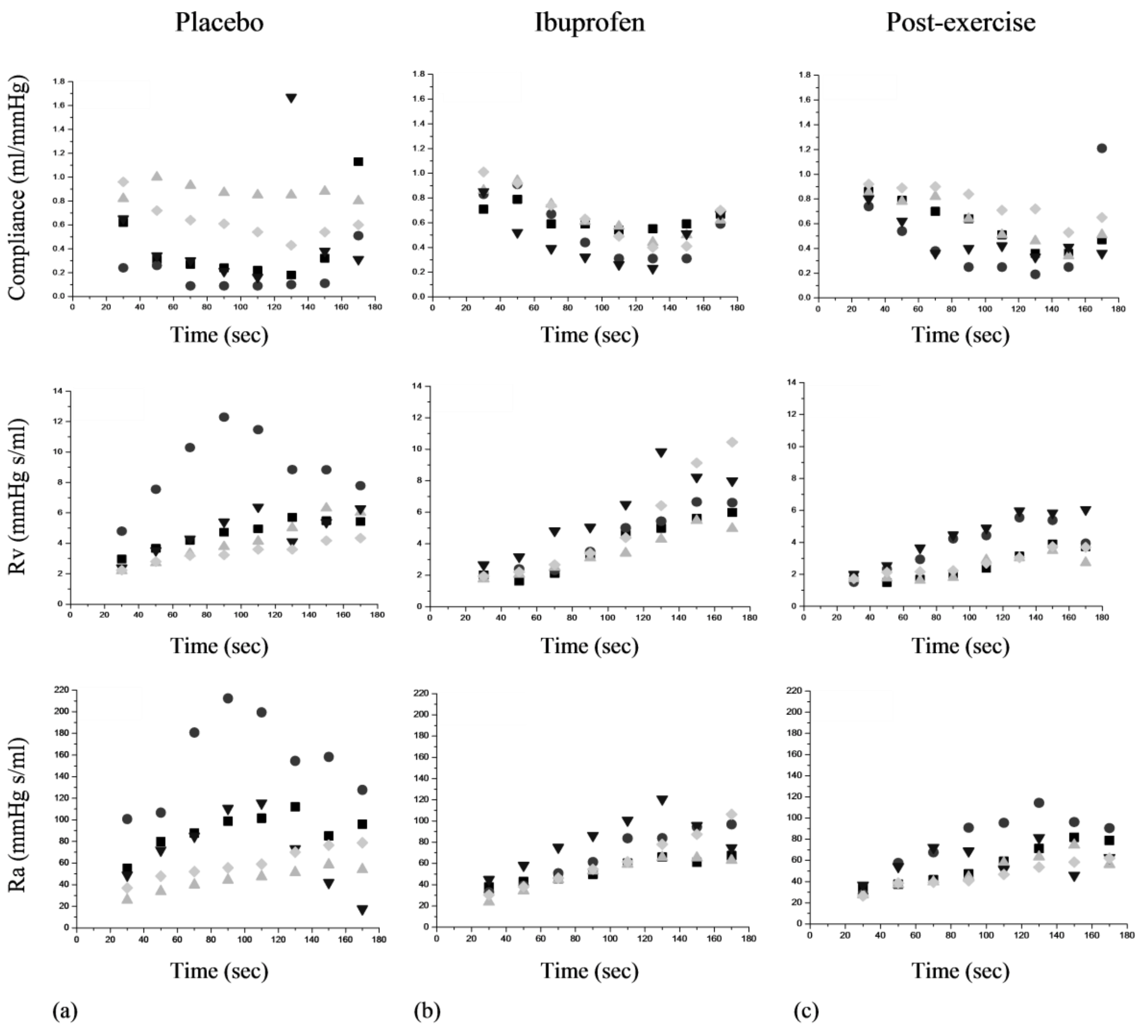


Figure 4. Values of venous compliance (1st line), venous resistance (2nd line) and arterial resistance (3rd line) calculated by the model for each of the eight plethysmographic cycles of each volunteer in each of the experimental conditions: placebo (a) ibuprofen (b) and post-exercise (c). Each symbol represents a volunteer



3.2 - Parameters behavior between experimental groups

For group comparison, a linear regression was fitted at the eight estimated time points of each parameter (venous compliance, arteriolar resistance, and venous resistance) for each volunteer under each condition (placebo, ibuprofen, and post-exercise). The slope (angular coefficient) and intercept (linear coefficient) were extracted to characterize the magnitude of the reactive hyperemia response and the rate of temporal change, respectively. These parameters were considered as descriptors of vascular behavior (Figure 5). Table 1 summarized the main findings.

Figure 5. C_v, R_v and R_a tendency for a volunteer in the Placebo condition. The linear coefficient of the line allows inferring about the parameter magnitude at the time of release of the cuff that obstructed the forearm circulation (time=zero) and the angular coefficient estimates the rate of variation of this parameter over time

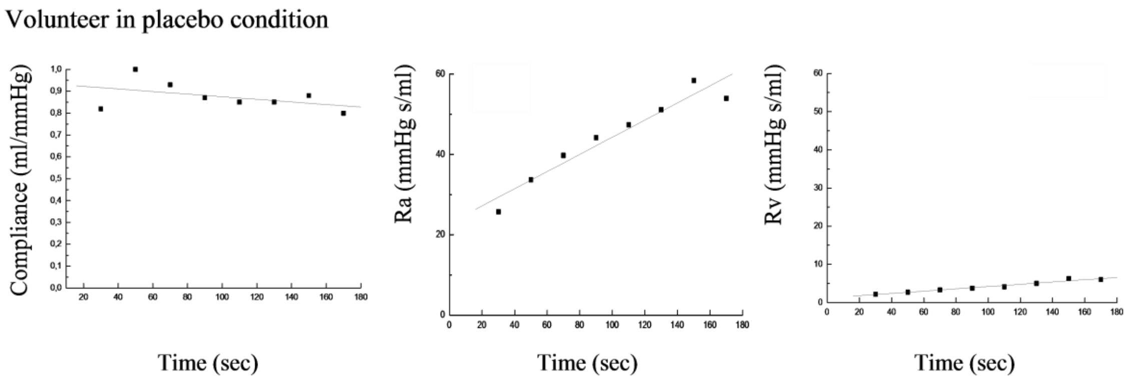


Table 1. Mean values (standard deviation) of the linear coefficient (intercept) and the angular coefficient of the line for each experimental group

	Parameters	Placebo	Ibuprofen	Post-exercise	*p-value*
		Experimental Group			
Linear Coefficient	*Cv*	0.51 (0.38)*	0.83 (0.18)	0.81 (0.26) *	0.009
	Rv	3.24 (2.55)*	0.31 (0.96)*	1.14 (0.29)	0.009
	Ra	69.55 (46.01)*	26.08 (15.11)*	29.32 (13.07)	0.009
Angular Coefficient	*Cv*	0.0002 (0.0017)	- 0.0024 (0.0013)	- 0.0023 (0.0018)	0.12
	Rv	0.019 (0.07)	0.042 (0.014)	0.020 (0.007)	0.12
	Ra	0.14 (0.22)	0.37 (0.13)	0.29 (0.14)	0.18

*For each parameter, the groups that showed a significant difference between them.

4. DISCUSSION

Reactive hyperemia is characterized by a marked increase in blood flow following the restoration of circulation after a period of temporary occlusion (Rosemberry; Nelson, 2020). Flow occlusion induces arteriolar dilation and reduces peripheral vascular resistance. Upon release of the occlusion, the resulting surge in blood flow exposes the endothelium to elevated shear stress, promoting endothelial hyperpolarization and the release of vasodilatory substances. This cascade ultimately leads to flow-mediated arterial dilation (Moyna and Thompson, 2004). In the present study, lower resistance values were observed after prolonged ischemia, as anticipated.

Regarding temporal behavior, both arteriolar and venous resistance increased over time. The rise in arteriolar resistance was expected within the context of reactive hyperemia. In contrast,

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local venous resistance behavior is rarely described in the literature. Nevertheless, the present findings are consistent with previous observations of vascular mechanics under baseline conditions—i.e., in the absence of induced reactive hyperemia (Macedo *et al.,* 2020). In that study, venous resistance was found to be lower post-exercise compared to the pre-exercise condition.

4.1. Behavior differences among the experimental groups

Venous compliance exhibited a downward trend over time under the ibuprofen and post-exercise conditions, although the decline was modest. This tendency is inferred from the mean angular coefficients. Assuming that the post-exercise response of this parameter follows the findings of Macedo *et al.,* (2020)—who reported reduced compliance post-exercise compared with pre-exercise under baseline conditions—the expected behavior during reactive hyperemia would be an initial decrease in compliance, followed by a gradual increase until a new equilibrium is reached. However, studies specifically addressing venous compliance during reactive hyperemia remain scarce, highlighting an important area for future investigation.

Under the placebo condition, compliance showed no clear temporal trend. The angular coefficient for the placebo group was approximately ten times lower than those observed in the other two experimental conditions. Based on this preliminary exploratory analysis, some hypotheses may be proposed.

Because the first plethysmographic cycle was excluded for all participants due to signal saturation, the analysis began 30 seconds after the release of ischemia. As the placebo group was not exposed to vasomotor stimuli induced by medication or exercise, it is reasonable to assume that vascular parameters returned to equilibrium more rapidly. Therefore, the minimal temporal variation in compliance in this group may reflect early stabilization, occurring approximately 30 seconds after restoration of forearm blood flow.

Several findings support this interpretation. The linear coefficient estimated for the placebo group (0.51 ml/mmHg) is close to the physiologically based estimate reported by Macedo *et al.,* (2020). Moreover, this value is closer to the baseline compliance values described by Macedo *et al.,* (2020) when the model was adjusted for non–reactive hyperemia conditions (placebo, ibuprofen, and post-exercise), which ranged from 0.27 to 0.34 ml/mmHg.

Considering that compliance in the placebo group is already close to baseline conditions due to the exclusion of the first plethysmographic cycle (likely the most important), it is reasonable that the initial linear coefficients for the Ibuprofen and Exercise groups were higher. The slower post-ischemic decline in compliance observed in these groups, as they returned toward basal levels, may reflect vascular alterations induced by pharmacological intervention and exercise.

The database analyzed was originally used to study flow behavior, for which signal saturation does not interfere with flow calculation (Hokanson, 1998). However, because these

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experimental data were provided for preliminary analyses of the dynamic behavior of vascular mechanics, future studies should adjust the acquisition protocol to preserve all plethysmographic cycles.

In this promising pilot study, ibuprofen and exercise were used to modify vascular mechanics in opposite directions. Nevertheless, a vasodilatory effect was observed in both cases. The vascular mechanics consistent with vasodilation was expected in exercise. Ibuprofen, a nonsteroidal anti-inflammatory drug that inhibits prostaglandin synthesis (Rainsford, 2009; Naylor *et al.,* 1999), was anticipated to induce vasoconstriction. However, vasodilatory effects following ibuprofen administration have been reported. Naylor *et al.,* (1999) and Macedo *et al.,* (2008; 2013) observed increased flow after ibuprofen intake, while other studies have reported no significant vascular changes. For instance, Richey *et al.,* (2023) did not detect alterations after ibuprofen administration compared with contralateral control during bilateral skeletal muscle exposure to thermal hyperemia.

Another expected effect outcome of ibuprofen and exercise was a slower return of compliance and resistance to baseline conditions compared with the placebo group. A delayed stabilization would theoretically be reflected by smaller angular coefficients. However, as previously mentioned, the exclusion of the first plethysmographic cycle limited this analysis. Furthermore, the small sample size restricts the ability to detect statistically robust differences. Despite these limitations, the trends observed and differences, even within this reduced sample, support the potential of the proposed methodological approach.

This pilot study aimed to develop a non-invasive technique to analyze vascular reactivity patterns by observing vascular mechanical parameters during the restoration of equilibrium following a stimulus-induced disturbance. The results obtained show the presence of parameters indicative of both physiological regulation and alterations in forearm vascular mechanics during flow control processes.

Prolonged ischemia was used as a perturbation of basal vascular reactivity. The resulting reactive hyperemia enables observation of the flow regulation process as the vascular system attempted to restore hemeoastasis. This stimulus proved effective, eliciting a marked increase in forearm volume and allowing the characterization of differences in vascular mechanics during flow regulation using VOP modeling.

Non-invasive techniques in vascular reactivity studies aim to enable early diagnosis and treatment, thereby contributing to the prevention and treatment of cardiovascular diseases (Trimarchi *et al.,* 2024; Chrysant, 2019). However, biological variability, as well as differences in instruments and protocols, contributes to inconsistencies across studies. Consequently, establishing normality parameters based solely on absolute or relative values obtained at one or two time points remains challenging. Moreover, few studies have investigated normal vascular mechanical patterns under dynamic conditions. In this context, the analytical framework proposed here represents a meaningful contribution, as it emphasizes the evaluation of the regulatory process rather than a static measurement of vascular response.

The small sample size and the exclusion of the first plethysmographic cycle are the major limitations of this pilot study. Because the dataset was originally collected for other purposes, signal saturation did not compromise the initial analyses. Including the first plethysmographic cycle would allow capturing the beginning of the reactive hyperemia process, improving comparisons between groups and physiological analyses. Despite these constraints, the preliminary findings highlight a promising methodological pathway for investigating vascular dynamics in response to perturbations and for identifying drug- and exercise induces changes.

Future methodological refinements may help overcome these limitations. Macedo *et al.,* (2013), seeking greater temporal resolution of flow data for mathematical modeling, increased the frequency of plethysmographic signal acquisition. This adjustment resulted in smaller-amplitude cycles, preventing saturation of the first plethysmographic cycle—an uncommon approach in plethysmography studies, but potentially well suited to the objectives of the present work. Further advancements in vascular dynamic analysis may include the application of multivariable nonlinear models, more comprehensive cardiovascular physiology models, cross-validation with Doppler ultrasonography, and sensitivity analyses of estimated parameters. Additionally, studies examining time-dependent mechanical vascular responses in populations with cardiovascular risk factors may reveal early functional alterations that precede structural vascular changes.

5. CONCLUSION

This study proposes a novel, non-invasive framework for assessing vascular mechanics during reactive hyperemia and the subsequent restoration of baseline conditions. By extending the VOP model developed by Macedo *et al.,* (2020), originally designed for basal signals, to plethysmographic recordings obtained after prolonged ischemia, the present approach enables dynamic estimation of arterial and venous resistance, venous compliance, and arterial and venous pressures throughout the regulatory process.

The findings demonstrate clear time-dependent vascular responses: arterial and venous resistances decreased and venous compliance increased immediately following reactive hyperemia, with all parameters progressively returning toward basal levels. Distinct physiological patterns were observed across experimental conditions. Ibuprofen administration was associated with a significant reduction in vascular resistance, whereas exercise promoted an increase in venous compliance, reinforcing the sensitivity of the proposed method to detect intervention-induced changes in vascular mechanics.

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Although these results are preliminary—limited to five of the ten volunteers due to signal saturation inherent to conventional plethysmography protocols—the observed trends highlight the potential of this modeling strategy to characterize dynamic vascular regulation. The exclusion of the first plethysmographic cycle represents a relevant limitation, as it likely contains critical information regarding the onset of reactive hyperemia. Therefore, methodological refinements aimed at capturing the complete waveform of all plethysmographic cycles are essential before extending this approach to larger samples.

Despite these limitations, the present work establishes a promising methodological pathway for analyzing vascular reactivity as a dynamic regulatory process rather than as a static outcome measure. This perspective may contribute to improving the physiological understanding of vascular adaptation and to advancing non-invasive tools for early detection of vascular dysfunction.

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STATEMENTS AND DECLARATIONS

Compliance with Ethical Standards: the study was performed in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and its subsequent amendments.

Conflict of interest: The authors declare that there are no financial or non-financial conflicts of interest to disclose.

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