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ORIGINAL PAPER

# Vascular reactivity in healthy subjects: simultaneous characterization of arterial pressure and diameter time profiles

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**Abstract** Endothelial cells are involved in the local regulation of blood flow and vessel diameter, playing multiple roles, both in health and disease. Changes in endothelial functions are defined as endothelial dysfunction (ED). In vivo non-invasive evaluation of ED and vascular reactivity can be performed by means of different approaches, where Flow Mediated Dilation (FMD) and Peripheral Arterial Tonometry (PAT) measurements (in terms of a post occlusive reactive hyperemia maneuver, PORH) are considered the most relevant. The main objective of this study was to perform the evaluation of FMD and PAT simultaneously, in healthy men and women, in order to characterize the pressure and diameter time profiles during PORH. Different exponential functions were fitted to systolic pressure and diameter responses, suggesting a differentiated vascular behavior between genders.

**Keywords** Flow mediated dilation · Peripheral arterial tonometry · Endothelial response

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## 1 Introduction

Endothelial cells (EC) play multiple roles, both in health and disease conditions, including: formation of a semi-permeable barrier, release of components that interact with smooth muscle cells, inhibition of platelet aggregation and leukocyte adhesion, among others [1]. Essentially, EC are involved in the maintenance of vascular tone through the local regulation of blood flow and vessel diameter. The production of endogenous substances, such as prostacyclin, the endothelium-derived hyperpolarizing factor, nitric oxide (NO) and hydrogen peroxide ($H_2O_2$), provide tonic vasodilators stimuli under in vivo physiological conditions. Particularly in healthy individuals, the endothelium exerts a protective effect on the vasculature through the production of nitric oxide (NO). This phenomenon can be attributed to the influence of agonists (acetylcholine, bradykinin, among others) that act on specific endothelial receptors in addition to the presence of mechanical forces (i.e. shear stress) exerted by the flowing blood [2]. Furthermore, ECs not only produce the potent vasodilator NO, but also synthesize endothelin-1 (ET-1), the most potent vasoconstrictor identified to date [3]. Nitric oxide and ET-1 physiologically interact in the regulation of vascular tone, locally regulated by shear stress. Alterations in NO synthase (or its augmented catabolism) affect the endothelial vasodilator function and contribute to excessive vasoconstriction, which is observed under different pathological conditions [4]. Changes of the endothelial phenotype to a pro-inflammatory and pro-thrombotic state, an augmented endothelial permeability and an imbalance in the NO vs. EC-1 relationship are defined as endothelial dysfunction (ED) [5]. It is well known that ED constitutes an important pathophysiological factor in atherosclerosis and precedes the morphological alterations in the arterial wall, thus playing a critical role in the context of atherogenesis [6]. As a result, the

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participation of EC and chronic inflammation [7] are directly associated with cardiovascular damage in several physiological conditions such as arterial hypertension, heart and renal failure, diabetes mellitus, intravascular coagulation, preeclampsia, inflammatory disease, sleep apnea and the regulation of cirrhosis and portal hypertension [8].

Evaluation of endothelial function (EF) has been proven to be clinically relevant in global cardiovascular risk (GCR) assessment. Typical risk factors such as arterial pressure values and blood lipids are usually selected for risk estimation, but since they are surrogates to suggest arterial damage they cannot be used to quantify it [9]. Nevertheless, due to the fact that EF determination is not yet strongly recommended by cardiovascular disease (CVD) management guidelines [10], different procedures carried out in the last few years (both invasive and non-invasive) can be implemented as part of policies of prevention and early detection of cardiovascular events. In this regard, coronary endothelial function assessment may be considered the 'gold standard' of endothelial function testing, but the utility of this technique is limited in clinical practice as a consequence of its invasive nature [11, 12]. However, since ED constitutes a systemic process that simultaneously affects different vascular beds, it has been demonstrated that EF measures performed at the peripheral vasculature are related to endothelial coronary function, making them an acceptable predictor of CVD [13–16]. Therefore, non-invasive techniques focused on the analysis of the arterial wall structure (including EF) constitute a significant complement to traditional clinical studies, particularly during the early stages of arterial pathologies development [7]. In vivo non-invasive evaluation of EF and VR can be performed by means of different approaches [17], where Flow Mediated Dilation (FMD) and Peripheral Arterial Tonometry (PAT) measurements (both evaluated in terms of a post-occlusive reactive hyperemia maneuver, PORH) are considered the most relevant [18]. Currently, FMD is the most widely used technique, but the need for a highly skilled technician for the acquisition and post-processing of the obtained echography images still constitutes the main obstacle in clinical practice [19]. In contrast, PAT was developed as a more reproducible and simple method. However, and regardless of the technique, VR indicators are generally assessed from the ratio between baseline values (arterial pressure or lumen diameter characteristic variations) and those observed at maximal vasodilation, after cuff deflation [18]. In this sense, the application of concepts derived from the system identification theory to a continuous evaluation of those physiological parameters could provide complementary information to VR standard assessments.

To our knowledge, simultaneous characterization of arterial pressure and lumen diameter time profiles has been barely reported [20, 21]. Accordingly, FMD and PAT measurements were performed simultaneously in male and female subjects, during this study. Vascular reactivity was then modeled during the first sixty seconds of PORH, considering time evolution of arterial pressure and diameter time series as 'a system response' to a flow stimulus.

## 2 Material and methods

### 2.1 In vivo measurements: FMD and PAT

Non-invasive measurements of EF are usually performed on the forearm, where left brachial or cubital arteries flow is obstructed (five minutes of ischemia) with the help of a pressure cuff. Reactive hyperemia is induced when the ischemia is finished after a few minutes, as a result of the pressure cuff release. The theoretical basis, general protocols, and methodological aspects regarding VR tests are described in guidelines for the ultrasound assessment of endothelial-dependent FMD, applied to the brachial artery [19]. Under normal conditions, the resulting increase of flow causes an endothelial-dependent vasodilation (NO release), which can be detected through the changes in brachial artery flow and diameter. In this study, the arterial conduit was visualized longitudinally above the antecubital crease using a high-resolution B-Mode ultrasound device (Sonosite, MicroMaxx Inc., USA) (Fig. 1). Video sequences were recorded at rest, during forearm occlusion and after cuff deflation. Subsequently, recordings were analyzed off-line using an automated step-by-step algorithm, which was applied to each digitalized image in order to obtain the brachial lumen diameter (BD) values corresponding to each stage of the analysis [22].

Simultaneously, PAT measurements were performed over the radial artery (identified through the palpatory method) by means of a device especially designed by our team. The probe consisted of a high frequency response piezoresistive sensor (Konigsberg Inc., Pasadena, USA), which was placed over the measuring point and attached to the wrist (Fig. 1). This ad-hoc probe partially compresses the radial artery allowing the acquisition of the arterial pressure waves. Previous to the beginning of the occlusive maneuver, the device was adjusted in order to detect the most stable and pronounced pressure pulse values. By using this method, there was no need for the operator to intervene in the measuring procedure. During the experiment, BP signals were recorded with an acquisition system (developed in our laboratory as well) [23], at a sampling rate of 500 Hz and 16-bit resolution. The tonometric signals were then calibrated, assuming mean minus diastolic blood pressure constant throughout the large artery tree. Algorithms for data processing were developed using the MatLab® computing platform (Mathworks Inc., Natick, USA).

Prior to the time series analysis, existing trends (i.e. respiration-induced fluctuations, electrical artifacts, etc.) were eliminated by means of digital filtering. For both methods, 20

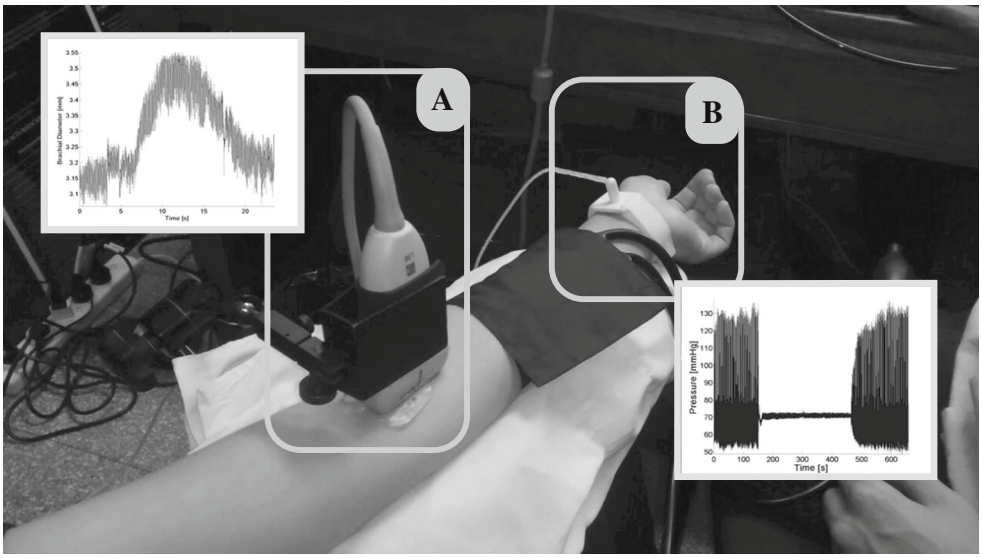


**Fig. 1** Simultaneous Flow Mediated Dilation (FMD, **a**) and Peripheral Arterial Tonometry (PAT, **b**) measurements. The occlussion period is not completely shown

stable cycles were recorded in baseline state, followed by a 5 min. Occlusion state (cuff insufflation) and ending with a 3-min PORH (cuff release).

### 2.2 Evaluated subjects

Ten adults (five males and five females), free of known CVD and aged between 20 and 35 years old, were included in this study. All subjects were asymptomatic, nondiabetic, nonsmoking and normotensive. None had congestive heart failure or any other serious disease. Vascular reactivity measurements were in accordance with the usual preparation of this kind of technique. Individuals abstained from ingesting coffee or caffeinated beverages or performing exercise at least 3 h prior to the evaluation and were studied in a single visit. Initially, a clinical interview was carried out in order to obtain information related to lifestyle habits and personal history, including a verbal consent. Values of height and weight were taken, and the body mass index (BMI) was calculated. Next, after 10 min of rest in supine position, BP systolic and diastolic measurements (SBP and DBP, respectively) were taken using a sphygmomanometer (Omron HEM-433INT Oscillometric System, Omron Healthcare Inc., Illinois, USA) with each volunteer's arm aligned with their thorax, in accordance to the Guidelines of European Society of Hypertension [24]. Mean blood pressure (MBP) was derived from the standard equation usually employed at the peripheral level: MBP = DBP + 1/3(SBP − DBP). Subjects with BP values higher than 140/90 mmHg, diabetes mellitus and/or renal failure, coronary artery disease and traditional cardiovascular risk factors were excluded from the experiment. Heart rate signal (HR) was computed from a 1 lead digitized electrocardiogram (ECG). The study was approved by an independent institutional review board.

### 2.3 Characterization of FMD and PAT responses

Characterization of SBP and systolic brachial diameter (SBD) temporal profiles during PORH was implemented by fitting the beat to beat maximal values of BP and BD evolution (identified through the ECG measurements) to exponential functions. This approach is based on the methodology proposed by the system identification theory (in time domain), where a response (in this case a pressure or diameter time profile) to an abrupt change of the system input ('a step of flow') is analyzed. Combinations of exponential curves are frequently observed in first or second order systems responses. The presence of artifacts was eliminated by signal processing (continuous wavelet transform). About this, the morphology acquired by BD profiles after cuff deflation is well described by Thijsen et al. [19]. Consequently, SBD time evolution, observed during this period (both in males and in females), was fitted to the following exponential expression:

$$SBD(t) = \alpha_D\left(1-e^{-\beta_D t}\right) \tag{1}$$

where $\alpha_D$ is the constitutive coefficient and $\beta_D$ is the exponential constant. Additionally, FMD was quantified as percentage of change in diastolic brachial diameter (DBD), considering its baseline levels ($DBD_{BAS}$) and those measured one minute after cuff deflation ($DBD_{CD}$):

$$FMD\% = \frac{DBD_{CD}-DBD_{BAS}}{DBD_{BAS}}\,100\% \tag{2}$$

Same methodology was used to characterize BP variations, acquired simultaneously at the radial artery. However, a first analysis was previously performed in order to evaluate SBP evolution in terms of a gender differentiation. The normalized area (under the curve) was calculated for each case, considering the time lapse between the beginning of

PORH and the first stable systolic pressure values. Subsequently, SBP time evolution in males ($SBP_M$) after cuff release was described by Eq. (1) while a different type of exponential curve was used to describe SBP in females ($SBP_F$):

$$SBP_M(t) = \alpha_{MP}\left(1-e^{-\beta_{MP}t}\right) \quad (3)$$

$$SBP_F(t) = \alpha_{FP}\left(e^{\beta_{FP}t}\right)-1 \quad (4)$$

where $\alpha_{M,F}$ are the constitutive coefficients of both expressions and $\beta_{M,F}$ are the exponential constants assessed during the first 60s of PORH. Finally, both BD and BP types of curves were referenced to their initial values (immediately observed after the cuff release) and fitted to the exponential functions by applying a non-linear regression analysis.

### 2.4 Statistical analysis

Data were expressed as mean ± standard deviation. After the application of non-linear regression analysis, the coefficient of determination ($\boldsymbol{R^2}$) was assessed in order to obtain information about how well pressure and diameter beat to beat alterations fitted the exponential curves. Changes in demographic and physiological parameters were evaluated using a two tailed paired Student t-test, where $P < 0.05$ was considered as statistically significant.

## 3 Results

Recordings were successfully obtained from all subjects. The mean duration of the studies was 1 h approximately. Baseline demographic parameters, including mean values of SBP, DBP are summarized in Table 1. The mean age of the 10 evaluated subjects was 26.6 ± 8.4 years, they were all normotensive and had normal heart rate.

**Table 1** Obtained demographic data. BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, Hr: heart rate. Values are expressed as mean ± standard deviation

| Baseline Demographic Characteristics | | | |
|---|---|---|---|
| 10 Subjects (5/5) | Gender | Males | Females |
| | Height [cm] | 173.60 ± 6.66* | 162.00 ± 3.74 |
| | Weight [kg] | 67.80 ± 7.89 | 65.50 ± 5.20 |
| | Age [years] | 24.40 ± 5.64 | 28.00 ± 12.19 |
| | BMI [$cm^2$/kg] | 22.44 ± 1.57 | 24.96 ± 1.84 |
| | SBP [mmHg] | 123.00 ± 10.82 | 120.50 ± 11.47 |
| | DBP [mmHg] | 67.00 ± 8.43 | 72.50 ± 11.82 |
| | HR [bpm] | 72.17 ± 16.55 | 71.17 ± 12.48 |

*p < 0.05 was considered as statistically significant

Changes in BD as a consequence of the step of flow (system input) are described in Fig. 2. Regarding FMD response, the obtained mean values tended to be higher in females in comparison to males (NS). However, one subject of each group was non-responsive to the maneuver.

Figure 3 shows SBD behavior during the first 60s of PORH, for a typical case (upper panels). Evolution of SBP during the same period is also depicted (lower panels). Nevertheless, differentiated concavities were observed (i.e. concave up and concave up) in men and women pressure profiles, a different situation than diameter profiles morphology (only concave down). As a result, both BP and BD responses were modeled using the proposed exponential functions (dashed lines).

Table 2 shows results obtained from SBD evaluation. During the first 60s of PORH, exponential curves were fitted with a $\boldsymbol{R^2}$ of 70.22 ± 8.05 % for males and 71.7 ± 15.9 % for females (Eq. 1). Non-significant differences were observed in $\boldsymbol{\alpha_D}$ and $\boldsymbol{\beta_D}$ between men and women. However, corresponding values $\boldsymbol{\beta_D}$ in women tended to be lower than in men.

In Table 3, coefficients obtained from the characterization of SBP (Eqs. 3 and 4) are detailed. Normalized area assessments showed significant higher values in men than in women. Regarding the exponential curves, a goodness of fit around 75 % was obtained for both genders.

## 4 Discussion

Endothelial dysfunction (ED) is a pathologic condition that impairs vascular homeostasis. This systemic disorder leads to the development of cardiovascular diseases and its association with several clinical entities is well established. Early detection of this abnormality is truly important to establish appropriate therapeutic measures to avoid, or at least delay, the development of certain pathologies.

In the present work, VR was continuously evaluated by means of FMD and PAT measurements during PORH. As a result, different types of exponential functions were proposed as fitting curves for men and women, during the first 60s after cuff release. Characterization was proposed in terms of a *response to a step of flow*, which is a commonly used technique in systems identification theory. As expected, SBD time profiles were fitted to a unique exponential function. However, the increase of SBP was observed to be significantly different in men and women, which was verified by the calculation of normalized area under the systolic pressure curves. Typically, mean changes in arterial vasodilation (%FMD) were around 8.5 %, with respect to its baseline state. Female values were higher than in males, which is in accordance with previous studies [8]. However, non-significant differences were obtained, possibly due to the reduced number of studied subjects. Moreover, two

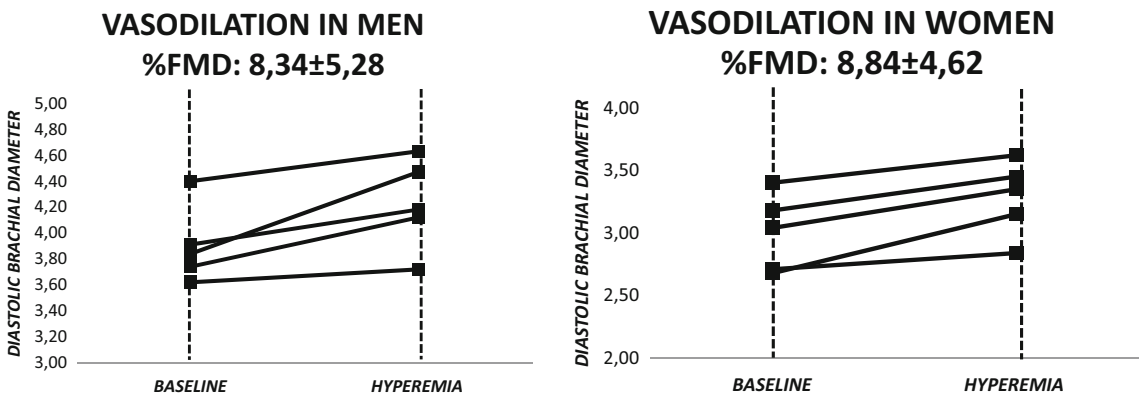


**Fig. 2** Changes in diastolic diameter as a consequense of post oclussive reactive hyperemia (PORH). Flow Mediated Dilation (FMD) values tended to be higher in women than in men

subjects (20 % of the total amount) were non-responsive to the maneuver. This could be attributed to a particular baseline state of the brachial artery being studied, which is close to the upper limit of its dilation and therefore prevented from further elastic deformation [19]. In such cases, the lack of dilation should not be interpreted as endothelial or

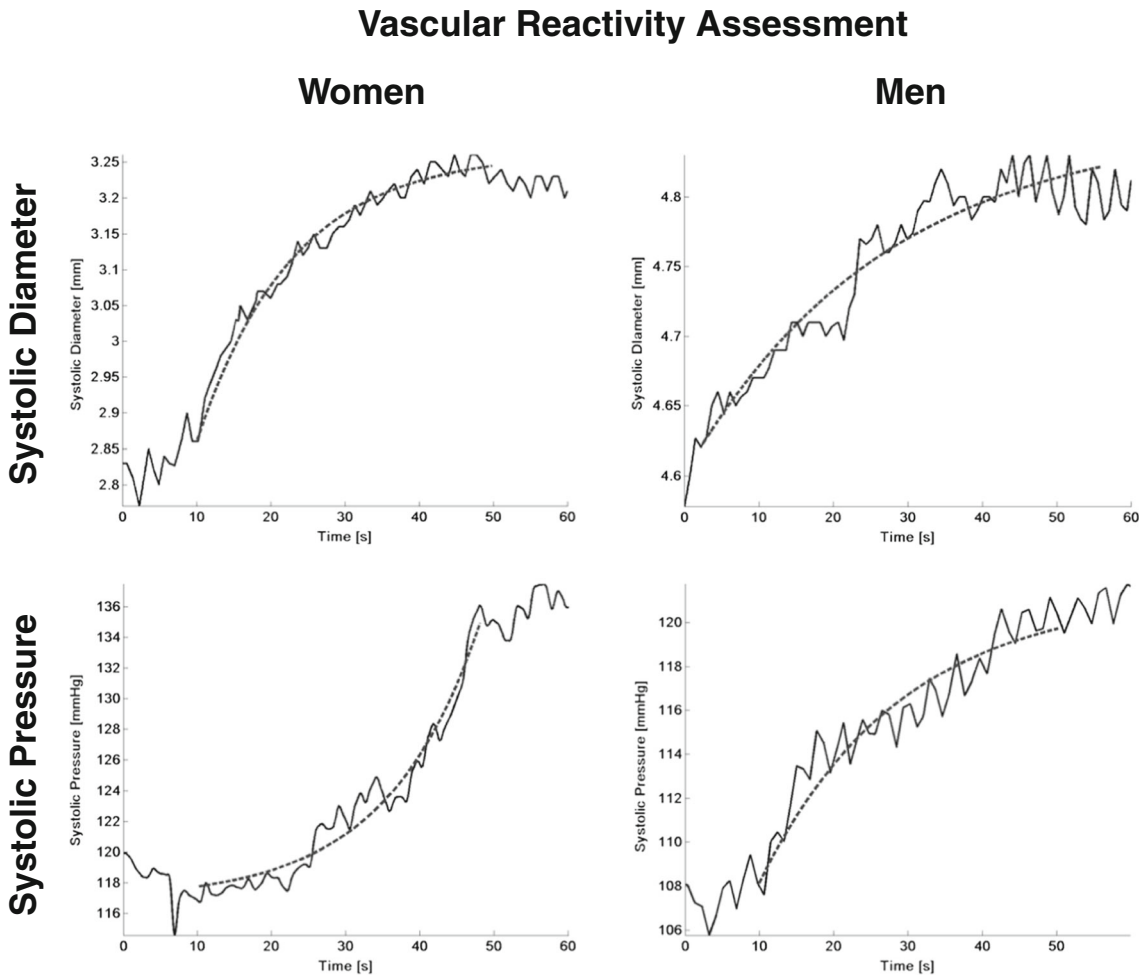


**Fig. 3** Upper Panel: Systolic Brachial Diameter (SBD) evolution after post occlussive reactive hymeremia (PORH) maneuver (first 60s are shown), for a typical case (*solid line*). Female and male responses are visualized in left and right panels, respectively. SBD time profiles were fitted to concave down exponential functions (*dashed lines*). Lower Panel: First 60s of systolic blood pressure (SBP) evolution as a consequence of PORH, for a typical case (*solid line*). Female and male responses are visualized in left and right panels, respectively. SBP time profiles were fitted to exponential fuctions of different concavity (*dashed lines*)

**Table 2** Diameter profile characterization. ***A*** and ***B*** are the corresponding coefficients of the fitted exponential curves. FMD is the flow mediated dilation. $r^2$ is the determination coefficient

| Flow Mediated Dilation Parameters | | | |
|---|---|---|---|
| | $\alpha_D$ [mm] | $\beta_D$ [$10^{-3}$ $s^{-1}$] | $R^2$ (%) |
| Men | 0.19 ± 0.08 | 58.14 ± 39.82 | 70.22 ± 8.05 |
| Women | 0.32 ± 0.18 | 49.06 ± 32.67 | 71.66 ± 15.94 |

VR dysfunction. As a result, a higher number of subjects need to be considered in future protocols.

Although FMD is a well-known technique, several limitations can be addressed. Lack of unified criteria related to the specific site of the measurements, poor sensitivity for detecting early alterations in endothelial function, time-lapse of each stage of evaluation and occlusion pressure levels can be mentioned, among others [25, 26]. Additionally, the technique is difficult to implement and ultrasound recordings need to be provided by an experienced operator [19]. Furthermore, a stereotactic arm support assembly is essential to ensure image quality and the insonation angle should be carefully verified [27].

Regarding PAT measurements, relatively novel techniques analyze the changes in volume pulse waveforms, acquired at the finger's microvasculature zone. In this case, accessibility, simplicity, low inter-and intra-operator variability and good agreement with invasive measures of microvascular function can be considered as their main advantage [28]. However, acquired signals may be affected by agents that are not related to endothelial factors and, due to the fact that measures are in the microvasculature, this approach could be useless in patients with peripheral vascular diseases such as Thromboangiitis Obliterans, Raynaud disease and Acrocyanosis [29]. For this reason, pressure measurements were preferred over the radial artery in this work.

The obtained results showed that for the same methodology, acquired time profiles of SBP during the first 60s of PORH (i.e. SBP response to a step of flow) were different in men and women. However, both diameter dilations followed a similar law although FMD values tended to be higher in females, as expected [32]. Regarding the concavity of the pressure curves, an exponential concave up curve was fitted for women's response, while a concave down was used for men (as for the diameter profile in both genders). These findings suggest that more pronounced non-linear mechanisms may be mediating in the pressure-diameter (i.e. stress vs. strain) relationship for females than for males. In this sense, several reports revealed gender-specific differences regarding the incidence and development of CVDs, including atherosclerosis, hypertension, heart failure, and myocardial remodeling [30]. Premenopausal women have been found to manifest lower levels of cardiovascular morbidity and mortality in comparison to men of the same age groups. This condition is related to the presence of high serum estrogen levels that stimulate the release of endothelium-derived nitric oxide (NO), thus contributing to a cardio-protective action [31]. Likewise, clinical studies have found higher endothelium dependent vasodilator responses associated with an increased amount of endogenous or exogenous estrogen. Brachial FMD responses have also been found to be significantly increased during pregnancy and during the follicular phase of the menstrual cycle in premenopausal women [31]. Even so, it should be noted that the differences or tendencies described between groups could be explained due to the discrepancies in weight, height or even body mass index or body surface (with their corresponding correlation with arterial tree variations), beyond hormonal profiles. Nevertheless, such discrepancies could also be found between individuals of the same group, in terms of the same parameters.

**Table 3** Pressure profile Characterization. ***NA*** is the Normalized Area under the curve. ***A*** and ***B*** are the corresponding coefficients of the fitted exponential curves. $\boldsymbol{R^2}$ is the determination coefficient

| Peripheral Tonometry Parameters | | | | |
|---|---|---|---|---|
| Men | NA | $\alpha_{MP}$ [mmHg] | $\beta_{MP}$ [$10^{-3}$ $s^{-1}$] | $R^2$ (%) |
| | 0.61 ± 0.06* | 14.93 ± 6.67 | 37.76 ± 3.91 | 74.44 ± 5.20 |
| Women | NA | $\alpha_{FP}$ [mmHg] | $\beta_{FP}$ [$10^{-3}$ $s^{-1}$] | $R^2$(%) |
| | 0.40 ± 0.12 | 0.32 ± 0.18 | 1.078.06 ± 497.02 | 73.14 ± 5.75 |

*p < 0.05 was considered as statistically significant between genders

## 5 Conclusion

Arterial blood pressure and diameter beat to beat variations were characterized simultaneously during PORH, in healthy men and women. Further studies are needed to determine the clinical utility of the obtained findings, especially in relation to systolic pressure time profiles. Furthermore, this technique should be implemented in individuals with risk factors associated to an altered endothelial response, such as aging, diabetes mellitus, hypertension, cigarette smoking and preeclampsia, among others.

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**Compliance with ethical standards**

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Conflict of interest** Claudia R. Arbeitman, Leandro J. Cymberknop, Ignacio Farro, Juan Cardelino and Ricardo L. Armentano declare that they have no conflict of interest.

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