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Original Article

Vascular Parameters for Ambulatory Monitoring of Congestive Heart Failure Patients: Proof of Concept

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Abstract

Purpose—Prompt detection of congestion is an essential target in order to prevent heart failure (HF) related hospitalization, being ambulatory monitoring a promising strategy to do so. A successful non-invasive ambulatory monitoring system requires automatic devices for physiological data recording; these data must give information about HF deterioration early enough to predict HF-related adverse events. This work aims to evaluate seven vascular parameters for the ambulatory monitoring of congestive heart failure patients.

Methods—Seven vascular parameters are proposed as indicators of HF deterioration. These parameters are obtained using venous occlusion plethysmography; a technique that uses hardware able of being miniaturized and easily integrated into wearables for ambulatory monitoring. The ability of the proposed vascular parameters to detect congestion is evaluated in eight healthy volunteers and ten congestive heart failure patients with different congestion levels—mild, moderate and severe.

Results—Most parameters distinguish between healthy volunteers and heart failure patients, and some of them present significant differences between volunteers and low levels of congestion—mild or moderate.

Conclusion—Home monitoring of some of the proposed parameters could detect HF deterioration on its onset and alert to health personnel.

Keywords—Venous occlusion plethysmography, Decompensated heart failure, Telemonitoring, Wearables.

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ABBREVIATIONS

ADIP	Analog–digital impedance plethysmograph
ANOVA	Analysis of variance
BF	Blood flow
C_{calf}	Venous compliance
CFC	Capillary filtration coefficient
DAP	Diastolic arterial pressure
ECG	Electrocardiogram
HF	Heart failure
HV	Healthy volunteers
M	Mild congestion
MAP	Mean arterial pressure
MoC	Moderate congestion
NFF	Net fluid filtration
OC	Occluder cuff
P	Patients
SAP	Systolic arterial pressure
SC	Severe congestion
SVR	Systemic vascular resistance
VC	Venous capacitance
VOP	Venous occlusion plethysmography

INTRODUCTION

The estimated worldwide population with heart failure (HF) reaches 26 million people,[30] being this syndrome the principal cause of elderly hospitalization

(> 65 years) in developed countries.[29] A huge number of these hospitalizations is a consequence of venous congestion. When signs and symptoms of congestions are evident, patient decompensation has already started. Thus, prompt detection of congestion is an essential target in order to prevent HF-related hospitalization.[13]

In the last years, ambulatory monitoring has gained attention as a promising strategy to improve the care and management of HF patients. Patient follow-up involves the measurement of hemodynamic and physiological parameters (using invasive or non-invasive devices) and usually aims to identify congestion or edema as a prognosis indicator of heart failure admissions.[6,9] Ambulatory monitoring using implantable devices showed some promising results.[2,3,7,28] However, there is only a small number of patients that can get access to this technology or for which its use is justified because it is invasive and expensive. For these reasons, low cost, easy to use and non-invasive technologies are more attractive for remote patients follow up. Some clinical trials that involve this kind of monitoring and telemedicine techniques for prompt detection of HF decompensation have been carried out; they aim to achieve a reduction of hospitalizations and mortality through fast medical intervention.

On the one hand, Kitsiou *et al.*[20] performed an overviewed of systematics reviews—15 reviews published between 2003 and 2013—and identified five main types of non-invasive technologies used for ambulatory monitoring of HF patients: (a) video consultation—communications between patients and health personnel by means of videoconference equipment- with or without transmission of vital signs—blood pressure, cardiac sounds, weight; (b) automated device based telemonitoring—weight scales, sphygmomanometer and/or question/answer devices that ask about diet, physical activity and treatment adherence—(c) web-based telemonitoring, that uses computers for manual input of vital signs and answers of questions about symptoms, with feedback and educational material; (d) interactive response systems that involve manual data input using the mobile phone keyboard; (e) mobile telemonitoring using mobile phones, personal digital assistants and devices for measurement of physiological parameters and vital signs (ECG, blood pressure and weight), usually connected *via* Bluetooth.[20] They conclude that only automated device based telemonitoring and mobile telemonitoring were effective in reducing the risk of all-cause mortality and HF-related hospitalizations. Also, in the systematic review about telemonitoring of HF patients published by Purcell *et al.*[26] a reduction of mortality risk, hospitalizations, health care cost and an improvement of quality of life are found when compared with usual care.

On the other hand, Abraham[1] states that the effectiveness of non-invasive ambulatory monitoring systems remains unknown and there is evidence that suggests that they have limited value. According to Abraham, one possible reason why this kind of systems fails to improve HF clinical results is the low sensitivity of changes in weight, sign, and symptoms to predict hospitalizations—for example, weight change sensitivity is about 10 to 20%.[2] Weight gain and clinic congestion symptoms are late manifestations of heart failure deterioration, thus, by the time changes occur, the opportunity to prevent hospitalizations could be already lost.

Taking everything into consideration, the development of a successful non-invasive ambulatory monitoring system—regarding the reduction of HF-related mortality and hospitalization—requires automatic devices for physiological data recording connected with computers or mobile phones to transmit data to control centers where health personnel can detect and act when a risk situation occurs. Also, physiological data to be recorded must give information about HF deterioration early enough to predict HF-related adverse events, being sensitive and specific.

Wearables are a promising technology that fulfills the above-mentioned requirements. They usually include a garment with sensors, actuators and wireless communication modules that connect with a PC or mobile phone, which locates data into the cloud where health personnel can access and detect a critical situation. However, up to date, the parameters registered by noninvasive wearables which are oriented to the detection of congestion are low sensitive or delayed,[1] so it is necessary to find new ones to overcome these weaknesses.

In this paper, seven vascular parameters are proposed for prompt detection of congestion; they are venous compliance (C_{calf}), venous capacitance (VC), net fluid filtration (NFF), blood flow (BF), systemic vascular resistance (SVR) and two additional parameters that give information about venous drain (τ and *Span*). These parameters are obtained using venous occlusion plethysmography (VOP); a technique that uses miniaturized hardware easily integrated into wearables. The ability of the proposed vascular parameters to detect congestion is evaluated in eight healthy volunteers and ten congestive heart failure patient with different congestion levels—mild, moderate and severe.

MATERIALS AND METHODS

Venous Occlusion Plethysmography

This technique consists in recording the volume of an extremity of the body when a venous occlusion is

carried out above the measuring site using an oclusor cuff (OC). Venous occlusion is achieved with pressure values around 60 mmHg; at this pressure, the venous drain is interrupted while arterial inflow is unaffected until distal pressure reaches the occlusive one.[37]

In the first part of the venous filling—after occlusion—volume increases linearly. The slope of this part corresponds to resting arterial inflow.[22] Then, distal venous pressure increases, veins under the cuff start to open and venous flow reduces gradually—due to venous drain-, which causes a curvature in the volume graph. Then, volume increases at a constant rate again as a consequence of extravascular liquid accumulation due to capillary pressure increase.[23] Venous congestion is maintained with the OC during a fixed time − 8 min in this work- and then pressure is released and venous drain occurs (Figs. 1c and 1d).

A common method to obtain VOP signals consists in recording extremity volume changes by means of impedance measurements. This is because the impedance of the extremity is related to the fill of the vessels contained[32] and it can be obtained by measuring the voltage of the extremity when a constant amplitude alternating current − 20 to 100 kHz is injected.[11]

As detailed next, the seven vascular parameters proposed for prompt detection of congestion can be obtained non-invasively using VOP.

Subjects

In order to determine the ability of the proposed parameters to detect congestion, ten HF patients (congestive subjects, seven males and three females, 64 ± 14 years) admitted at the Coronary Unit of the "Instituto de Cardiología" (San Miguel de Tucumán, Tucumán, Argentina) with acute HF—according to the Framingham criteria—were studied. These patients also met the following two criteria: (1) New York Heart Association (NYHA) functional class II to IV before the acute exacerbation leading to hospital admission, (b) left ventricular ejection fraction (LVEF) < 45% on echocardiography performed at the beginning of the hospitalization. The exclusion criteria were: (1) use of implantable electrical devices and (2) venous insufficiency.

Also, eight healthy volunteers (non-congestive subjects, four males and four females, age 28 ± 5 years) with no risk factors for cardiovascular disease, with a normal cardiovascular examination and a normal electrocardiogram were recruited as control subjects.

Study Protocol

The investigations were performed at the "Instituto de Cardiología" in a temperature-controlled environment (22–24 °C). All studies were performed with the subjects having fasted and abstained from caffeine-containing drinks for at least 6 h.

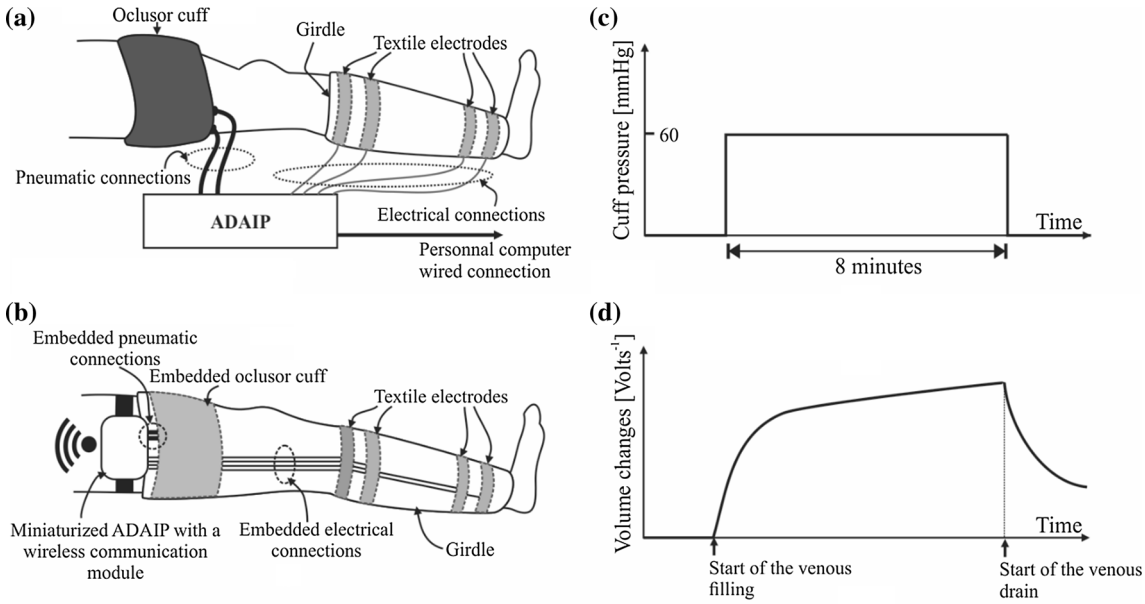

FIGURE 1. (a) Lower extremity with the elements necessary for venous occlusion plethysmography—oclusor cuff, textile electrodes embedded into a girdle and pneumatic and electrical connections—connected to the impedance plethysmograph. (b) Sketch of a wearable—girdle—with all the elements embedded. In this case, the plethysmograph is miniaturized and fastened to the leg. It transmits the recorded signals using a wireless communication module. (c) Idealized cuff pressure [mmHg]. (d) Volume changes in synchronism with cuff pressure changes, the start of the venous filling and venous drain are shown.

VOP recording was carried out in the lower extremity using a custom-made automatic analog-digital impedance plethysmograph (ADIP)—its technical description and validation has been reported elsewhere[15] and textile electrodes made of *Stretch* conductive fabric (LessEMF, Latham, NY), which have also been validated as VOP electrodes elsewhere.[14] The ADIP applies a 60 mmHg pressure on the extremity using a cuff and allows recording, visualizing and storing VOP records. These records are in units of votls seconds^{-1} and, when visualized inverted, they are proportional to volume changes. It must be noted that the intention is to find variations of the proposed parameters among congestion levels, being the absolute value of parameters not really important, so the fact that their units are not the traditional ones is not worrisome.

The subject was placed in a supine position with the oclusor cuff and electrodes located as in Fig. 1(a). Before recording, a 15 min period is necessary for electrode stabilization.[14]

VOP records are obtained once in healthy volunteers—to count with reference values for no congestion—and every 24 h in HF patient as congestion decreases because of the received treatment. The treating physician classifies daily congestion as mild (MC), moderate (MoC) or severe (SC) using the proposal of Gheorghiade *et al.*[12] This proposal consists in a combination of available measurements (bedside assessment, laboratory analysis, and dynamic manoeuvers) to classify the degree of congestion. When available, the physician also considered the information of echocardiography and chest X-ray for congestion classification. Data of the patients—age, sex, day of hospitalization, diary congestion level, heart rate and treatment—is included as supplementary material.

This study conforms to the principles outlined in the Declaration of Helsinki and was approved by our local ethics committee. All volunteers and patients gave written informed consent.

Vascular Parameters

Venous Compliance (Ccalf)

Venous compliance can be estimated from VOP records using pressure–volts relationship during venous outflow. This relationship is quadratic and can be described by Eq. (1); where ΔV is the voltage change, p is the cuff pressure and $\beta 1$[V mmHg^{-1}] and $\beta 2$[V mmHg^{-2}] are regression coefficients. C_{calf} is defined as the first derivative of the pressure–volts curve, resulting in a linear pressure-compliance relationship (Eq. 2), the slope of this relationship ($2.\beta 2$), as well as, the regression coefficients can be used as estimators for C_{calf}.[33] In this case, $\beta 2$ will be used as C_{calf} estimator.

$$\Delta V = \beta_0 + \beta_1 \cdot p + \beta_2 \cdot p^2 \tag{1}$$

$$C_{calf} = \beta_1 + \beta_2 . p \tag{2}$$

Venous Capacitance (VC), Net Fluid Filtration (NFF) and Capillary Filtration Coefficient (CFC)

VC is the maximum blood volume that a vein can store at a given pressure. The time needed to complete VC is a function of applied pressure, and it has been demonstrated that it is between 3 and 4 min when pressure is 60 mmHg.[17] Thus, in this paper, VC is estimated as the voltage change that occurs at 4 min from the beginning of the VOP record.

Also, from minute 4 of the VOP record, it can be observed—in some cases—a slow and linear voltage change caused by net fluid filtration into the extravascular space. In this paper, NFF is presented as the percentage [%] of the voltage change at minute 4 (ΔV_4), with respect to the total voltage change (ΔV_T) during the VOP recording (Eq. 3).

$$NFF = \frac{\Delta V_T - \Delta V_4}{\Delta V_T} \cdot 100 \tag{3}$$

Then, CFC can be calculated dividing NFF by the cuff pressure, which is constant in this case—60 mmHg—and as CFC and NFF are directly proportional and reflect the same changes, only NFN will be obtained in this work.

Blood Flow (BF)

BF [V s^{-1}] can be estimated from VOP recording as the initial slope of the volume changes.[16] In this paper, this slope is calculated using a linear regression during the first 20 s of the records.

Systemic Vascular Resistance (SVR)

SVR [mmHg.s.V^{-1}] can be estimated by dividing mean arterial pressure by BF.[33] During rest, mean arterial pressure (MAP) can be approximated using systolic (SAP) and diastolic (DAP) pressure using Eq. (4).

$$MAP \cong DAP + \frac{1}{3}(SAP - DAP) \tag{4}$$

Venous Drain: τ and Span

Venous drain can be studied from VOP recording from the segment of the curve obtained after cuff deflation. Anderson *et al.*[4] demonstrated that venous drain follows a first order exponential-decay (Fig. 2) (Eq. 4). In this paper, the venous drain is analyzed using two parameters from exponential-decay fits; they are time constant τ[s]—the time when the exponential value is ~ 37% of its initial one (Y_0) and *Span*[V]—the difference between Y0 and plateau of the exponential.

$$Y(t) = (Y_0 - Plateau) \cdot \exp\left(-\frac{t}{\tau}\right) + Plateau \qquad (5)$$

Statistical Analysis

Data from VOP Records are Grouped into Five Groups

- Healthy volunteers (HV) (n = 8, n: number of samples), non-congestive group;
- Mild congestion (MC) (n = 6), moderate congestion (MoC) (n = 12) and severe congestion (SC) (n = 5). These three groups include the values of the parameters obtained the days that patients have mild, moderate or severe congestion, respectively. Which was classified according to the scale proposed by Gheorghiade *et al.*[12]
- Patients (P) (n = 24), values of the parameters obtained from all patients and all days of measurement; i.e. it group includes the data of all degree of congestions for each parameter. This aggrupation is implemented in order to know if each one of the proposed parameters can distinguish between healthy volunteers and congestive patients.

The existence of significant differences is evaluated (a) between healthy volunteers and patients using Student *t* test, and (b) among volunteers and the three levels of congestion—mild, moderate and severe—using ANOVA. These tests are carried out for each parameter. Before *t*-test, normality of data and variance homogeneity are assessed. When these assumptions cannot be accepted nonparametric *t*-test—Mann–Whitney test—or nonparametric ANOVA—Kruskal–Wallis test—is performed.

When ANOVA indicates that there is sufficient evidence to reject the null hypothesis of mean equality, which means that congestion modifies the value of the parameter understudy, a pair comparison method—Duncan test—is carried out among samples.

Statistical tests were performed using the software R, adopting a significance level of 5%.

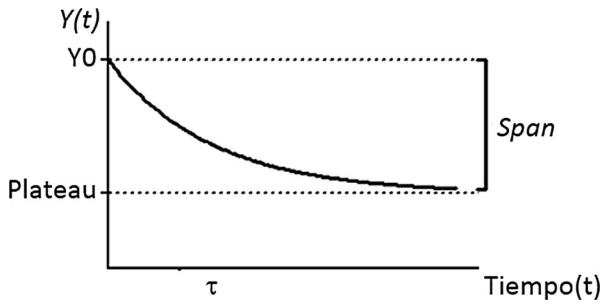

FIGURE 2. Waveform and parameters of an exponential decay.

RESULTS AND DISCUSSIONS

Descriptive statistics for each parameter and group are summarized in Figs. 3a–3g. Then, Table 1 presents results from statistical analysis—t-test between HV and P groups; ANOVA and Duncan Test among HV, MC, MoC and SC groups-.

Table 1 shows that for six of the seven proposed vascular parameters—C_{calf}, VC, NFF, BF, SVR, and *Span*—there is sufficient evidence to reject the null hypothesis of equality of means when HV and P groups are compared. Also, it is found—using ANOVA—that these six parameters present sufficient evidence to reject the null hypothesis of equality of means when HV, MC, MoC and SC groups are compared. Therefore, congestion modifies their values. Then, through pair comparison—Duncan test—significant differences of means are found among HV and: (a) MC, MoC and SC groups when BF and *Span* are analyzed; (b) MoC and SC groups when VC is analyzed; and (c) SC when C_{calf}, SVR y NFF are analyzed. Almost no parameter shows significant differences among congestive groups—MC, MoC and SV, except NFF, which presents a significant difference between MC and SC.

Figures 3a, 3b, and 3d and Table 1 show that the modulus of C_{calf}, VC and BF are augmented in healthy volunteers with respect to patients, which agrees with bibliography. HF is characterized by peripheral vasoconstriction,[38] which implies low VC and BF, and abnormal vascular compliance—C_{calf}.[27] Besides, many studies have demonstrated that patients with heart failure have reduced peripheral blood flow—BF—at rest and during exercise.[21,35,39] Also, changes in the tone of veins can change the amount of blood that is contained at a given transmural pressure—VC[36]; Ogilvie *et al.*[25] demonstrated that total vascular capacitance decreased substantially in dogs in which HF was induced by pacing. While Gay[10] found—with experiments on rats—that Ccalf is decreased in HF;

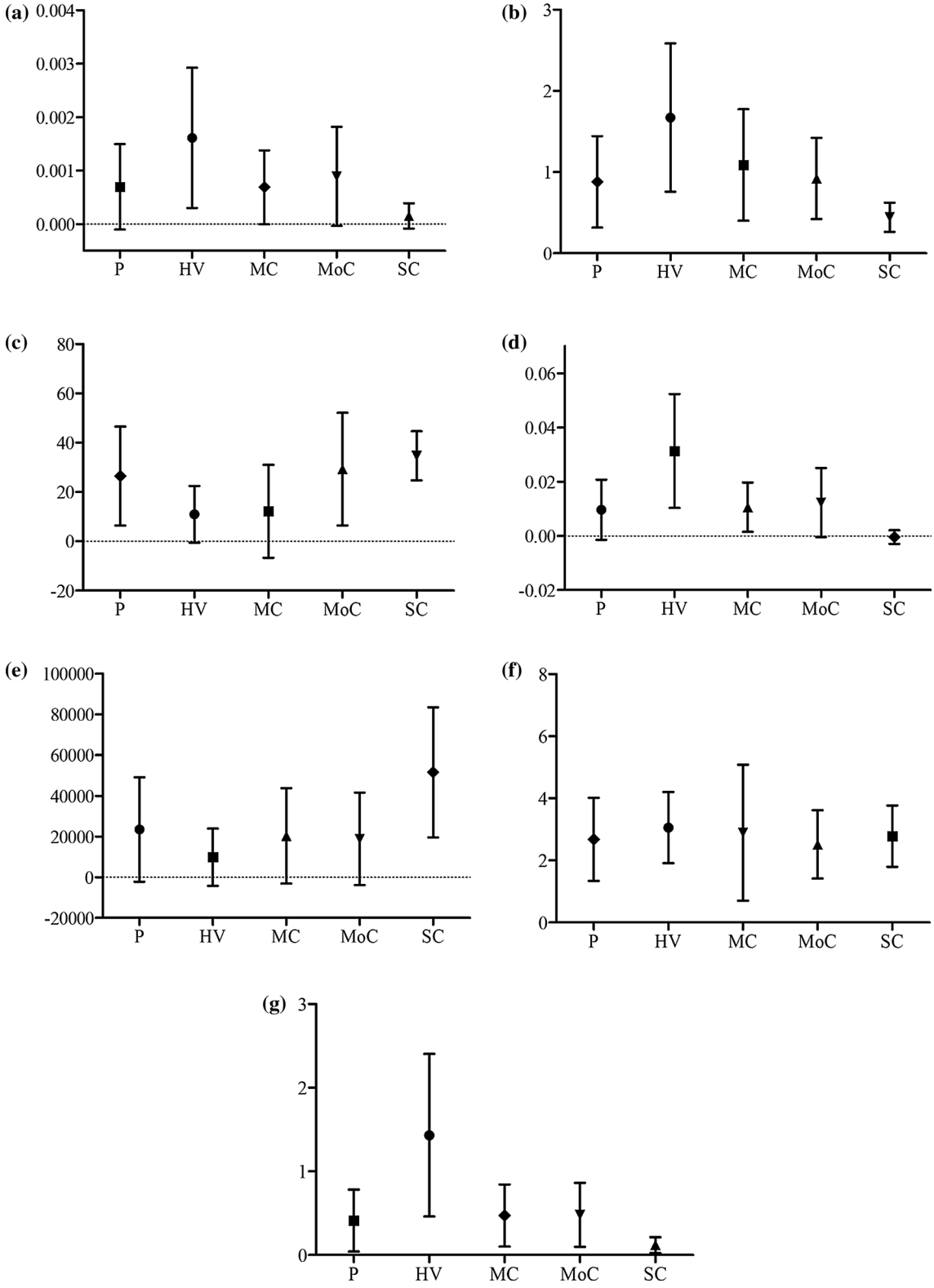

FIGURE 3. Descriptive statistics for each parameter and group [patients (P), healthy volunteers (HV), mild congestion (MC), moderate congestion (MoC), and severe congestion (SC)]. The central symbol represents the mean and the whiskers the standard deviation. (a) C_{calf}, (b) VC, (c) NFF[%], (d) BF[V/s], (e) SVR[mmHg s/V], (f) τ[s] and (g) *Span*[V].

TABLE 1. Results from the statistical analysis: t-test between healthy volunteers (HV) and patients (P) groups; ANOVA and Duncan Test among HV, MC—mild congestions, MoC—moderate congestion, and SC—severe congestion groups.

Parameter	Group	ANOVA	Duncan Test (means with a common letter are not significantly different)	
$\beta 2$	HV	p-value = 0.0029	A	
	MC	(Kruskal–Wallis test)	A	B
	MoC		A	B
	SC			B
	HV vs. P (Mann–Whitney test)	p value = 0.021		
VC	HV	p value = 0.0017	A	
	MC		A	B
	MoC			B
	SC			B
	HV vs. P (Mann–Whitney test)	p value = 0.003		
NFF	HV	p value = 0.0032	A	
	MC	(Kruskal–Wallis test)	A	
	MoC		A	B
	SC			B
	HV vs. P (Mann–Whitney test)	p value = 0.0064		
BF	HV	p value = 0.0001	A	
	MC	(Kruskal–Wallis test)		B
	MoC			B
	SC			B
	HV vs. P (Mann–Whitney test)	p value $<$ 0.0001		
SVR	HV	p value = 0.0165	A	
	MC		A	B
	MoC		A	B
	SC			B
	HV vs. P (Mann–Whitney test)	p value = 0.0077		
τ	HV	p value = 0.6620	–	
	MC			
	MoC			
	SC			
	HV vs. P (Mann–Whitney test)	p value = 0.1632		
Span	HV	p value $<$ 0.0001	A	
	MC	(Kruskal–Wallis test)		B
	MoC			B
	SC			B
	HV vs. P (Mann–Whitney test)	p value $<$ 0.0001		

and Magrini *et al.*[24] found the same thing in patients with HF and massive peripheral edema.

Regarding NFF—which is directly proportional to CFC, the higher modulus obtained for patients when compared to the control group (Fig. 3c and Table 1) could explain edema formation in congestive HF patients. There is evidence that CFC is increased in edematous extremities of patients with different affections, such as breast cancer-related lymphedema,[19] nephrotic syndrome,[22] post reconstructive edema,[34] deep vein thrombosis,[31] ischemic edema[5] and proximal femur fracture.[18] These findings have physiological sense since when CFC is increased fluid filtration is increased too and if the fluid is not reabsorbed or removed by lymphatic vessels then fluid accumulation in the interstitial space occurs—edema. Up to now, there has not been found in the literature a study of the possible contribution of CFC changes to the formation and maintenance of peripheral edema observed in HF patients, this work is the first approach to this.

Also, Cotter *et al.*[8] proved that systemic vascular resistance—SVR—is increased in patient with pulmonary edema, which was found in this work too when comparing congestive patient against healthy volunteers (Fig. 3e).

Finally, this is the first time that venous drain—τ and Span—is measured in HF patients as a possible indicator of congestion. Span modulus is also augmented in healthy volunteers—Fig. 3g; it is hypothesized that this is because healthy volunteers have more blood stored in veins—higher VC value- as a consequence of the VOP maneuver, therefore a higher venous drain could be expected. In the case of τ, there are

no significant differences among groups—Fig. 3f and Table 1.

Thus, most proposed vascular parameters show a significant difference between the control group—-HV—and patients—P—and between HV and at least one level of congestion—mild, moderate or severe-. Therefore, they allow distinguishing between healthy volunteers and sick patients and, more importantly, some of them—BF, *Span* and VC—present significant difference from low levels of congestion—mild or moderate—when compared to healthy volunteers. Which indicates that these three last parameters could detect the onset of congestion.

Furthermore, it is important to emphasize that most parameters show a tendency to increase or decrease with the level of congestion Fig. 3, but the group variability prevents to find significant differences among congestive groups. The large standard deviation obtained can be a consequence of: (a) The size of the population being studied (this is why this work is considered a proof of concept or pilot study). (b) Variances among subjects since in the groups MC, MoC and SC there are data that belong to different subjects. In the future, the idea is to make a long—3 month—ambulatory follow-up of patients on the risk of HF decompensation. And, evaluate the variation of the parameters—in the same subject-during the evolution of congestion before and after HF decompensation. It will be tried to determine if the parameters can announce a worsening of their disease state and to predict a decompensation. After that, the threshold values, of each one of the parameters, that indicates the beginning of fluid accumulation should be identified.

Finally, prompt detection of congestion could be achieved at home using a wearable system Fig. 1b that includes a miniaturized venous occlusion plethysmograph incorporated into a garment, for example a girdle, with an embedded oclusor cuff and textile electrodes such as the presented ones by Goy *et al.*[14] The system should also include a wireless communication module connected with an application installed on a PC or mobile phone for data transmission, visualization, and processing. The threshold values of the proposed vascular parameters should be used to set alarms that indicate when some threshold is reached, to alert to the healthcare staff. The endpoint of the proposal is to be able to prevent and diminish heart failure hospitalizations.

This is the first report where a set of vascular parameters are proposed as indicators of the level of congestion in HF patients. It is well known that some of them are modified in these patients, as mentioned above, but their possible variation with different levels of congestion has not been studied yet. These parameters could be an attractive choice for non-invasive ambulatory monitoring of HF patients. Besides, the fact that all of them can be measured using a single, portable and miniaturized devices makes their ambulatory follow up possible. Up to now, the measurement of these parameters was performed with equipment that is impossible to be used at home and by the user—catheterism and strain gage based plethysmography performed with highly complex devices.

Telemedicine is a promising tool for the reduction of heart failure-related hospitalization, using congestion ambulatory monitoring, but this technology is underdeveloped.[13] Congestion ambulatory monitoring can be implemented using wearables, and this new proposal is a great step forward in this area.

CONCLUSION

In this paper, seven vascular parameters are proposed as indicators of congestion level in heart failure patients, all of them can be obtained non-invasively by venous occlusion plethysmography using a miniaturized device, which can be incorporated into wearables. Most parameters distinguish between healthy volunteers and heart failure patients, and some of them present significant differences between volunteers and low levels of congestion—mild or moderate. Results imply that home monitoring of these parameters could detect HF deterioration on its onset and alert to health personnel.

ELECTRONIC SUPPLEMENTARY MATERIAL

The online version of this article (https://doi.org/10.1007/s13239-019-00432-3) contains supplementary material, which is available to authorized users.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

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