

# Hemodynamic differences among hypertensive patients with and without heart failure using impedance cardiography

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## Abstract

**Background:** Impedance cardiography is a reliable, well-tolerated, and non-invasive method used to obtain hemodynamic measurements and could potentially be useful in heart failure (HF) diagnosis, hemodynamic monitoring of critically ill patients, and help in the choice of antihypertensive therapy. The objective of this study was to determine the differences between hemodynamic parameters in a study population of hypertensive patients with and without HF, using impedance cardiography.

**Methods:** A case-control study was designed and named the TARGET study. Participants were enrolled in two study groups: control group C, hypertensive patients without HF and the HF group, hypertensive patients with HF. A descriptive analysis was carried out to characterize the sample and differences in continuous variables were tested for statistical significance by independent sample *t* test.

**Results:** The study included 102 hypertensive outpatients. The control group consisted of 77 individuals (58.4% males; mean age  $63.9 \pm 12.5$  years old) and the HF group consisted of 25 individuals (44.0% males; mean age  $74.2 \pm 8.7$  years old). The mean Cardiac Index (CI) was  $2.70 \pm 1.02$  L.min.m<sup>-2</sup> ( $2.89 \pm 1.04$  versus  $2.12 \pm 0.70$ ;  $p < 0.001$ ), mean Stroke Index (SI) was  $35.5 \pm 14.7$  mL.m<sup>-2</sup> ( $37.7 \pm 15.2$  versus  $28.5 \pm 10.8$ ;  $p = 0.006$ ), mean Ejection Phase Contractility Index (EPCI) was  $33.7 \pm 12.7$  1000 s<sup>-2</sup> ( $35.8 \pm 13.1$  versus  $27.2 \pm 9.2$ ;  $p = 0.003$ ), mean Inotropic State Index (ISI) was  $74.3 \pm 28.2$  100 s<sup>-2</sup> ( $78.8 \pm 28.9$  versus  $60.6 \pm 20.7$ ;  $p = 0.005$ ), and mean Left Stroke Work Index (LSWI) was  $51.3 \pm 23.1$  g.min.m<sup>-2</sup> ( $55.4 \pm 23.5$  versus  $38.9 \pm 16.6$ ;  $p = 0.002$ ).

**Conclusions:** In this study, hypertensive patients with HF had significantly lower values of blood flow parameters, contractility, and left work indices compared with hypertensive patients without HF. These differences reflected the incorrect hemodynamic pattern (mostly hypodynamic) of these patients. Impedance cardiography (ICG) seems to be an adequate method to reflect these differences.

**Keywords:** heart failure, hemodynamics, hypertension, impedance cardiography, TARGET study, thoracic bioimpedance

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## Introduction

Impedance cardiography (ICG) is a reliable, well tolerated and non-invasive method used to assess the hemodynamic pattern of the cardiovascular system, which may be useful in heart failure (HF) diagnosis, hemodynamic monitoring of critically ill patients, and help in the choice of antihypertensive therapy.<sup>1–3</sup> The symbol *Z* denotes impedance

and is a measure of the effective resistance that the body offers to a low-intensity alternating current. Compared with the high resistance of thoracic tissue ( $\rho = 200\text{--}5000 \Omega \cdot \text{cm}^{-1}$ ), blood and fluids ( $\rho = 65\text{--}150 \Omega \cdot \text{cm}^{-1}$ ) provide much lower resistance to current. Thus, regions of the body with higher blood or fluid content will present with lower impedance, but regions with more

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**Figure 1.** TARGET study logo.

solid tissue will show higher impedance. This physical basis has been exploited to assess hemodynamic measurements and fluid accumulation in pulmonary congestion.<sup>1</sup>

Over the last decade, non-invasive hemodynamic assessment methods including ICG, echocardiography, brain natriuretic peptide (BNP) or lung ultrasound have been increasingly used.<sup>4,5</sup> ICG enables continuous, beat-by-beat, operator-independent cardiac output (CO) monitoring in medical or surgical patients.

In 2017 a randomized, prospective double-blind study enhanced the utility of maternal hemodynamic monitoring during spinal anesthesia for cesarean section<sup>6</sup> and relevant recent studies have shown that ICG hemodynamic monitoring in the operating theater reduces morbidity and shortens the length of hospital stay following surgery.<sup>7</sup>

The PREDICT study, in 2006, demonstrated that ICG was able to identify HF patients with a higher risk of hospitalization and death.<sup>8</sup> Facchini and colleagues<sup>9</sup> evidenced that ICG and pulmonary ultrasonography were methods with greater sensitivity and specificity in the detection of pulmonary congestion. ICG has demonstrated the further potential for cardiovascular disease (CVD) detection in asymptomatic patients with cardiovascular risk factors,<sup>2</sup> allowing cardiac remodeling prevention.<sup>10-12</sup>

In HF monitoring, ICG presented hemodynamic results comparable with those obtained by cardiac magnetic resonance<sup>13</sup> and good correlation with invasive methods determinations (notably the Swan-Ganz catheter), with correlation coefficients between 0.76 and 0.89.<sup>4,14</sup>

In addition, characterization of the hemodynamic pattern of hypertensive patients is of increasing interest to the medical and scientific community, helping to personalize antihypertensive regimens, guiding them to the pathophysiological mechanism responsible for hypertension.<sup>15-17</sup>

Hemodynamic characterization normally involves pressure determination in heart chambers and in the peripheral arterial system, assessing CO, systemic and pulmonary vascular resistance, and cardiac indices. It requires invasive and noninvasive diagnostic tests including pulmonary artery catheterization or echocardiography. However, these methods cannot always be used when attending to a patient's clinical condition and their availability is limited. Their operation requires a high level of differentiation and experience.<sup>18,19</sup>

In the majority of cases, clinical history and physical examination are not enough for a personalized therapeutic intervention and the proper stratification of the prognosis of HF patients.<sup>4,15,20</sup> Hemodynamic monitoring, particularly the assessment of CO, stroke volume, and left ventricular filling pressures are useful when selecting an appropriate approach of these patients, considering that pulmonary congestion is the main determining factor of symptoms and hospitalization. However, at the current time, there are no clear indications regarding therapy based on hemodynamic measurements and their criteria values, which limits the possibilities for using ICG in clinical practice.

The objective of this study was the determination of differences among hemodynamic parameters including: Cardiac Index (CI), Stroke Index (SI), Ejection Phase Contractility Index (EPCI), Inotropic State Index (ISI,) and Left Stroke Work Index (LSWI) in a study population of hypertensive patients with and without HF, using an ICG device.

## Methods

### Study design

A case-control study was designed and named the TARGET study (The role of impedance cARdi-oGraphy in hypErTensive patients). The study logo is represented in Figure 1.

Patients were enrolled in two study groups: control group C, hypertensive patients without HF,

**Table 1.** Hemodynamic variables studied by ICG.

Variable	Brief definition	Unit	Calculation formula	Reference range (19)
<b>Blood flow</b>				
CI	Volume of blood pumped by the left ventricle per minute indexed to BSA	L/min./m <sup>2</sup>	CO/BSA	2.5–4.7
SI	Volume of blood pumped by the left ventricle per heartbeat indexed for BSA	mL/m <sup>2</sup>	SV/BSA or CI/HR	35–65
<b>Contractility and work indices</b>				
EPCI	Peak velocity of blood flow in the aorta	1000 s <sup>-1</sup>	(dZ/dt) <sub>max</sub> × TFC	33–65
ISI	Initial acceleration of blood in the aorta after aortic valve opening	100 s <sup>-2</sup>	(d <sup>2</sup> Z/dt <sub>2</sub> ) <sub>max</sub> × TFC	70–170
LSWI	Indicator of the amount of work exerted by the left ventricle in each minute to pump blood into the systemic circulation	g.min.m <sup>-2</sup>	SI × (MAP–PAOP) × 0.0144	51.6–74.3

BSA, body surface area; CI, Cardiac Index; EPCI, Ejection Phase Contractility Index; ICG, impedance cardiography; ISI, Inotropic State Index; LSWI, Left Stroke Work Index; SI, Stroke Index.

and the HF group, hypertensive patients with HF. For each patient, the hemodynamic variables were determined using an ICG device (HOTMAN® System for Adults W/EXT-TEBCO®), which requires four pairs of external, disposable electrodes: two pairs were placed on the neck base and two pairs on the lower limit of the patient's chest, along the mid-axillary line. The four sensors placed superiorly generate an electrical alternating current of high frequency and very low intensity (approximately 7 µA) undetectable for the patient, and the remaining four electrodes detect variations in the electrical impedance of chest cavity. This ICG procedure is well tolerated and can be compared with a standard 12-lead electrocardiograph.<sup>21</sup> Table 1 summarizes the hemodynamic variables and their calculation formulas.<sup>22</sup>

The patients were instructed to breathe normally, remain stationary and not to speak or cough during the procedure. After stabilization of hemodynamic parameters, at least three measurements were determined for each variable and the mean value was considered. Pulmonary artery occlusion pressure (PAOP) was not determined by invasive methods and the arbitrary value recommended by the device manufacturer had been considered: PAOP = 9 mm Hg.

Diabetes and abdominal obesity were defined according to the International Diabetes Federation

criteria.<sup>23,24</sup> Dyslipidemia diagnosis was defined according to the European Society of Cardiology and the European Atherosclerosis Society guidelines as a function of total cardiovascular risk and low-density lipoprotein cholesterol level.<sup>25</sup>

The obtained information was registered in a case report form (CRF) and subjected to verification and quality control procedures, conducted by two investigators independently. An identification code was given to each patient to ensure their anonymity.

#### Study population

Study inclusion criteria comprised patients with over 18 years of consecutive hypertension, previously diagnosed according to the European Society of Cardiology Guidelines.<sup>26</sup> The study was carried out in the Department of External Consultation of Tondela-Viseu Hospital Center from October to December 2014. HF was also previously diagnosed according to ESCG<sup>27</sup> and New York Heart Association (NYHA) functional classification was determined according to patient symptoms before ICG measurements.

Exclusion criteria comprised patients with arrhythmias or cardiac pacemakers, a personal history of thoracic surgery in the last 6 months, hemodynamic instability (pale or cool skin,

diaphoresis, systolic blood pressure under 90 mm Hg or heart rate above 120 bpm), current diagnosis of pregnancy, chronic renal failure grade IV (or higher), severe hepatic impairment (Child-Pugh score C), or oncologic pathology with a life expectancy <1 year. The study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was approved by the Tondela-Viseu Hospital Center and the Health Sciences Faculty of Beira Interior University Ethics Committee, process CE-FCS-2014-030. Written informed consent was obtained from all patients prior to their inclusion in the study.

### ICG

A number of factors can affect bioimpedance including electrode placement, movement or postural change, skin moisture, blood composition (hemoglobin levels and specific resistivity of blood), body composition (including lung tissue, chest wall fat, air), and even environmental radiofrequency 'noise' can affect the conductivity and signal vectors.<sup>1</sup>

ICG technical limitations were considered in the inclusion and exclusion criteria definition: the presence of dysrhythmias, which alter the stability of the HR dependent variables; the presence of a cardiac pacemaker, since the correct determination of hemodynamic variables is dependent on correct detection of QRS complexes; following recent chest surgery, which decreases the magnitude of the electrocardiographic signal; in left bundle branch block due to QRS complex widening; and in sepsis or extremely obese patients because CI is incorrectly underestimated.

As a result of these limitations, eight patients were excluded: six for arrhythmia, one for extreme obesity, and one had a cardiac pacemaker.

### Statistical analysis

Categorical variables are presented as frequencies, percentages, and continuous variables as means and standard deviations or medians and interquartile ranges for variables with skewed distributions.

The sample size was calculated in order to demonstrate differences between groups assuming a

two-sided alpha risk of 0.05, a power of 80% and an enrollment ratio of 3:1 (C group: HF group). The power analysis suggested that a sample size of 96 patients (72 in C group and 24 in the HF group) was required to detect a 20% difference between groups.

Normal distribution was confirmed using the Kolmogorov–Smirnov test, or skewness and kurtosis. Differences among groups were tested with an independent sample *t* test. All reported *p* values were two-tailed, with a *p* value <0.05 indicating statistical significance. Analyses were performed using SPSS software, version 22.0.

### Results

The study involved 102 hypertensive patients: 77 in group C, hypertensive patients without HF and 25 in group HF, hypertensive patients with HF. The general characteristics of the study population are reported in Table 2, including risk factors for CVD. All patients were previously diagnosed with hypertension and HF, according to study inclusion criteria.

Hemodynamic variables determined using ICG are presented in Table 3 and Figure 2.

### Discussion

Hypertension is a consequence of a hemodynamic imbalance within the circulation and represents a major cause of mortality, doubling the risk of CVD, including coronary arterial disease (CAD), HF, ischemic and hemorrhagic stroke, renal failure and peripheral arterial disease, and significantly contributes to the rising costs on health care.<sup>28</sup> It is a multifactorial disease, reflecting changes in physiological and hemodynamic mechanisms including intravascular volume, autonomic nervous system, the renin–angiotensin–aldosterone system, and others (hypertrophic vascular remodeling and endothelial dysfunction).<sup>15</sup>

In addition, HF involves a set of hemodynamic changes that need to be controlled, and knowledge of these is critical for effective and targeted therapeutic monitoring. HF is a complex and progressive clinical syndrome that occurs in patients affected by abnormalities in the heart structure, cardiac functions or both. There are a large number of indications and symptoms that

**Table 2.** General characteristics of the study population.

	C group (n = 77)	HF group (n = 25)	p value
Age, (years) mean ( $\pm$ sd)	63.9 $\pm$ 12.5	74.2 $\pm$ 8.7	<0.01
Gender	45/77 (58.4%) males	11/25 (44.0%) males	0.211
<b>Biometric parameters</b>			
Weight, kg ( $\pm$ sd)	79.8 ( $\pm$ 15.4)	81.2 ( $\pm$ 18.3)	0.724
Height, cm ( $\pm$ sd)	164.0 ( $\pm$ 8.5)	161.6 ( $\pm$ 7.1)	0.218
Waist circumference, cm ( $\pm$ sd)	100.2 ( $\pm$ 11.7)	102.9 ( $\pm$ 16.2)	0.436
BMI, kg/m <sup>2</sup>	29.7 ( $\pm$ 5.1)	31.1 ( $\pm$ 6.7)	0.282
<b>Blood pressure</b>			
Systolic blood pressure (mm Hg)	154.5 ( $\pm$ 25.1)	148.7 ( $\pm$ 31.0)	0.346
Diastolic blood pressure (mm Hg)	86.4 ( $\pm$ 12.5)	77.4 ( $\pm$ 18.7)	0.033
Heart rate (beats per minute)	78.6 ( $\pm$ 13.1)	75.8 ( $\pm$ 11.5)	0.342
<b>Risk factors for CVD</b>			
HT, n/total (%)	77/77 (100%)	25/25 (100%)	–
Abdominal obesity, n/total (%)	58/77 (75.3%)	16/25 (64.0%)	0.275
Dyslipidemia, n/total (%)	51/77 (66.2%)	14/25 (56.0%)	0.360
Diabetes, n/total (%)	52/77 (67.5%)	17/25 (68.0%)	0.966
<b>NYHA functional classification</b>			
I	–	9	–
II	–	12	–
III	–	4	–
IV	–	0	–
BMI, body mass index; C group, hypertensive patients without HF; HF group, hypertensive patients with HF; HT, hypertension; NYHA, New York Heart Association			

lead to frequent hospitalizations, deterioration of quality of life, and lower life expectancy. The mortality at 5 years is approximately six times higher than the general population.<sup>29</sup>

In this study, the authors aimed to determine differences between hemodynamic parameters including blood flow (CI and SI), contractility (EPCI and ISI) and LSWI, providing information on how these variables change in the presence or absence of HF in hypertensive subjects.

The authors found significant differences in multiple hemodynamic variables: hypertensive patients with HF demonstrated lower blood flow parameters and impaired cardiac function (lower CI and SI).

The majority of patients with ventricular dysfunction remain asymptomatic in the early stages of the disease. This could be due to some compensatory hemodynamic mechanisms: the renin–angiotensin–aldosterone system activation that helps to

**Table 3.** Hemodynamic differences between study groups.

	C group	HF group	p value
<b>Blood floww</b>			
CI mean ( $\pm$ sd)	2.89 ( $\pm$ 1.04) (1.00–6.30)	2.12 ( $\pm$ 0.70) (0.88–3.58)	<0.001
SI mean ( $\pm$ sd)	37.7 ( $\pm$ 15.2) (10.7–89.3)	28.5 ( $\pm$ 10.8) (12.0–52.0)	0.006
<b>Contractility and cardiac work</b>			
EPCI mean ( $\pm$ dp)	35.8 ( $\pm$ 13.1) (14.7–81.3)	27.2 ( $\pm$ 9.2) (11.5–46.6)	0.003
ISI mean ( $\pm$ dp)	78.8 ( $\pm$ 28.2) (32.0–192.0)	60.6 ( $\pm$ 20.7) (25.0–103.0)	0.005
LSWI mean ( $\pm$ dp)	55.4 ( $\pm$ 23.5) (17.8–128.6)	38.9 ( $\pm$ 16.6) (13.5–74.9)	0.002
C group, hypertensive patients without HF; CI, Cardiac Index; EPCI, Ejection Phase Contractility Index; HF group, hypertensive patients with HF; ISI, Inotropic State Index; LSWI, Left Stroke Work Index; SI, Stroke Index.			

maintain the CO, increasing sodium and water retention and consequent increasing the volume; the autonomic nervous system stimulation, releasing adrenergic mediators and increasing cardiac contractility; and the release of vasodilator molecules that includes the atrial natriuretic peptides and BNP, prostaglandins (PGE<sub>2</sub> and PGI<sub>2</sub>) and nitric oxide, which compensates for excessive peripheral vasoconstriction.<sup>18</sup>

At some stage in HF evolution, these neurohormonal compensatory mechanisms become insufficient, resulting in hemodynamic changes including reduced stroke volume, reduced CO, and increased left ventricular filling pressure.<sup>30</sup>

When contractility and cardiac work indices were analyzed, the authors observed that, in this study, EPCI, ISI, and LSWI mean values are lower in patients with HF.

EPCI is a variable proportional to blood flow in the aorta, providing an indication of maximum myocardial contractility during systole. This parameter is influenced either by the Frank-Starling mechanism (intravascular volume amendment) or pharmacologically by inotropic agents. ISI (second derivative of electrical bioimpedance) indicates the maximum acceleration of blood flow in the aorta, providing an accurate marker of the inotropic state, independent of preload and afterload and is

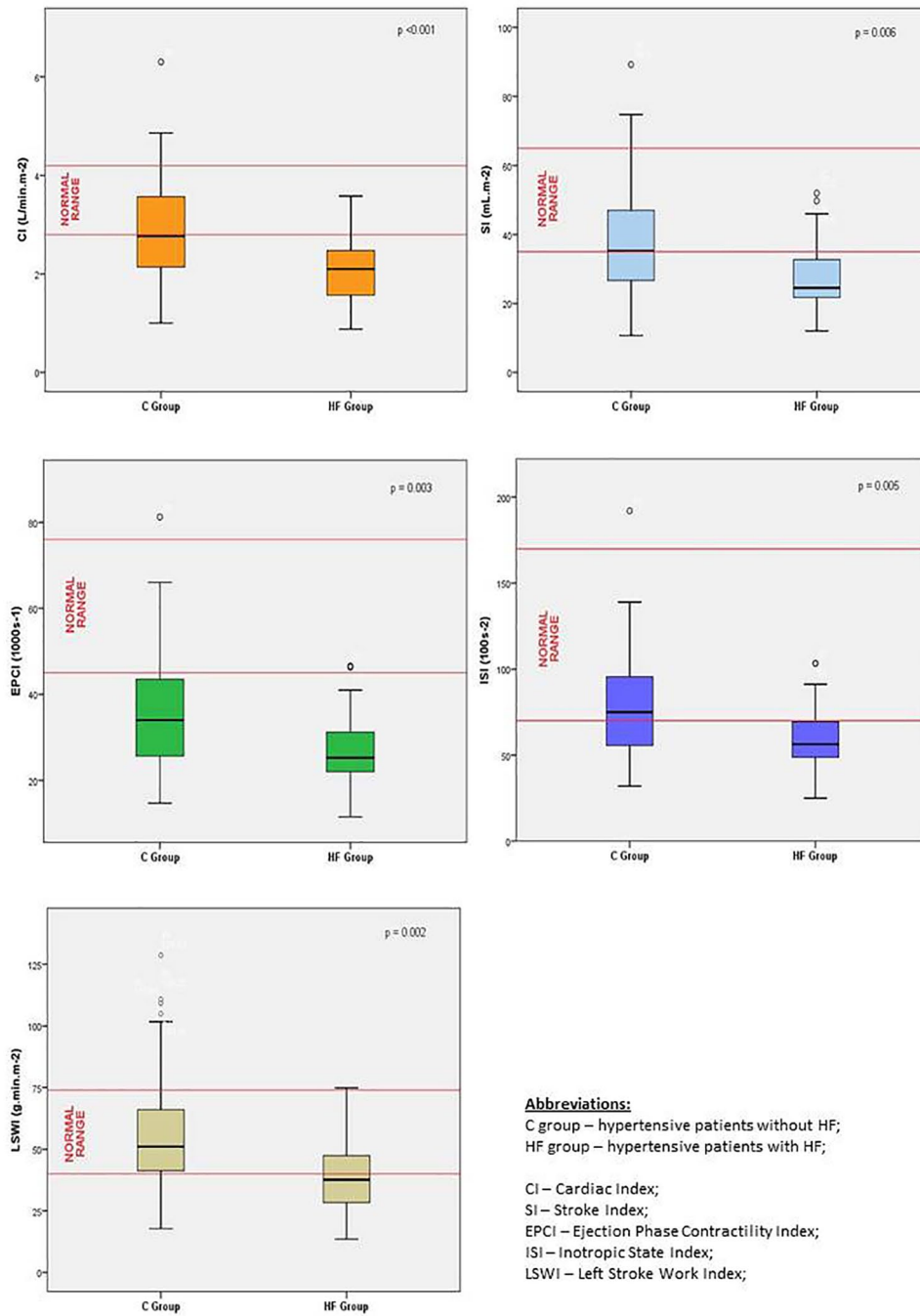
influenced mainly by inotropic agents, reflecting left ventricular pulse produced at the aortic valve opening. LSWI is the work that the heart spends in the time interval between two heartbeats, directly related to myocardial oxygen consumption. Because increased oxygen consumption occurs during isovolumic contraction and the rest during the ejection phase, LSWI is also related to myocardial contractility along with stroke mechanism.<sup>31</sup> Overall, these three variables briefly summarize the heart pump contractile ability.

Irrespective of the trigger that causes a functional loss of myocytes, HF is characterized during its evolution by a progressive inability of the pumping mechanism,<sup>18</sup> which is corroborated by the results obtained in this study.

#### Study limitations

The study included consecutive hypertensive outpatients for convenience reasons. This fact determined that there was some bias in the study group composition, the most relevant was the mean age difference between group C and the HF group.

Another aspect that should be highlighted as an important limitation is the inclusion of decreased and preserved ejection fraction (EF) HF patients in the same group because HF etiology is not the same and consequently hemodynamic



**Figure 2.** Hemodynamic differences between groups.

performance may not be similar. However, there is a considerable disease overlap in patients with HF, namely hypertension, CAD, chronic volume overload (valvular disease, cardiac shunts) and hypertrophic cardiomyopathy.

In addition, only patients with pathology were included (all patients have hypertension). The

authors' purpose was to determine the hemodynamic differences in a hypertensive population, with and without HF, isolating this variable. Therefore, in future studies, a control group of patients without disease should be included.

Antihypertensive therapy is a confounding factor that could not be eliminated from the study and

could have a major impact on the analysis of variables that reflect cardiac inotropy.

### Conclusion

This work intended to determine hemodynamic differences between hypertensive patients with and without HF, using the ICG method. In clinical practice, these variables are generally evaluated by echocardiography or invasively by pulmonary artery catheterization. Both methods require specific training, therefore, they are not available everywhere.

ICG appears to be a reliable, non-invasive and inexpensive method for determining hemodynamic parameters, which can be performed routinely in a medical office or at the patient bedside.

This study reported that hypertensive patients with HF presented significantly lower values of blood flow parameters (CI and SI), contractility (EPCI and ISI) and LSWI compared with hypertensive patients without HF. These results are in line with what would be expected because HF triggers a set of hemodynamic changes that can result in reduced blood flow and in a progressive inability of the heart to pump blood around the body.

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### Conflict of interest statement

The authors declare that there are no conflicts of interest.

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