

Vascular Doppler ultrasonographic indices in cirrhosis: a case–control study with emphasis on the common carotid arteries

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Received: 17 August 2014 / Accepted: 17 February 2015
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Abstract

Purpose To compare vascular Doppler waveform indices, particularly in the common carotid arteries, between cirrhotic and healthy subjects.

Materials and methods A total of 60 patients with Class-B cirrhosis and 60 healthy matched counterparts were enrolled in this prospective study. Vascular Doppler waveform parameters including resistance and/or pulsatility indices (RI and PI, respectively) were obtained from the common carotid, renal, celiac, superior mesenteric, femoral and brachial arteries.

Results Compared to patients, healthy subjects had significantly higher mean PI and RI obtained from the common carotid (1.53 ± 0.20 vs. 1.43 ± 0.14 , $p = 0.03$; 0.75 ± 0.02 vs. 0.72 ± 0.02 , $p < 0.001$, respectively) and celiac arteries (2.00 ± 0.36 vs. 1.81 ± 0.34 , $p = 0.03$; 0.80 ± 0.03 vs. 0.78 ± 0.02 , $p < 0.001$, respectively). Both the mean PI and RI derived from the renal arteries, in contrast, were significantly higher in patients compared to that in controls

(1.05 ± 0.13 vs. 1.11 ± 0.07 , $p = 0.03$; 0.59 ± 0.03 vs. 0.63 ± 0.03 , $p < 0.001$, respectively). The mean vascular impedance values obtained from the remaining arteries were comparable between the two groups.

Conclusions Blood flow increases in the common carotid and celiac arteries of Class-B cirrhotic patients with elevated renovascular impedance.

Keywords Hemodynamic change · Cirrhosis · Doppler ultrasound · Common carotid artery

Introduction

It is now over two decades that the hypothesis of ‘peripheral arterial vasodilation’ has been used to explain a hyperdynamic circulatory state in combination with renal dysfunction in cirrhosis [1].

The underlying vasodilation has been located generally in the splanchnic vascular bed that brings about compensatory vasoconstriction through renin–angiotensin interaction, sympathetic nervous system, and antidiuretic hormone. The natural outcome is sodium and water retention, intrarenal vasoconstriction, renal failure, and finally death [2].

Although a consensus exists among investigators with regard to the vasodilation in the splanchnic circulation of cirrhotic patients, reports on the remaining vascular beds are conflicting [2, 3], possibly due to recruiting patients with varying severities of the disease [2], or because of deficient methodologies [4].

Duplex Doppler examination is a noninvasive, valid, and reproducible technique for estimating vascular impedance and evaluating arterial blood flow; and has been widely used in cirrhotic patients with or without ascites [5]. The resistive

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and pulsatility indices (RI and PI, respectively) are known as reliable indicators of vascular blood flow in patients with cirrhosis [6]. Pulsatility index, in comparison with RI, is preferred because it is more sensitive in detecting waveform abnormalities; it is not affected by the angle between the direction of the Doppler beam and the blood vessel, yielding a high observer agreement; and it is along with small inter-observer variability in various vascular beds [4].

The carotid arteries are important principally by virtue of their major role in the brain blood supply and their contribution to hemodynamic stability on account of the presence of baroreceptors in the carotid sinuses [7].

To the best of the authors' knowledge, the hemodynamic status in the carotid arteries of cirrhotic patients has not been investigated in the literature.

This study sought to compare vascular Doppler waveform indices including those obtained from the common carotid arteries between cirrhotic and healthy subjects.

Materials and methods

Study design and participants

The ethics committee of the Tabriz University of Medical Sciences approved this study. A total of 60 patients with biopsy-proven, Class-B cirrhosis according to the Child–Turcotte–Pugh classification were enrolled in this prospective, cross-sectional, single-center study. Sixty age- and sex-matched healthy subjects served as the controls. Participants were recruited from a referral, teaching center (Imam Reza Teaching Hospital) from September 2012 through to April 2014. Informed written consents were obtained from participants.

The exclusion criteria were any cardiovascular disease, any renal/renovascular disease or abnormality, transplanted kidney, taking vasorelaxant/vasoconstrictor medication, smoking, and diabetes mellitus.

Doppler ultrasound examination

A single skilled sonologist specialized in Doppler ultrasonography of the vascular system with over 10 years of experience performed Doppler imaging using a standard ultrasound machine (Aloka Model Prosound 3500, Tokyo, Japan) equipped with a 7 MHz transducer.

At 9.00 AM, following overnight fasting and a 10-min resting in the supine position, each subject underwent bilateral color duplex examination of the celiac, superior mesenteric, brachial, common femoral, renal (main and intraparenchymal branches), and common carotid arteries (Fig. 1). At the time of imaging all subjects were hemodynamically stable and the heart rate was within normal

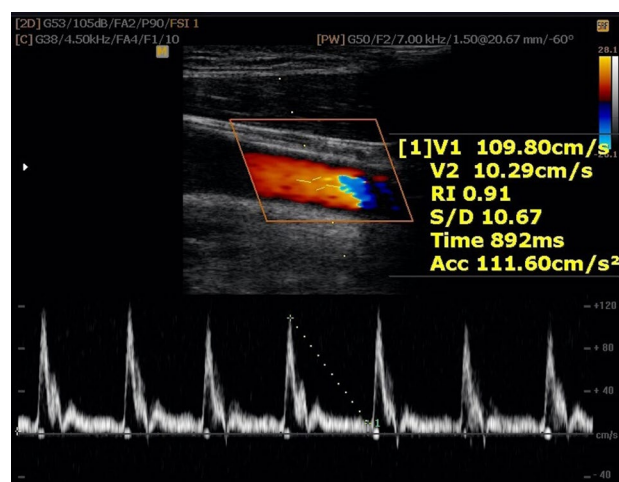


Fig. 1 Color duplex examination of the common carotid artery

range. Blood pressure and heart rate were assessed during Doppler ultrasound examination using an automatic sphygmomanometer.

The common carotid arteries were examined on both sides with the patient in the supine position and a slight extension of the neck away from the side under examination immediately after a normal expiration.

Following previously described methods [8], the same observer measured PI and RI values in the renal, celiac, and superior mesenteric arteries by Doppler ultrasonography. In the brachial and common femoral arteries only PI values were measured due to technical limitations.

To ensure maximum quality only waveforms with clear envelopes and stable signals were accepted. The sample volume cursor was placed in the middle of the diameter of the vessels.

Doppler ultrasound examinations were carried out bilaterally and the final result was averaged. On each side, the measurements were done in triplicate in the same session and averaged.

RI and PI were calculated automatically according to the following equations [8]:

$$RI = (\text{Maximum} - \text{minimum velocity}) / \text{maximum velocity}$$

$$PI = (\text{Maximum} - \text{minimum velocity}) / \text{mean velocity}$$

To ensure intra-observer agreement, data from three sets of all measurements in the same session were compared in 15 randomly selected patients. Accordingly, the mean difference was 0.02 for PI and 0.03 for RI values, with corresponding standard deviations of the difference of 0.001 and 0.002, respectively. The limits of agreements were within 5 % of the mean value.

Tense ascites was present in one patient. Due to difficulty in obtaining accurate results from the splanchnic

arteries, Doppler ultrasonography was performed after paracentesis in this patient.

Serum albumin less than 3.5 g/dL was considered hypoalbuminemia. Malnutrition was investigated using previously established criteria [9].

Sample size calculation and statistics

At a significant level of 5 %, the power of 90 %, and a standard deviation of 0.07 for PI of the renal arteries in cirrhotic patients [10], at least 41 patients were required in each wing to detect at least 0.05 difference between the groups. This number was augmented to 60 patients in each group to allow for any possible drop out or technical difficulty.

Analysis of data was performed with the SPSS for Windows V 16.0 (SPSS Inc., IL, USA). Based on the results of the Shapiro–Wilk *W* test and the quantile–quantile plot (Q–Q plot), all quantitative data were distributed normally. Statistical methods included Chi square test, independent-samples *t* test, and one-way ANOVA along with an appropriate post hoc test (Tukey’s). Correlations were examined using Pearson’s *r*. *p* < 0.05 were considered statistically significant.

Results

Demographic data of the two study groups are set out in Table 1. They were comparable in this regard. Ascites was present in 26 cirrhotic patients (43.3 %).

Mean PI and RI values obtained from different arteries are compared between patients and controls, as well as between controls and patients with and without ascites in Table 2.

Controls versus patients

The mean PI and RI in both the celiac and carotid arteries were significantly higher in the healthy group compared

with those of cirrhotic patients. In contrast, both mean PI and RI in the renal arteries were significantly higher in patients than in controls. The mean PI and RI in the other arteries did not differ significantly between the two groups (Table 2).

Controls versus patients with and without ascites

Based on the results of one-way ANOVA, significant differences were found between the three groups of healthy subjects, patients with ascites, and patients without ascites for the mean PI and RI in the celiac, renal, and carotid arteries (Table 2).

The mean PI in the celiac artery was significantly lower in patients with ascites compared with that in controls (Tukey post hoc *p* = 0.03). Paired comparisons between controls and patients without ascites, and between the two groups of patients with and without ascites, however, did not show significant differences (Tukey post hoc *p* = 0.55 and 0.28, respectively). In contrast, the mean RI in the celiac artery was significantly lower in both patient groups with and without ascites in comparison with that in controls (Tukey post hoc *p* = 0.04 and 0.02, respectively). The two groups of patients were comparable in this regard (Tukey post hoc *p* = 0.99).

In the renal artery, the mean RI was significantly higher in patients with or without ascites in comparison with that in controls (Tukey post hoc *p* < 0.001 for both).

In the carotid artery, both the mean PI and RI were significantly higher in controls compared with those in patients with and without ascites (Tukey post hoc *p* = 0.003 and 0.001, respectively). Patients with and without ascites were comparable in this regard (Tukey post hoc *p* = 0.97).

Correlations between PI and RI values in the carotid and other examined arteries are summarized in Table 3 individually for patients and controls. No significant correlation was documented.

Table 1 Demographic information of study groups

Variable	Healthy subjects (<i>n</i> = 60)	Patients			<i>p</i> value ¹	<i>p</i> value ²
		Total (<i>n</i> = 60)	With ascites (<i>n</i> = 26)	Without ascites (<i>n</i> = 34)		
Age (years)	36.37 ± 6.74 (23–47)	35.03 ± 7.06 (22–48)	33.69 ± 8.63 (22–48)	36.06 ± 5.65 (27–45)	0.46	0.50
Gender						
Male	30 (50)	32 (53.3)	10 (38.5)	22 (64.7)	0.72	0.12
Female	30 (50)	28 (46.7)	16 (61.5)	12 (35.3)		

Data are shown as mean ± standard deviation (min–max) or frequency (%)

¹ *p* value: healthy subjects vs. patients (independent samples *t* test for age; Chi square test for gender)

² *p* value: healthy subjects vs. patients with ascites vs. patients without ascites (one-way ANOVA for age, Chi square test for gender)

Table 2 Mean pulsatility and resistive index (PI and RI) values in different arteries of study groups

Artery	Index	Healthy subjects (<i>n</i> = 60)	Patients			<i>p</i> value ¹	<i>p</i> value ²
			Total (<i>n</i> = 60)	With ascites (<i>n</i> = 26)	Without ascites (<i>n</i> = 34)		
Celiac	PI	2.00 ± 0.36 (1.29–2.77)	1.81 ± 0.34 (1.17–2.41)	1.70 ± 0.33 (1.17–2.13)	1.89 ± 0.33 (1.18–2.41)	0.03*	0.03*
	RI	0.80 ± 0.03 (0.73–0.86)	0.78 ± 0.02 (0.73–0.82)	0.78 ± 0.02 (0.74–0.80)	0.78 ± 0.03 (0.73–0.82)	<0.001*	0.01*
Superior mes- enteric	PI	2.20 ± 0.27 (1.49–2.57)	2.25 ± 0.24 (1.81–2.63)	2.25 ± 0.24 (1.81–2.63)	2.25 ± 0.25 (1.86–2.61)	0.44	0.75
	RI	0.81 ± 0.02 (0.76–0.84)	0.82 ± 0.03 (0.77–0.86)	0.82 ± 0.03 (0.78–0.86)	0.82 ± 0.03 (0.77–0.86)	0.10	0.26
Renal	PI	1.05 ± 0.13 (0.92–1.43)	1.11 ± 0.07 (0.99–1.21)	1.12 ± 0.06 (1.02–1.21)	1.10 ± 0.07 (0.99–1.21)	0.03*	0.07
	RI	0.59 ± 0.03 (0.55–0.67)	0.63 ± 0.03 (0.58–0.68)	0.64 ± 0.03 (0.58–0.67)	0.63 ± 0.03 (0.58–0.68)	<0.001*	<0.001*
Femoral	PI	4.91 ± 0.82 (3.56–7.45)	4.72 ± 0.53 (3.82–5.73)	4.73 ± 0.54 (4.00–5.63)	4.72 ± 0.55 (3.82–5.73)	0.31	0.60
Brachial	PI	4.06 ± 0.64 (3.03–5.34)	3.98 ± 0.45 (3.07–4.88)	3.78 ± 0.38 (3.07–4.28)	4.13 ± 0.45 (3.41–4.88)	0.59	0.20
Carotid	PI	1.53 ± 0.20 (1.22–1.89)	1.43 ± 0.14 (1.21–1.87)	1.45 ± 0.14 (1.32–1.87)	1.41 ± 0.14 (1.21–1.71)	0.03*	0.05*
	RI	0.75 ± 0.02 (0.69–0.79)	0.72 ± 0.02 (0.69–0.78)	0.72 ± 0.03 (0.69–0.78)	0.72 ± 0.02 (0.69–0.75)	<0.001*	<0.001*

Data are shown as mean ± standard deviation (min–max)

* *p* value <0.05 is statistically significant

¹ *p* value: healthy subjects vs. patients (independent samples *t* test)

² *p* value: healthy subjects vs. patients with ascites vs. patients without ascites (one-way ANOVA)

Table 3 Correlations between pulsatility and resistive index (PI and RI) in the carotid and other arteries in cirrhotic and healthy subjects

Index (carotid artery)	Celiac		SMA		Renal		Femoral	Brachial
	PI	RI	PI	RI	PI	RI	PI	PI
PI-patients								
Pearson's <i>r</i>	−0.44	−0.16	0.28	0.15	0.02	0.14	0.43	0.02
<i>p</i> value	0.11	0.39	0.13	0.43	0.91	0.46	0.12	0.91
RI-patients								
Pearson's <i>r</i>	−0.05	−0.04	0.46	0.20	0.12	0.31	0.26	0.29
<i>p</i> value	0.78	0.84	0.21	0.29	0.51	0.10	0.17	0.13
PI-controls								
Pearson's <i>r</i>	0.32	0.37	0.47	0.28	0.02	−0.09	0.16	0.07
<i>p</i> value	0.09	0.15	0.11	0.13	0.93	0.63	0.39	0.72
RI-controls								
Pearson's <i>r</i>	0.19	0.38	0.29	0.08	0.11	−0.15	−0.03	0.29
<i>p</i> value	0.33	0.14	0.12	0.68	0.56	0.44	0.87	0.13

SMA superior mesenteric artery

Patients with and without malnutrition/hypoalbuminemia

Malnutrition/hypoalbuminemia was present in 31 cirrhotic patients (51.7%). The mean PI and RI values are compared between patients with and without malnutrition/hypoalbuminemia in Table 4. Accordingly, no significant difference was found between the two groups.

Discussion

Many previous studies have shown hemodynamic changes in patients with cirrhosis, including peripheral arterial

vasodilation and vasoconstriction in the renal circulation [4, 10–13].

In agreement with these reports, the mean PI and RI in the celiac artery were significantly higher in our healthy subjects as compared with those in cirrhotic patients. Similar comparison in the superior mesenteric arteries, however, did not show a significant difference between patients and controls. The latter comparable results between the two groups could be explained by the fact that the measurements were performed in fasting state. Iwao et al. [4] compared the mean PI and RI in the superior mesenteric artery in fasting state and after a meal and found that the Doppler indices decreased significantly in nonfasting state.

Table 4 Mean pulsatility and resistive index (PI and RI) values in cirrhotic patients with and without malnutrition/hypoalbuminemia

Artery	Index	Malnutrition/hypoalbuminemia		<i>p</i> value
		Yes (<i>n</i> = 31)	No (<i>n</i> = 29)	
Celiac	PI	1.79 ± 0.31	1.82 ± 0.28	0.28
	RI	0.78 ± 0.01	0.78 ± 0.02	0.67
Superior mesenteric	PI	2.21 ± 0.21	2.25 ± 0.27	0.34
	RI	0.82 ± 0.02	0.82 ± 0.03	0.89
Renal	PI	1.11 ± 0.04	1.11 ± 0.09	0.87
	RI	0.63 ± 0.02	0.64 ± 0.03	0.45
Femoral	PI	4.71 ± 0.57	4.73 ± 0.35	0.55
Brachial	PI	3.97 ± 0.78	4.10 ± 0.25	0.35
Carotid	PI	1.43 ± 0.13	1.39 ± 0.12	0.29
	RI	0.72 ± 0.01	0.72 ± 0.01	0.88

Data are shown as mean ± standard deviation

The mechanism(s) of splanchnic vasodilation in cirrhosis is not fully understood. Excessive synthesis and release of local vasodilating factors such as nitric oxide, calcitonin-gene related peptide, endogenous cannabinoids, adrenomedullin, and carbon monoxide; the presence of an extensive systemic or portosystemic collaterals; and a poor liver function all have been implicated [2].

Some authors believe that high diastolic velocities in the splenic arteries take place as an adoptive response to abnormally hypokinetic venous flow in portal hypertension [14]. Due to portal hypertension, splanchnic vascular resistance progressively decreases because of arteriolar vasodilatation or translocation of intestinal bacteria and/or their vasoactive products such as carbon monoxide and nitric oxide [2]. When the disease is compensated, plasma volume and cardiac output increase to maintain the effective arterial volume and the arterial pressure. In advanced disease, however, the splanchnic vasodilatation is pronounced and both the effective arterial volume and the arterial pressure are diminished. At this stage, major endogenous vasoconstricting and sodium-retaining systems such as the renin–angiotensin–aldosterone system, the sympathetic nervous system and antidiuretic hormone (ADH) become activated and consequent renal vasoconstriction and sodium and fluid retention develop [15].

Despite the presence of a partial consensus on hemodynamic changes in the splanchnic vasculature, reports regarding the status of blood flow in the extremities of cirrhotic patients are conflicting [16]. In a study on 12 healthy subjects, 12 patients with compensated cirrhosis, and 35 patients with both cirrhosis and ascites, Maroto et al. [17] showed that the arteriolar vasodilation responsible for hyperdynamic circulation in cirrhosis does not occur in brachial and femoral vascular territories. In contrast,

Iwao et al. [13] showed an increased femoral artery vascular tone in patients with advanced cirrhosis in comparison with those who had less advanced disease. In another study by Cazzaniga et al. [12] flow-mediated dilation was determined in 32 cirrhotic patients and 12 controls. They demonstrated an enhanced shear stress-induced peripheral vasodilation in patients with cirrhosis.

We did not find a significant difference between the two groups with and without cirrhosis for the mean PI values in either the brachial or femoral arteries. It has been suggested that arterial vasodilation in peripheral vessels such as the brachial and femoral arteries cannot be induced under resting conditions unless a physiological stimulus of shear stress is instigated [12]. Concomitant renal failure [18] and different classes of cirrhosis [13] may also contribute to this heterogeneity.

Hepatorenal syndrome, which is the development of renal failure in the absence of any identifiable causes of renal pathology, is a frequent finding in patients with advanced cirrhosis with an estimated frequency of 40 % [19]. This syndrome with extremely constricted renal vasculature, significant reduction of renal blood flow and diminished glomerular filtration rate (GFR) is the most severe complication of cirrhosis [2]. It is along with low arterial pressure, significant sodium and water retention, high blood level of renin, antidiuretic hormone, and norepinephrine, and elevated renal vascular resistance [20]. It is thought that the hepatorenal syndrome takes place because of vasoconstriction of the renal circulation, which is a compensatory physiologic response to intense systemic arteriolar vasodilatation secondary to splanchnic pooling of blood [10, 19, 21, 22]. In other words and briefly, this syndrome is a consequence of disturbances in the systemic activation of vasoconstrictors and the local synthesis of vasodilators [23].

Renal Doppler of interlobar arteries has been found as an accurate, noninvasive method for detecting renal hemodynamic disturbances in cirrhotic patients at very early stages, even when clinical manifestations are not emerged [24]. According to available data, cirrhotic patients have considerably higher renal RI and PI compared with their healthy counterparts [2, 10, 22, 25, 26]. A direct connection between renovascular impedance and the severity of cirrhosis, refractory ascites and mortality has been also reported [10, 24].

In line with previous reports, the mean renal PI and RI were significantly higher in our cirrhotic patients compared with those in the control group.

At initial stages of the disease, vasoconstriction in efferent arteries causes decrease in renal blood flow, which is more striking than the fall in GFR. This condition leads to an increase in filtration fraction and alterations of oncotic and hydrostatic forces in the peritubular capillaries.

Prostaglandins, nitric oxide, kinins, and natriuretic peptides are the main intrarenal vasodilators that contribute to maintain renal blood flow and activation of the main vasoactive systems in cirrhotic patients [27]. A physiological homeostatic response to vascular underfilling causes increase in renal vascular RI in cirrhosis. A direct correlation has been found between the renal arterial constriction and the renal arterial resistance obtained by Doppler ultrasonography [28]. When the underfilling is not severe, the kidneys increase their synthesis of vasoactive agents that effectively counteracts renal vasoactive substances. In more intense cases, however, the endogenous vasoconstrictor systems are activated and renal vasoconstriction ensues [29]. In addition to renal vasoconstriction, concomitant interstitial nephritis or vacuities particularly in those with cirrhosis secondary to infectious etiologies [30], and destruction of renal vessels, which is evident in hepatorenal syndrome, may also underlie renal pathogenesis in cirrhosis [25].

To the best of the authors' knowledge there is no Doppler ultrasonographic study on the carotid arteries in cirrhosis. Hemodynamic changes in the carotid arteries are of critical importance from two aspects: (1) the carotid arteries are main blood suppliers to the brain; and (2) the most important arterial baroreceptors are located in the carotid sinus at the bifurcation of external and internal carotids [31].

The mean carotid PI and RI were significantly lower in our cirrhotic patients than in healthy controls. An inverse, albeit insignificant, correlation between these parameters and PI and RI in the celiac arteries, as well as an observation of insignificant correlations between PI and RI in the carotid arteries and renovascular impedance may indicate that the baroreceptors are intact in the carotid sinuses [32, 33] and they act independent of renal regulation at least in our class of patients.

In line with previous reports [2, 11, 18], we found significant differences between cirrhotic patients with and without ascites in terms of vascular impedance values in the renal, celiac and carotid arteries. It is thought that the effect of ascites on hemodynamic changes in cirrhotic patients is for the most part mechanical [34, 35], i.e. the presence of tense ascites is more likely along with hemodynamic compromise in patients with cirrhosis.

Some limitations of the present study should be acknowledged here. Despite an acceptable intra-observer agreement, the presence of only one observer might be regarded as a limitation in this work. According to previous data, however, inter-observer variability of PI and RI measurements in various vascular beds in cirrhosis is small, especially when the observer is experienced [36].

While some studies have found good correlations between Child class and renal hemodynamic changes in cirrhotic patients [28, 37], such associations with other splanchnic and extrasplanchnic vascular hemodynamics

are probably different [13]. To overcome this heterogeneity and owing to shortcomings in dealing with some patients, particularly those with more advanced disease (i.e. Class C cirrhosis), we decided to recruit only patients with intermediate severity of the disease (i.e. Class B cirrhosis). To draw a solid conclusion in this regard, however, future studies including Class A and C patients are recommended.

While hemodynamic changes in cirrhotic patients might be of great prognostic value [38], the common carotid artery, as a major central trunk with consequential clinical influences in the body [39, 40], has not been adequately examined in this regard. Although investigation of such clinical contributions was out of the scope of the present study, our findings could pave the way for relevant researches in the future.

Finally, hemodynamic status in the venous districts has been attributed to physiopathology of arterial hemodynamic changes [2]. Due to the nature of the present study, however, we did not include venous hemodynamics in this investigation. Further studies are recommended in this regard.

In summary, this study, for the first time in the literature, showed that patients with Class-B cirrhosis have increased blood flow in the common carotid arteries.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards Research involving human participants and/or animals: 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.

Informed consent Informed consent was obtained from all individual participants included in the study.

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