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Post-operative wall shear stress in the superior mesenteric artery: Biomarker of long term outcome in patients with residual disease after incomplete cytoreductive surgery for pseudomyxoma peritonei

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ABSTRACT

Background: After incomplete cytoreductive surgery (CRS), the assessment of pseudomyxoma peritonei (PMP) progression remains challenging. The objective was to assess the efficacy of wall shear stress (WSS) measured in superior mesenteric artery (SMA) to predict PMP progression in the postoperative setting to propose additional treatments.

Methods: In a prospective study, 52 patients with PMP had Doppler-ultrasound examination of the SMA with WSS calculation within one year after CRS with a mean follow-up of 43.3 ± 18.3 months. Patients were categorized according to the completeness of CRS and clinical outcome: Group-1 (n = 19): complete CRS and no recurrence, group-2 (n = 20): incomplete CRS with slowly progressive disease (alive at 2 years without severe clinical symptoms), group-3 (n = 13): incomplete CRS and severe clinical symptoms or dead within two years. Results of WSS were compared between groups and to 24 healthy subjects.

Results: WSS measured in the SMA was superior in Group-3 (19.6 ± 8.2 dynes/cm^2) than in Group-2 (9.2 ± 1.8 dynes/cm^2, $p = 1.10^{-6}$), Group-1 (10.4 ± 2.8 dynes/cm^2, $p = 8.10^{-5}$), and healthy patients (8.7 ± 2.8 dynes/cm^2, $p = 9.10^{-7}$). One year after surgery, among patients with incomplete CRS a cut-off value of 12.1dynes/cm^2 allowed distinguishing patients without from those with severe disease progression with a sensitivity of 100% and a specificity of 100% ($p < 1.10^{-4}$) AUC = 1.000 [95%CI: 0.897 −1.000].

Conclusion: Post-operative assessment of the WSS in the SMA in patients with incomplete CRS for PMP should be considered as biomarker of tumor progression in the postoperative setting. Therefore, WSS could be useful to target patients needing adjuvant systemic chemotherapy one year after CRS.

Introduction

Pseudomyxoma peritonei (PMP) is a rare peritoneal tumor characterized by intra-abdominal mucinous ascites with a low cellularity but a sustained tumor angiogenesis [1–3]. Thus, PMP is responsible of a consistent and permanent increase of the blood flow volume (BFVol) and blood flow velocity (BFVel) in the superior mesenteric artery (SMA) [4,5]. Curative treatment combines complete cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) [6]. In case of incomplete CRS with macroscopic residual disease, treatment strategy is debated. Some patients have an aggressive disease with early recurrence of symptoms including abdominal pain and malnutrition, and should require systemic treatment. Other patients experience a non-progressive disease with a good quality of life and limited symptoms that are managed with a "wait and see" strategy. In our practice, we propose a systemic chemotherapy in case of high grade

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PMP, if recurrence, and, conversely, a "watchful waiting" strategy in case of low grade PMP even if extended residual disease with altered general status. To the best of our knowledge, no prognosis factor is effective and disease progression remains difficult to predict [1,2]. Thus, predictive factors are urgently needed in order to propose a personalized strategy, adapted to the patient and to the disease.

It has been demonstrated that tumor angiogenesis results in a drop in vascular impedance and induces strong upstream hemodynamic modifications [4,5,7,8]. Consequently, changes in BFVol and BFVel in the SMA have been previously suggested as a biomarker of disease progression in PMP [4,5]. In patients with PMP, it has been demonstrated that BFVol measured in the SMA one year after surgery is able to predict tumor progression [4].

Increases in metabolic needs result in a transient increase of the BFVol, BFVel and wall shear stress (WSS) that stimulates endothelium derived nitric oxide (NO) production [9]. As it happens in the native conduit artery supplying an organ with permanent augmentation of the metabolic needs, the continuous up-regulation of the endothelial NO synthase is responsible for long-term structural arterial remodeling [10,11]. This arterial remodeling consists in permanent arterial diameter enlargement, wall thickening, and fibrosis [10,12–14]. More precisely, arterial remodeling aims to reestablish baseline mechanical conditions, particularly the WSS [15–17].

Here, we hypothesized that microvascular angiogenesis in PMP exposes the SMA to continuous elevated BFVol, BFVels and WSS which could consecutively initiate arterial remodeling. It has been demonstrated even in atherosclerosis and hypertension that arterial remodeling evolves over a relatively long time-course (over few months in humans) [18]. Periods of growth of the PMP vascular network would lead to lasting elevated BFVols and submit the feeding arteries to transient periods of arterial remodeling. Thus, imbalance between arterial inflow and downstream microvascular network expansion would result in increased WSS. Conversely, during periods of stability or PMP remission, achievement of arterial remodeling processes with SMA inner diameter enlargement would lead to the normalization of the BFVel and WSS although BFVol remains elevated.

WSS measured in the afferent arteries of superficial arteriovenous malformations (sAVM) has been previously demonstrated as a simple reliable criterion to distinguish progressive from stable sAVM. WSS should be considered to monitor patients with facial sAVM and to guide the therapeutic strategy [19]. The objective of this study was to assess the efficacy of WSS measured in the SMA using Doppler ultrasound to predict PMP progression in the post-operative setting.

Patients and methods

The institutional review board (IRB) approved the study (ID GRIVIL 09-11-016), all patients gave their informed consent. All patients had a peritoneal exploration and determination of the peritoneal carcinomatosis index (PCI) during a CRS. The completeness of CRS determined the decision to perform HIPEC [20–24]. All patients had a pathological analysis with an evaluation of the tumor grade according to the WHO classification [1]. Doppler ultrasound was performed in the SMA 16.3 ± 5.7 months [min-max: 7.6–24.8 months] after CRS (±HIPEC), with a mean follow-up of 43.3 ± 18.3 months [min-max: 9.6–53.9 months] after surgery. All patients had serum tumor markers measurements of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) at the same time of Doppler Ultrasound. The use of post-operative systemic chemotherapy or bevacizumab was noticed in Table 1; this use was not driven by the Doppler ultrasound findings and the clinical practitioner or the surgeon was blind of these findings.

Patients were distributed into 3 groups according to their clinical outcome. Completeness of resection was graded according to Sugarbaker's complete cytoreduction (CCR) score as follows: CCR0: no residual tumor; CCR1: residual tumor < 0.25 cm; CCR2: residual tumor between 0.25 and 2.5 cm; CCR3: residual tumor > 2.5 cm

Table 1
Patients' characteristics.

	Controls (n = 24)	Group-1 (CCR0-1, stable) (n = 19)	Group-2 (CCR2-3, stable) (n = 20)	Group-3 (CCR2-3, progression) (n = 13)	X^2 test p value	One-way ANOVA (between Cont., G1, G2, G3 or between G1, G2, G3)
Age (years)						
Mean	43	57	64 *	65 **		p < 0.001
(SD)	(13)	(14)	(8)	(12)		
[range]	[22–69]	[33–78]	[52–73]	[46–87]		
Gender [Patients (n)]						
Women	10	13	3	9	0.091	–
Men	14	6	17	3		
PCI [Patients (n)]						
Mean	–	18	35 †	29		0.002
(SD)		9	5	4		
[range]		[1–27]	[30–39]	[24–36]		
Grade [Patients (n)]						
Low	–	16	6	7	0.182	–
High		3	2	6		
Delay between diagnosis and surgery (years)						
Mean	–	3.1	1.0	1.4		0.291
(SD)		(4.6)	(1.4)	(1.5)		
[range]		[0.1–10.1]	[0.2–4.2]	[0.1–3.3]		
Post-operative chemo therapy [Patients (n)]						
yes	–	0	2	2	0.088	–
no		0	0	0		
Post-operative bevacizumab [Patients (n)]						
yes	–	0	1	1	0.516	–
no		0	0	0		

Note. *SD* standard deviation, *PCI* Peritoneal Cancer Index at surgery, *CCR* complete cytoreduction score; *p < 0.005, **p < 0.001: *vs* controls; †p < 0.005: *vs* group-1; -: NA.

[23]. Group-1 (n = 19): patients with complete resection (CCR0) and HIPEC without any recurrence within three years after surgery; Group-2 (n = 20): patients with incomplete resection (CCR1, CCR2 or CCR3 score) and slowly progressive disease: alive 3 years after surgery or at last during follow-up without progression of the disease (i.e. progression-free). Group-3 (n = 13) included patients with incomplete resection (CCR1, CCR2 or CCR3 score) with active progressive disease. Progression was defined as follows: clinically, patients with active progression had performans status>1 or were dead related to the disease within 3 years after surgery, whereas patients with slow progression were alive 3 years after surgery or at last during follow-up without progression of the disease (i.e. progression-free) with a performans status ≤1. Carcinoembryonic antigen or carbohydrate antigen 19-9 elevation was considered as biological criteria of progression or recurrence. The onset of new mucinous deposit on cross-sectional imaging (magnetic resonance imaging or computed tomography) within 6 months was considered as a recurrence or active progression. Patients' characteristics are reported in Table 1. The cohort of patients was partly previously described in a study aiming to determine the modifications of the BFVols in the SMA (30/52 patients; 57%) [4].

Doppler Ultrasound

Ultrasonographers were blind to past history, clinical and radiological examinations of all patients and inversely the clinical practitioner or the surgeon and the radiologist were blind from the results of the Doppler Ultrasound.

Method of measurement of Doppler ultrasound values have been previously published [4,7,8,25]. Briefly, Doppler-US was performed after an overnight fast at rest in patients in semi-seating or seating position to minimize the gas interposition between the US probe and the SMA. SMA inner diameter measurements were performed using M-mode with an echograph ACUSON S2000 (Siemens, Erlangen, Germany) equipped with a curvilinear transducer type CH4-1 (3.5 MHz). Spatial-average-time-average (Mean-BFVel) velocity was measured from the spectral analysis of the Doppler blood flow velocity waveforms. The Mean-BFVel is the computed-derived value calculated by integrating the area under instantaneous mean velocity. Indeed, blood flow velocity profile is parabolic in peripheral vessels, thus total displacement of blood is represented by the displacement of all the layers of blood on the arterial section. The Mean-BFVel is representative of the blood displacement over the whole arterial section and per time's unit.

BFVol must be calculated with Mean-BFVel following the formula:

$$BFVol = \pi . r^2 . \text{Mean-BFVel}.60$$

where BFVol is the blood volume in mL/min, Mean-BFVel is the spatial-averaged-time-averaged mean blood flow velocity in cm/s, and r the radius of the artery in cm. Each measurement was taken in triplicate during quiet respiration and averaged.

Wall Shear stress is calculated following the formula:

$$\tau = 4.\mu.BFVol/\pi.r^3 \text{ or } \tau = 8.\mu.\text{Mean-BFVel}/d$$

where τ is the WSS in dynes/cm^2, μ is the blood viscosity in poise (P), mean BFVel is the spatial-averaged-time-averaged BFVel (cm/s), d is the diameter (cm). In conduit arteries, blood acts like a Newtonian fluid and a value of 0.035 P for viscosity can be used to calculate the WSS; normal value for WSS ranges around 8–10 in conduit arteries to 50 dynes/cm^2 in the arterioles [26]. Doppler ultrasound was considered as representative of vascular network modifications of the disease only if performed during the previous 6 months before disease progression. Healthy adults (n = 24) were enrolled as controls.

Previously to this work, the repeatability of measurements was investigated in 24 control subjects for intra-observer and in 10 controls for inter-observer repeatability. In each case, two series of paired measurements (mBFVelocities and WSS) separated by a 30 min interval were recorded by one experienced and two new trained (6 months) practitioners used to explore sAVM patients. The repeatability coefficient (RC) was calculated as defined by the British Standard Institution [27], *i.e.* according to the formula $RC^2 = \Sigma Di^2/N$, where Di is the relative (positive or negative) differences within each pair of measures, N the sample. This coefficient is the standard deviation of the estimated difference between two repeated measurements. The intra-observer RC values were 1.5 cm/s for the mBFVels and 0.02 mm for the SMA inner diameter. The inter-observer RC values were 1.7 cm/s and 0.03 mm respectively for the mBFVels and the SMA inner diameter. All differences exhibited by the different parameters between the different groups of patients were largely superior to their corresponding RC values.

Great care must be taken into the choice of the US Doppler device used for mean blood flow velocities measurements. Some devices calculate the mBFVelocity from raw data with accuracy, others from post-treatment analysis of the recorded spectral Doppler waveforms with unacceptable variations due to the level of setting of the trace sensitivity.

Statistics

Continuous variables are reported as mean ± standard-deviation (SD), and range: [min-max]. The Gaussian distribution of the continuous variables was assessed using the D'Agostino-Pearson test, particularly the WSS values in all patients' groups. Categorical data were analyzed using the Chi-squared test when appropriate. Continuous variables (arterial diameters, BFVel, BFVol and WSS) were analyzed with a one-way ANOVA according to the score of surgery (CCR0 or CCR1-3) and stability or recurrence/progression of the disease. In both cases, when ANOVA was significant, differences between groups were evaluated with post-hoc Student-Newman-Keuls and unpaired Student t-test. In all case, power of the tests were verified and considered as significant when >80% (http://www.anastats.fr, ANASTATS, Rilly Sur Vienne, France) [28].

A receiver operating characteristics (ROC) curve of Doppler measurements was built and cut-off values were calculated to discriminate: between patients who had severe active progressive disease (Group-3) from those with slowly progressive disease (Group-2). Sensitivity, specificity and areas under curves (AUC) with their 95% confidence intervals (95%CI) were calculated. Cut-off for WSS values was computed. (MedCalc® Statistical Software version 18.2.1, MedCalc Software bvba, Ostend, Belgium). Only P values < 0.05 were considered significant [29].

Results

Results of Doppler ultrasound findings are reported in Table 2.

BFVol was increased in patients with residual PMP one year after CRS in Group-2 and -3 due to the presence of a downstream abnormal vascular network and to the increase in metabolic demand. BFVol was higher in Group-3 (615 ± 194 mL/min) than in Group-2 (414 ± 161 mL/min, $p = 2.6.10^{-3}$), Group-1 (270 ± 107 mL/min, $p = 3.10^{-7}$) and healthy volunteers (232 ± 50 mL/min, $p = 9.10^{-11}$). BFVol was higher in Group-2 than in Group-1 ($p = 1.2.10^{-3}$) and healthy volunteers ($p = 2.10^{-6}$, Fig. 1A). One year after surgery, among patients with incomplete CRS a cut-off value of 433 mL/min allowed to distinguish patients without from those with severe disease progression with a sensitivity of 83.3%

Table 2
Doppler ultrasonography and laboratory findings.

	Controls (n = 24)	Group-1 CCR0 stable (n = 19)	Group-2 CCR1-3 stable (n = 20)	Group-3 CCR1-3, progression (n = 13)	One-way ANOVA (between Cont., G1, G2, G3 or between G1, G2, G3)
SMA Diameter (cm)					
Mean	0.54	0.53	0.64 **, ††	0.57 #	p < 0.001
(SD)	(0.06)	(0.09)	(0.06)	(0.08)	
[range]	[0.41–0.66]	[0.41–0.66]	[0.49–0.76]	[0.49–0.72]	
SMA BFVel (cm/s)					
Mean	16.9	19.3	20.7	38.6 **, †† ##	p < 0.001
(SD)	(4.8)	(4.1)	(4.9)	(13.3)	
[range]	[9.5–25.6]	[9.9–24.2]	[8.5–29.2]	[22.7–65.9]	
SMA BFVol (mL/min)					
Mean	232	270	414 **	615**, † #	p < 0.001
(SD)	(50)	(107)	(161)	(194)	
[range]	[125–309]	[150–474]	[165–763]	[375–1035]	
SMA WSS (dynes/cm^2)					
Mean	8.7	10.4	9.2	19.6 **, †† ##	p < 0.001
(SD)	(2.8)	(2.8)	(1.8)	(8.2)	
[range]	[5.0–13.3]	[4.3–16.5]	[5.7–12.1]	[12.4–37.4]	
Delay Surgery/Doppler-US (years)					
Mean	–	1.2	1.3	1.4	p = 0.448
(SD)		(0.5)	(0.5)	(0.7)	
[range]		[0.6–2.0]	[0.7–2.0]	[0.7–2.8]	
Delay Surgery/recurrence or progression (years)					
Mean	–	–	–	1.6	–
(SD)				(1.2)	
[range]				[0.6–3.9]	
Time delay of follow-up after surgery (years)					
Mean	–	4.5	2.8	2.4 *	p = 0.003
(SD)		(1.5)	(1.0)	(1.2)	
[range]		[1.1–6.6]	[0.8–3.8]	[1.1–4.5]	
CEA (μg/l)					
Mean	–	5.0	52.6	93.9	p = 0.199
(SD)		(5.5)	(113.5)	(162.1)	
[range]		[0.5–17.0]	[2.4–450.0]	[4.0–600.0]	
CA19-9 (μg/l)					
	–	7.6	370.5	341.3	p = 0.268
		(5.3)	(3054.0)	(300.6)	
		[2.0–20.0]	[0.6–3054.0]	[0.6–900.0]	

Note. *SD* standard deviation, *SMA* superior mesenteric artery, BFVel mean blood flow velocity, *BFVol* blood flow volume, WSS wall shear stress, CEA carcinoembryonic antigen, **p < 0.001: *vs* controls; †: p < 0.005, ††: p < 0.001: CCR0 vs CCR1-3, #p < 0.005, ##P < 0.001: group-3 vs group-2.

and a specificity of 66.7%, ($p = 5.10^{-4}$), AUC = 0.782 [95%CI: 0.604–0.906].

SMA inner diameter was adapted only in Group-2 to the increased BFVol . SMA inner diameter was superior in Group-2 (0.64 ± 0.06 cm), than in Group-3 (0.57 ± 0.08, $p = 4.5.10^{-3}$), Group-1 (0.53 ± 0.09, $p = 6.10^{-5}$) and healthy volunteer (0.54 ± 0.06 cm, $p = 2.10^{-6}$). No difference was seen between SMA inner diameter of Group-3, Group-1 and healthy volunteers (Fig. 1B). One year after surgery, among patients with incomplete CRS a cut-off value of 0.58 cm allowed the distinction of patients without from those with severe disease progression with a sensitivity of 61.5% and a specificity of 90.5% ($p = 1.1.10^{-3}$) AUC = 0.787 [95%CI: 0.610–0.906].

BFVel was increased only in patients with progressive residual PMP after CRS (Group-3). BFVel was higher in Group-3 (38.6 ± 13.3 cm/s) than in Group-2 (20.7 ± 4.9 cm/s, $p = 1.10^{-6}$), Group-1 (19.3 ± 4.1 cm/s, $p = 2.10^{-6}$) and healthy volunteers (16.9 ± 4.8 cm/s, $p = 2.10^{-8}$). BFVel was similar between Group-2, Group-1 and healthy volunteers (Fig. 1C). One year after surgery, among patients with incomplete CRS a cut-off value of 25.0 cm/s allowed the distinction of patients without from those with severe disease progression with a sensitivity of 92.3% and a specificity of 85.7% ($p < 1. 10^{-4}$) AUC = 0.945 [95%CI: 0.809–0.994].

WSS was increased only in patients with progressive residual PMP after CRS (Group-3). WSS measured in the SMA was superior in Group-3 (19.6 ± 8.2 dynes/cm^2) than in Group-2 (9.2 ± 1.8 dynes/cm^2, $p = 1.10^{-6}$), Group-1 (10.4 ± 2.8 dynes/cm^2, $p = 8.10^{-5}$), and healthy patients (8.7 ± 2.8 dynes/cm^2, $p = 9.10^{-7}$). No difference was seen in WSS measured in the SMA between Group-2, Group-1 and healthy volunteers (Fig. 1D). One year after surgery, among patients with incomplete CRS a cut-off value of 12.1dynes/cm^2 allowed the distinction of patients without from those with severe disease progression with a sensitivity of 100% and a specificity of 100% ($p < 1.10^{-4}$) AUC = 1.000 [95%CI: 0.897–1.000] (absence of superposition of the data distribution of stable patients versus patients with progressive disease).

Pathological grade of the disease, CEA and CA19-9, and the use of systemic chemotherapy were similar between groups. Results of laboratory findings are reported in Table 2.

Discussion

The results of this study demonstrate that after CRS for PMP, WSS >12.1 dynes/cm^2 in the SMA is associated with a worse outcome among patients with residual disease. Consequently, upstream WSSs' increase reflects an ongoing expansive arterial remodeling, consecutive to the ongoing expansion of the pathological vascular network. On the other hand, delayed achievement of arterial remodeling corresponding to a normalized WSS could reflect the stability of PMP whatever the level of the BFVol. Moreover, the use of WSS is more accurate and sensitive than the use of BFVol, BFVel or SMA inner diameter for prediction of clinical outcome at one-year after CRS.

Patients without residual disease or slow progressive disease

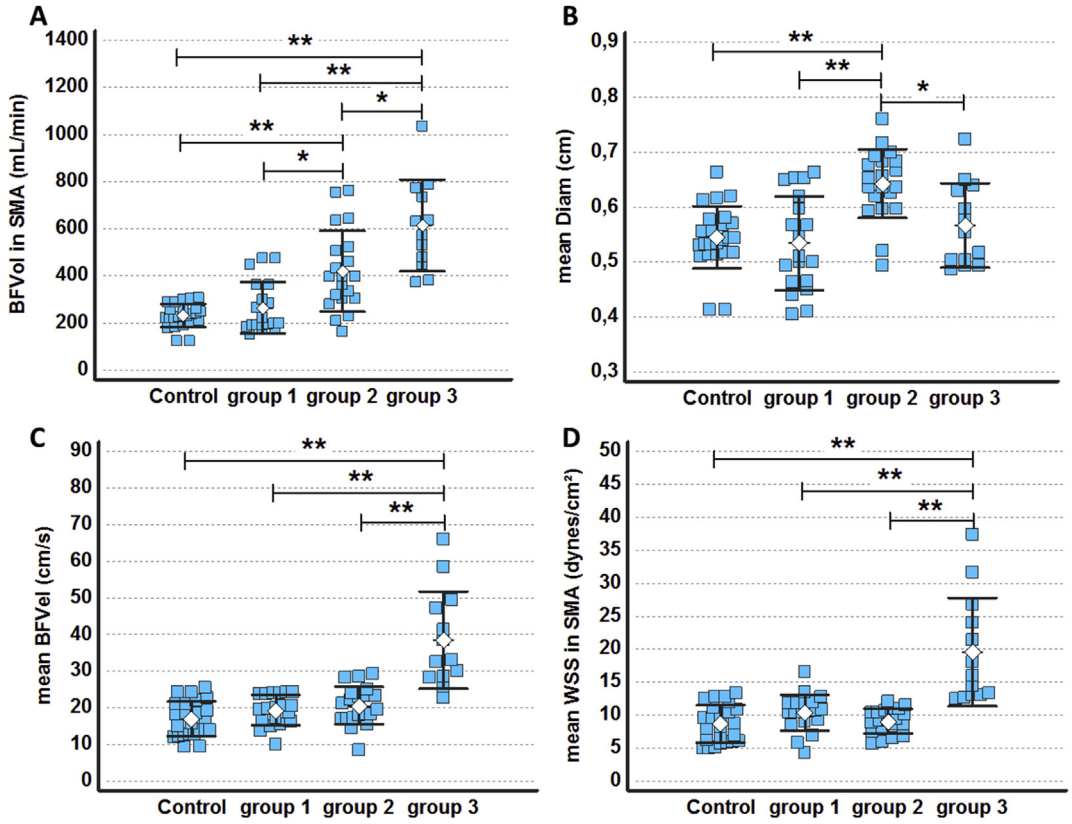

Fig. 1. Doppler Ultrasound findings in the superior mesenteric artery (SMA) in patients with a pseudomyxoma peritonei (PMP) one year after cytoreductive surgery. Group-1: patients with complete resection (CCR0) and HIPEC without any recurrence, Group-2: patients with incomplete eradication of the disease (CCR1, -2, -3) and slowly progressive disease, Group-3: patients with incomplete eradication of the disease (CCR1, -2, -3) and active progressive residual PMP. **(A)**, blood flow volume (BFVol) in the superior mesenteric artery; **(B)**, superior mesenteric artery inner diameter; **(C)**, mean blood flow velocity (BFVel) in the superior mesenteric artery; **(D)**, wall shear stress (WSS) in the superior mesenteric artery. (*: $p < 0.005$, **: $p < 0.001$ between groups).

after surgery showed normal WSS compared to controls. More precisely, in Group-1, patients with total ablation of the PMP abnormal vascular network had BFVols, SMA inner diameters, BFVels and WSSs similar to that of healthy subjects. Only 9/19 Group-1 patients had a Doppler ultrasound examination before surgery. In these 9 patients, values after *vs* before CRS+HIPEC were respectively: 214 ± 46 *vs* 390 ± 127 mL/min ($p = 0.0012$), 0.51 ± 0.05 *vs* 0.59 ± 0.05 mm ($p = 0.0049$), 17.3 ± 1.8 *vs* 24.3 ± 6.1 cm/s ($p = 0.0074$) and 9.6 ± 1.6 *vs* 11.5 ± 2.8 dynes/cm^2 ($p = 0.1126$). The normalization of the SMA hemodynamic values suggests an achieved regressive arterial remodeling with adjustment (decrease) of the arterial lumen diameter to the decreased BFVol for normalization of the BFVel and the WSS in physiological ranges. This was illustrative of a recovered balance between a stable and normalized downstream vascular network and the upstream SMA hemodynamics. Similar findings were also observed in the afferent arteries which supplied superficial arteriovenous malformations after total resection of the nidus [19]. On the other hand, in Group-2, incomplete ablation of the PMP abnormal vascular network, without progression entailed a stable elevation of the BFVol in the SMA. This elevation resulted in an expansive arterial remodeling responsible of an increase in the SMA inner diameter inducing the normalization of the WSS illustrative of a recovered balance between a persistent but stable downstream tumor and native vascular network and the upstream SMA hemodynamics. These two opposite adaptive response reflected the achievement of the arterial remodeling processes over few months.

Conversely in Group-3, incomplete ablation of the PMP abnormal vascular network, with progression of the disease, i.e. with progressive extension of the downstream microvascular network, is associated with a persistent and continuously rising BFVol without sufficient SMA inner diameter enlargement leading to an elevated WSS. This is suggestive of a persistent imbalance between the growing downstream tumor vascular network and the upstream SMA hemodynamics thus of an ongoing vascular remodeling. In addition, these group-3 patients presented as high WSSs as long was the time between the US Doppler examination and the recurrence diagnosed by the surgeon based on the semi-annual clinical/radiological examinations (delayed arterial remodeling). The extended distribution of the WSSs values can be explained by the variable delay between the US Doppler examination and the recurrence of the disease (7.2 ± 3.0 months). More precisely, group-3 patients had US Doppler examination from 1 month to 1 year before the recurrence. Nevertheless, WSSs were higher in all group-3 patients and could represent a predictive marker of progression of the PMP tumor vascular network obviously parallel to the progression of the disease whatever the unforeseeable time-delay between the US Doppler examination and the recurrence.

Arterial remodeling requires coordinated changes in cellular proliferation, apoptosis, migration, cell organization, and matrix-integrin interactions throughout the layered structure of the vessel. The association of blood flow with arterial remodeling has been studied in various experimental techniques and conditions. In this regard, one of the most comprehensive models to investigate small artery response was developed by Jo de Mey [30]. Persistent

changes in blood flow were induced in juvenile rats by ligating every first-order side branch of the SMA [31]. Patent arteries were exposed to high flow (roughly twice that normally observed), while occluded mesenteric arteries had practically no blood flow. This chronic low flow resulted in decreased passive lumen diameter, hypotrophy of the arterial wall, and both loss and atrophy of smooth muscle cells. On the contrary, high flow led to increased lumen diameter and arterial wall hypertrophy. Similarly, in the rabbit, Tronc et al. evidenced the enlargement of the common carotid artery after creation of an arteriovenous fistula between the common carotid artery and the jugular vein [32].

Plasma or tissue tumor markers have been suggested as prognosis factors to monitor treatment response and to detect tumor recurrence in gastrointestinal tumors [33]. In PMP patients, it has been shown a reduction or normalization of CEA, and in less measure of CA 19.9 and CA 125, after CRS [34]. However, it is admitted that treatment decisions should not be based solely on an increased CAE or CA 19-9 [33,34]. In our study, both tumor markers did not reached the statistical significant level because of the wide distribution of the individual values. Dohan et al. reported that post-operative BFVols after incomplete surgery in patients with PMP, might aid in identifying patients who may benefit of post-operative therapy [4]. More precisely, they reported that BFVol was superior in patients with incomplete CRS and active progressive disease than in patients with slow progressive disease. In addition they found that a cut-off of 530 mL/min could discriminate between slow progressive disease and active progressive disease with a sensitivity of 80% and a specificity of 93%. In our study, patients with incomplete CRS and progressive disease had a mean BFVol of 615 ± 194 mL/min, and the cut-off value was established at to 432 mL/min with a sensitivity of 83.3% and a specificity of 65.0%, consistent with their result. However, WSS demonstrated higher performances with sensitivity and specificity of 100%. In addition, our study has a greater sample of post-operative patients with 52 patients versus 30 patients in their study. The time of US examination was enlarged (16.2 ± 6.4 months) and reflects the heterogeneity of origin of our patients. Indeed, as a reference centre our institution treats remote and foreign patients for whom the combination of all imaging examinations along with the biannual surgical appointments for follow-up may be difficult. However, we recommend that imaging examinations should be performed at 6 months and one year after surgery, then every year.

In conclusion, an elevated WSS measured in the SMA of patients with PMP after CRS is associated with disease progression. Moreover, patients with residual disease after CRS and a WSS>12.1 dyn/cm^2 in the SMA have a poorer outcome. WSS measurement in the SMA of patients with PMP after CRS should be considered as biomarker of tumor progression.

Conflict of interest statement

The authors have no conflict of interest to declare. The data that support the findings of this study are available from the corresponding author.

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