Joint Analysis of Cardiovascular Control and Shear Wave Elastography to Assess the Vulnerability of Carotid Artery Plaque

Vlasta Bari[1,2], Beatrice Cairo[1], Francesca Gelpi[1], Fabiana Fancoli[3], Nicoletta Curcio[4,5], Giulia Matrone[5], Giovanni Nano[1,3], Alberto Porta[1,2], Daniela Mazzaccaro[3]

[1]Department of Biomedical Sciences for Health, University of Milan, Milan, Italy
[2]Department of Cardiothoracic, Vascular Anesthesia and Intensive Care, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy
[3]Operative Unit of Vascular Surgery, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy
[4]3D and Computer Simulation Laboratory, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy
[5]Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Pavia, Italy

Abstract

Noninvasive characterization of the carotid plaque is important in asymptomatic carotid artery stenosis patients because plaque's vulnerability contributes to the risk of stroke. This study proposes the joint evaluation of elastographic and cardiovascular control markers for a deeper characterization of plaque vulnerability. Autonomic and baroreflex markers were derived from spontaneous fluctuations of heart period (HP) and systolic arterial pressure (SAP) in 78 patients scheduled for carotid endarterectomy (age: 74.3+7.7 yrs, 30 females) evaluated in supine position (REST) and during active standing (STAND). The Young's modulus (YM) was computed via shear wave elastography. Thirty-six patients featured vulnerable (VULN) and 42 stable (STABLE) plaque according to post-surgery evaluation. VULN patients had a lower YM and higher baroreflex sensitivity at REST, as estimated from the transfer function gain from SAP to HP in high frequency (HF: 0.15-0.4 Hz) band ($TFG_{HP\text{-}SAP}(HF)$), that decreased during STAND solely in VULN. A multivariate logistic regression model was built using YM and $TFG_{HP\text{-}SAP}(HF)$ at REST to predict plaque vulnerability. Compared to the sole YM the addition of $TFG_{HP\text{-}SAP}(HF)$ at REST increased the area under the receiver operating characteristic curve from 0.625 to 0.649. Markers of elastography and baroreflex could be fruitfully combined to assess carotid plaque vulnerability.

1. Introduction

Carotid artery stenosis (CAS) is due to the formation of carotid plaque reducing blood flow to the brain. Symptomatic CAS patients are surgically treated with carotid endarterectomy (CEA), while in asymptomatic situations the indication for surgery or for medical treatment only is still under debate [1]. Recent studies suggest that, assigned the level of CAS, the composition of the carotid plaque is one of the major determinants of the stroke [2]. Given this consideration there is a growing interest on validating methods for the non-invasive assessment of the vulnerability of the plaque. Shear wave elastography [3] has been suggested as a tool able to preoperatively identify mechanical characteristics of the plaque, with plaque with lower Young's module (YM) being more vulnerable [4].

Markers of the autonomic function and baroreflex control, derived noninvasively from the analysis of spontaneous fluctuations of heart period (HP) and systolic arterial pressure (SAP), have been utilized to characterize the impact of CEA [5-7]. However, the ability of cardiovascular control markers in predicting the vulnerability of the plaque in association with the YM has not been proved yet. We hypothesize that the combined assessment of cardiovascular control markers and elastographic indexes could improve the characterization of the vulnerability of the plaque.

Thus, the aim of this study was to evaluate the incremental value of autonomic and baroreflex control markers with respect to the YM, all assessed preoperatively, in predicting the vulnerability of the plaque in asymptomatic CAS patients scheduled for CEA. According to the *a posteriori* evaluation of the plaque, patients were divided in two groups featuring a vulnerable (VULN) or stable (STABLE) plaque.

2. Methods of analysis

2.1. Experimental protocol

Seventy-eight consecutive patients (age: 74.2+7.7 yrs, 27 females) with asymptomatic CAS ranging from 70% to 99% scheduled for CEA were enrolled at the Operative Unit of Vascular Surgery of IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy. The exclusion criteria were listed in [4]. The study was approved by San Raffaele Hospital ethical committee on 20 June 2019 (110/int/2019) and registered on ClinicalTrial.gov (NCT05566080). Patients signed an informed consent prior to participate. Subjects underwent the acquisition of electrocardiogram (ECG) from lead II (BioAmp, ADInstruments, Australia) and of photoplethysmographic arterial pressure (AP) via volume clamp technique (CNAP, CNSytems, Graz, Austria) for 10 minutes while resting in supine position (REST) and for 10 minutes during active standing (STAND). Just after the REST session shear wave elastography was performed via a 7.5 MHz ultrasound probe (EsaoteTM, Genova, Italy) equipped with the Q-Elaxto software package [4]. Elastographic recording was performed with patients lying in supine position and placing the linear ultrasound probe along the longitudinal axis on the side of the CAS by a trained operator. Experimental sessions were performed one day before surgery. Subjects were labeled as VULN or STABLE according to post-surgery examination of the removed plaque. VULN plaque was defined the presence of at least one of the following features [8]: large intraplaque hemorrhage, ulceration, necrotic or lipidic core for more than 25% of the total area, ruptured or thin (<65 μm) fibrous cap, infiltration of inflammatory cells, neovascularization of the cap. Thirty-six patients were assigned to the VULN group (age: 73.14±8.55 yrs, 10 females) and 42 patients to the STABLE one (age: 75.05±6.96 yrs, 17 females).

2.2. Computation of elastographic, autonomic and baroreflex markers

From the elastographic images, the q-Elaxto software allowed the computation of the YM of the plaque as a marker of arterial stiffness [4].

From the ECG and AP signals, beat-to-beat time series of HP and SAP were extracted, approximating HP as the time distance between two R-wave peaks on the ECG and SAP as the maximum of AP inside the HP. Series were manually checked and corrected for ectopic beats or misdetections, extracting epochs of 256 beats at REST and STAND. From the series, time domain markers were computed as mean and variance of HP and SAP, labelled as μ_{HP}, σ^2_{HP}, μ_{SAP}, σ^2_{SAP} and expressed in ms, ms^2, mmHg, $mmHg^2$. Then, after linear detrending, power spectral density was computed according to an autoregressive model of the series. Levinson-Durbin recursion identified the model coefficients and Akaike information criterion allowed the selection of the best model order in the range 10-14 [9]. The power of HP series in the high frequency (HF) band (0.15-0.4 Hz), labeled as HF_{HP} and expressed in ms^2, was then taken as an index of vagal modulation directed to the heart [10]. The power of SAP in the low (LF) band (0.04-0.15 Hz), labeled as LF_{SAP} and expressed in $mmHg^2$, was taken as a marker of sympathetic modulation directed to the vessels [11].

Baroreflex was characterized via a model-based bivariate autoregressive approach [12]. Baroreflex sensitivity (BRS) was assessed via the transfer function gain from SAP to HP ($TFG_{HP\text{-}SAP}$), computed as the ratio of the modulus of the cross-spectral density function from SAP to HP to the SAP power spectral density. The squared coherence between HP and SAP ($K^2_{HP,SAP}$) was computed as the squared modulus of the cross-spectral density function from SAP to HP divided by the product of the HP and SAP power spectral densities. The phase of the cross-spectral density function from SAP to HP ($Ph_{HP\text{-}SAP}$) was taken as index of the HP-SAP delay, with negative values suggesting that HP lagged behind SAP. $TFG_{HP\text{-}SAP}$, $K^2_{HP,SAP}$, $Ph_{HP\text{-}SAP}$ were sampled at the peak of $K^2_{HP,SAP}$ in the LF and HF bands, and expressed in $ms \cdot mmHg^{-1}$, dimensionless units, and radians [13].

2.3. Statistical analysis

Markers of cardiovascular control were compared between VULN and STABLE patients at REST and STAND via a two-way analysis of variance (Holm-Sidak test for multiple comparisons). Differences between the YM of VULN and STABLE patients were tested via the unpaired t-test. A multivariate logistic regression model was built over factors able to separate the two groups with $p<0.1$. Regression coefficient, odds ratio, 95% confidence interval (CI) and type I error probability *p* of the multivariate regression model were computed. The receiver operating characteristic (ROC) curve was calculated and the area under the curve (AUC) was assessed. The Youden index was utilized to determine the best combination of specificity and sensitivity and to compute the negative and positive predictive value. A $p<0.05$ was taken as significant.

3. Results

YM of the plaque was lower in VULN patients with respect to STABLE ones (25.65±27.64 vs 46.21±45.38 kPa). Table 1 describes autonomic and baroreflex markers in VULN and STABLE patients at REST and during STAND. μ_{HP} was decreased during STAND only in VULN patients, while $TFG_{HP\text{-}SAP}$(HF) was higher in VULN than STABLE at REST and significantly decreased during STAND. All the other markers were unchanged between

Table 1. Time and frequency domain indexes computed at REST and during STAND in VULN and STABLE patients.

Index	STABLE		VULN	
	REST	STAND	REST	STAND
μ_{RR} [ms]	882.92±137.41	824.36±185.92	924.75±170.57	846.32±227.07*
σ^2_{RR} [ms^2]	581.86±568.46	509.99±506.19	687.05±617.74	660.14±639.33
HF_{RR} [ms^2]	153.98±264.35	110.8±161.11	157.97±191.69	128.14±179.63
μ_{SAP} [mmHg]	147.44±18.79	150.66±29.94	144.35±17.93	144.19±31.34
σ^2_{SAP} [mmHg^2]	35.29±30.43	35.49±25.94	31.38±32.82	36.04±27.03
LF_{SAP} [mmHg^2]	4.35±4.3	5.56±7.53	4.06±4.23	7.32±10.41
$K^2_{HP,SAP}$(LF)	0.34±0.18	0.33±0.17	0.31±0.19	0.36±0.17
$Ph_{HP\text{-}SAP}$(LF) [rad]	-1.15±1.37	-1.4±1.21	-1.42±1.22	-1.1±1.28
$TFG_{HP\text{-}SAP}$(LF) [ms·mmHg^{-1}]	2.69±1.98	2.35±1.71	3.34±2.85	2.64±1.96
$K^2_{HP,SAP}$(HF)	0.63±0.22	0.62±0.27	0.62±0.26	0.55±0.26
$Ph_{HP\text{-}SAP}$(HF) [rad]	-0.32±0.87	-0.25±1.12	-0.26±1.01	0.02±0.98
$TFG_{HP\text{-}SAP}$(HF) [ms·mmHg^{-1}]	4.01±4.12	3.42±3.15	6.16±6.19§	3.81±3.66*

REST = at supine resting; STAND = during active standing; VULN = patients with vulnerable carotid plaque; STABLE = patients with stable carotid plaque; HP = heart period; SAP = systolic arterial pressure; μ = mean; σ^2 = variance; LF = low frequency; HF = high frequency; K^2: squared coherence; TF: transfer function; Ph: phase of the TF; TFG= gain of the TF. The symbol * and § indicates $p<0.05$ with respect to REST and STABLE respectively.

groups and conditions.

The ROC curve relative to the VULN prediction using solely the YM gave an AUC of 0.625. $TFG_{HP\text{-}SAP}$(HF) at REST was the only marker able to separate the two groups with $p<0.1$, with an AUC of ROC curve equal to 0.616, and was then tested in multivariate analysis. YM and $TFG_{HP\text{-}SAP}$(HF) at REST entered a multivariate logistic regression model, whose parameters were shown in Tab.2. Remarkably, the association of YM was stronger than that of $TFG_{HP\text{-}SAP}$(HF) at REST, reporting a higher *p*-value. The ROC curve exhibited an AUC of 0.649 (Fig.1). The model reported a sensitivity and specificity of 0.500 and 0.786 respectively, with negative and positive predictive values of 64.7% and 66.7% respectively.

4. Discussion

The main findings of this work can be summarized as follows: i) STABLE patients had a higher YM; ii) baroreflex response to STAND was impaired in the STABLE group, while it was preserved in the VULN group; iii) the addition of BRS to the YM improved the vulnerability prediction of the plaque.

4.1. STABLE patients had a higher YM

As found in a preliminary study [4], VULN patients had a lower YM of the plaque than STABLE ones, thus confirming the ability of elastography to discriminate the two populations. The higher YM in STABLE is linked to the greater rigidity of the plaque.

4.2. Autonomic function is different in STABLE and VULN groups

Previous studies suggested that CEA induces a positive impact on autonomic function and baroreflex control [5-7]. However, no studies differentiated the behavior of cardiovascular control when asymptomatic CAS patients were classified according to the vulnerability of the plaque into STABLE and VULN groups. The original finding of this study is that BRS, as assessed via $TFG_{HP\text{-}SAP}$(HF) was higher at REST in VULN group, decreasing during STAND only in this group. Since this decrease is expected in a healthy population because of the sympathetic activation associated to STAND [13], and lower BRS is associated to a higher cardiovascular risk [14-15], we can conclude that VULN patients featured a more physiological response than STABLE ones, likely due to the less rigid substrate of the barosensitive areas where mechanoreceptors are located.

4.3. Predicting the vulnerability of the plaque

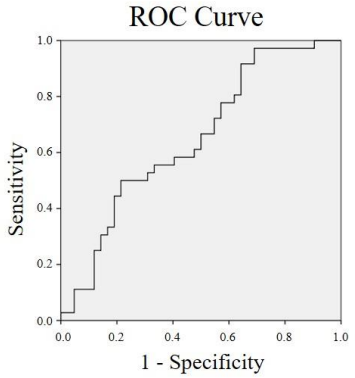

Figure 1. The line plot shows the ROC curve obtained from the multivariate logistic regression model built using YM values together with $TFG_{HP\text{-}SAP}$(HF) at REST.

Table 2. Results of multivariate logistic regression analysis for plaque vulnerability prediction.

Parameter	Regression coefficient	Odds ratio	95% CI	p-value
YM	-0.014	0.986	0.973-1.000	0.043
$TFG_{HP\text{-}SAP}$(HF) at REST	0.075	1.078	0.984-1.117	0.153
constant	-0.038	0.963		0.928

CI = confidence interval; YM =Young's modulus; HP = heart period; SAP = systolic arterial pressure; TFG = transfer function gain; HF = high frequency; $TFG_{HP\text{-}SAP}$(HF) = TFG from SAP to HP in the HF band; REST = at supine resting.

Present findings suggest the ability of baroreflex control markers in noninvasively predicting the vulnerability of the carotid plaque. Indeed, the sole consideration of $TFG_{HP\text{-}SAP}$(HF) at REST led to an AUC value of 0.616 comparable to that using solely the YM, namely 0.625. Moreover, their joint evaluation raised the AUC to 0.649.

5. Conclusions

This study proposes the joint analysis of elastography and cardiovascular control markers in asymptomatic CAS patients scheduled for CEA for the prediction of vulnerability of the carotid plaque. An index of arterial stiffness, such as the YM, and one of BRS, such as the $TFG_{HP\text{-}SAP}$(HF), contributed to separate patients with STABLE plaque from those with VULN one. The additional value of baroreflex control markers was supported by the multivariate logistic regression model combining YM and $TFG_{HP\text{-}SAP}$(HF).

Future studies should aim at increasing the population and testing advanced cardiovascular controls markers to determine whether the prediction could be further ameliorated. The study confirmed the clinical value of markers describing autonomic and baroreflex regulations [14,15]. While confirmed, noninvasive techniques could be used to detect plaque vulnerability to improve risk stratification for stroke in asymptomatic CAS patients.

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Address for correspondence:

Dr. Vlasta Bari
Department of Biomedical Sciences for Health,
University of Milan
IRCCS Policlinico San Donato, Via Morandi 30
20097 San Donato Milanese, Milan, Italy
email: vlasta.bari@unimi.it