Archivos de Cardiología de México

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RESEARCH ARTICLE

The rs4783961 and rs708272 genetic variants of the CETP gene are associated with coronary artery disease, but not with restenosis after coronary stenting

Los polimorfismos rs4783961 y rs708272 del gen CETP son asociados con la enfermedad arterial coronaria y no con la restenosis tras el implante de un stent coronario

*Gilberto Vargas-Alarcón[1], Oscar Pérez-Méndez[1], Rosalinda Posadas-Sánchez[2], Marco A. Peña-Duque[3], Marco A. Martínez-Ríos[3], Hilda Delgadillo-Rodriguez[3], and José M. Fragoso[1]**

[1]Department of Molecular Biology; [2]Department of Endocrinology; [3]Interventional Cardiology. Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico

Abstract

Objective: *We evaluated whether cholesteryl ester transfer protein (CETP) gene polymorphisms are associated with the presence of coronary artery disease (CAD) and/or restenosis in patients with coronary stent.* **Methods:** *Two polymorphisms of the CETP gene [–971 A/G (rs4783961), and Taq1B A/G (rs708272)] were genotyped by 5'exonuclease TaqMan assays in 219 patients with CAD (66 patients with restenosis and 153 without restenosis) and 607 control individuals.* **Results:** *The distribution of polymorphisms was similar in patients with and without restenosis. However, when the whole group of patients (with and without restenosis) was compared to healthy controls, under dominant model, the G allele of the Taq1B A/G polymorphism was associated with increased risk of CAD (odds ratio [OR] = 1.48, pC_{Dom} = 0.032). In the same way, under co-dominant, dominant, and additive models, the A allele of the –971 A/G polymorphisms was associated with an increased risk of developing CAD (OR = 2.03, $pC_{Co\text{-}dom}$ = 0.022, OR = 1.83, pC_{Dom} = 0.008, and OR = 1.39, pC_{Add} = 0.011, respectively). In addition, the linkage disequilibrium showed that the "AG" haplotype was associated with increased risk of developing CAD (OR = 1.28, p = 0.03).* **Conclusion:** *This study demonstrates that CETP Taq1B A/G and CETP –971 A/G polymorphisms are associated with an increased risk of developing CAD, but no association with restenosis was observed.*

Keywords: *Genetics. High-density lipoprotein cholesterol. Coronary artery disease.*

Resumen

Objetivo: *Evaluamos si los polimorfismos del gen CETP están asociados con la presencia de enfermedad arterial coronaria (EAC) y/o restenosis en pacientes con stent coronario.* **Métodos:** *En este estudio se genotiparon dos polimorfismos del gen CETP [–971 A/G (rs4783961) y Taq1B A/G (rs708272)] mediante ensayos de 5'exonucleasa TaqMan en 219 pacientes con EAC (66 pacientes con restenosis y 153 sin restenosis), y 607 individuos de control.* **Resultados:** *La distribución de polimorfismos fue similar en pacientes con y sin restenosis. Sin embargo, cuando se comparó todo el grupo de pacientes (con y sin restenosis) con controles sanos, bajo el modelo dominante el alelo G del polimorfismo Taq1B A/G se asocia con un*

Correspondence:
*José M. Fragoso
E-mail: mfragoso1275@yahoo.com.mx

Date of reception: 27-01-2021
Date of acceptance: 01-09-2021
DOI: 10.24875/ACM.21000039

Available online: 30-09-2021
Arch Cardiol Mex (Eng). 2022;92(3):334-341
www.archivoscardiologia.com

mayor riesgo de EAC (OR = 1.48, pC_{Dom} = 0.032). De la misma manera, bajo los modelos co-dominante, dominante y aditivo, el alelo A de los polimorfismos –971 A/G se asocia con un mayor riesgo de desarrollar EAC (OR = 2.03, $pC_{Co\text{-}dom}$ = 0.022, OR = 1.83, pC_{Dom} = 0,008 y OR = 1.39, pC_{Add} = 0.011, respectivamente). Adicionalmente, el desequilibrio de ligamiento mostró que el haplotipo "AG" se asocia con un mayor riesgo de desarrollar EAC (OR = 1.28, p = 0.03). **Conclusión:** *En resumen, este estudio demuestra que los polimorfismos CETP Taq1B A/G y CETP –971 A/G están asociados con un mayor riesgo de desarrollar CAD, pero no se observó asociación con restenosis.*

Palabras clave: *Genetica. Colesterol lipoproteinas de alta densidad. Enfermedad arterial coronaria.*

Introduction

Coronary artery disease (CAD) is a complex, multifactorial disease, influenced by pathophysiologic conditions as well as by genetic and environmental factors. Currently, the treatment strategy for this disease is the intracoronary stent. However, data in the literature has shown that after intracoronary stent placement between 12 to 32% of the patients develop restenosis[1-4]. The restenosis is the arterial wall's healing response to mechanical injury and comprises two main processes, one is the neointimal hyperplasia that involves the smooth muscle migration/proliferation, extracellular matrix deposition, and vessel remodeling and the other is the vessel remodeling[2-4].

Data in the literature, it has been suggested that the higher concentration of high-density lipoprotein (HDL) cholesterol has an important role anti-atherogenic in the development of the atherosclerotic plaque[5-7]. In addition, the evidences indicate that the risk of restenosis following a vascular intervention is inversely related to HDL cholesterol (HDL-C)[8-10]. Cholesteryl ester transfer protein (CETP) is an exchange protein, transporting cholesterol from HDL particles to apoB-containing lipoproteins (low-density lipoproteins [LDL] and very LDL) to replace it with triglycerides[5-7]. Nonetheless, changes in activity and concentrations of this protein impair reverse cholesterol transport and promote the atherosclerotic process[11], strongly suggesting that this protein may be an important pro-restenotic factor.

The CETP protein is encoded by *CETP* gene, which is located in chromosome 16q23-24. In addition, several studies have been associated two single-nucleotide polymorphisms (SNPs) in the CETP gene, one in the promoter region [position –971 *A/G* (rs4783961)] and other in intron 1 named *Taq1B* [position *A*5454-*G* (rs708272)], with an increased activity of CETP protein[12], and with risk of developing CAD, myocardial infarction, and dyslipidemia[12-16].

Considering the prominent role of this gene in the concentrations and remodeling of HDL-C, the aim of the study was to establish the role of the *CETP* –971 *A/G* and *CETP Taq1B A/G* polymorphisms in the susceptibility to developing restenosis after coronary stent placement in the Mexican population.

Materials and Methods

Study population

This case–control study was carried out in the Instituto Nacional de Cardiologia Ignacio Chavez. The sample size was calculated for matched cases and controls with OpenEpi software (http://www.openepi.com/SampleSize/SSCC.html). The study included 826 Mexican Mestizos individuals (219 patients with CAD and 607 healthy controls matched by age and gender). The patients with CAD were underwent coronary stent implantation at our institution during the period between October 2008 and October 2014. After 6 months went to follow-up, coronary angiography because of symptoms of ischemia documented in a myocardial perfusion imaging test. Basal and procedure coronary angiographies were analyzed for angiographic predictors of restenosis, and follow-up angiography was performed to screen for binary restenosis. Using a >50% stenosis at follow-up (50% reduction in the luminal diameter of the stenosis compared with the coronary angiography findings immediately following angioplasty) as the criterion to define restenosis, there were 66 patients with restenosis (30%) and 153 without restenosis (70%). Moreover, we included 607 healthy controls without a family history of CAD with negative calcium score, indicative of absence of subclinical atherosclerosis coming from the Genetics of Atherosclerosis Disease Mexican study previously described by Rosalinda-Posadas et al.[17]. The exclusion criteria included the use antidyslipidemic, antihypertensive, and antidiabetic drugs at the time of the study. Both groups (patients with CAD and healthy controls) were considered Mexican mestizos and ethnically matched according to ancestry informative markers using the ADMIXTURE software. This study was conducted according to the

principals of the Declaration of Helsinki and was approved by the Ethics and Research commission of Instituto Nacional de Cardiologia Ignacio Chavez. Written informed consent was obtained from all individuals enrolled in the study.

Laboratory analysis

Cholesterol and triglycerides plasma concentrations were determined by enzymatic/colorimetric assays (Randox Laboratories, UK). HDL-C concentrations were determined after precipitation of the apoB-containing lipoproteins by the method of the phosphotungstic acid-Mg^{2+}. The LDL-C concentration was determined in samples with a triglyceride level lower than 400 mg/dl with the Friedewald formula[18]. Dyslipidemia was defined as the presence of one or more of the following conditions: cholesterol > 200 mg/dl, LDL-C > 130 mg/dl, HDL-C < 40 mg/dl, or triglycerides > 150 mg/dl, according to the guidelines of the National Cholesterol Education Project Adult Treatment Panel (ATP III) (http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm). Type 2 diabetes mellitus (T2DM) was defined with a fasting glucose ≥ 126 mg/dL; it was also considered when participants reported glucose-lowering treatment or a physician diagnosis of T2DM. Hypertension was defined by a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or the use of oral antihypertensive therapy[17].

Genetic analysis

DNA extraction was performed from blood peripheral in agreement with the proposed method by Lahiri and Nurnberger[19]. The CETP −971 *A/G* (rs4783961) and CETP Taq1B *A*5454-*G* (rs708272) SNPs were genotyped using 5' exonuclease TaqMan genotyping assays on a 7900HT Fast Real-Time PCR system according to manufacturer's instructions (Applied Biosystems, Foster City, USA). Samples previously sequenced for the different genotypes of the studied polymorphisms were included as positive controls.

Inheritance models analysis

The association of the −971 *A/G* and Taq1B *A/G* SNPs with restenosis patients was perform under the following inheritance model: additive (major allele homozygotes vs. heterozygotes versus minor allele homozygotes), codominant (major allele homozygotes vs. minor allele homozygotes), dominant (major allele homozygotes vs. heterozygotes + minor allele homozygotes), overdominant (heterozygotes vs. major allele homozygotes + minor allele homozygotes), and recessive (major allele homozygotes + heterozygotes vs. minor allele homozygotes) using logistic regression, adjusting for cardiovascular risk factors[20,21].

Analysis of the haplotypes

The linkage disequilibrium analysis (LD, D") and haplotypes construction were performed using Haploview version 4.1 (Broad Institute of Massachusetts Institute of Technology and Harvard University, Cambridge, MA, USA).

Functional prediction analysis

Two *in silico* programs and SNP function prediction were used to predict the possible functional effect of *CETP* gene polymorphisms. Both programs (ESEfinder 2.0 and SNPinfo) analyze the location of the SNP (e.g. 5'-upstream, 3'-untranslated regions, and intronic) and its possible functional effects, such as amino acid changes in protein structure, transcription factor binding sites in promoter or intronic enhancer regions, and alternative splicing regulation by disrupting exonic splicing enhancers (*ESEs*) or silencers[22,23].

Statistical analysis

All statistical analyses in this study were performed using SPSS version 18.0 (SPSS, Chicago, IL). The Mann-Whitney U test was used for the comparison of continuous variables between control and CAD groups. For categorical variables, Chi2 or Fisher's exact tests were performed. The association of the SNPs with CAD and restenosis after coronary stenting was performed under five inheritance models using logistic regression test. The correction of the p-values (pC) was performed using Bonferroni test. The HAPLOVIEW version 4.1 software (Cambridge, MA, USA) was used for the haplotypes construction and linkage disequilibrium analysis (LD, D"). The Hardy–Weinberg equilibrium (HWE) among our study population was estimated through Chi-square test. The statistical power to detect an association with CAD was 0.80. We used the OpenEpi software [http://www.openepi.com/SampleSize/SSCC.html].

Table 1. Clinical and angiographic characteristics of the CAD patients with and without restenosis

	With restenosis, n (%)	Without restenosis, n (%)	p-value
Men*	51 (77)	119 (78)	NS
Restenosis	66 (30)	153 (70)	-----
Unstable angina*	26 (39)	43 (28)	NS
Stable angina*	6 (9)	34 (22)	0.017
Statin therapy*	53 (80)	131 (86)	NS
DES*	18 (27)	94 (61)	<0.001
BSM*	48 (73)	59 (39)	<0.001
Diameter smaller* 2.5 mm	20 (30)	30 (20)	0.04
Stent length* (mm)	39 (59)	85(56)	NS
Age* (years)	60.4 (54-67)	59.1 (53-65)	NS

*n (%): number and proportion of subjects with the clinical and angiographic characteristic in both groups. BMS: bare-metal stent; DES: drug-eluting stent.

Results

Characteristics of the study population

The angiographic characteristics of the patients with and without restenosis are presented on table 1. The patients who underwent coronary bare-metal stent implantation develop more restenosis (73%) than those of the patients who underwent drug-eluting stent implantation (27%) ($p \leq 0.001$). In addition, the presence of the stable angina (9%) as well as the diameter ≤ 2.5 mm (20%) was minor in patients with restenosis than without restenosis. On the other hand, when we analyzed the demographic characteristics and biochemical parameters as CAD patients and healthy controls, there are significant differences between patients with CAD and healthy controls in the biochemical parameters (Table 2). As can be seen, the CAD patients presented changed significant in several parameters such as body mass index (BMI), blood pressure, glucose, total cholesterol, and LDL-C than controls, most likely due to effect of antidyslipidemic, antihypertensive, and antidiabetic drugs used by the patients.

Allele and genotype frequencies

Genotype frequencies in the polymorphic sites were in HWE. In a first analysis, the allele and genotype frequencies of the *CETP* polymorphisms were similar in patients with and without restenosis (data no shown). However, the analysis made comparing the whole group of patients (with or without restenosis) and healthy controls showed that under dominant model, the carriers of *G* allele of the CETP *Taq1B A*5454-*G* polymorphism increased risk of developing CAD when compared to carriers of the *A* allele (odds ratio [OR] = 1.48, 95% CI: 1.03-2.14, $pC_{Dom} = 0.032$). Also under codominant, dominant, and additive models, the carriers of *A* allele of the *CETP* −971 *A/G* polymorphism were associated with increased risk of developing CAD when compared to carriers of the *G* allele (OR = 2.03, 95% CI: 1.20-3.43, $pC_{Co\text{-}dom} = 0.022$, OR = 1.83, 95% CI: 1.15-2.89, $pC_{Dom} = 0.008$, and OR = 1.39, 95% CI: 1.08-1.79, $pC_{Add} = 0.011$, respectively) (Table 3). All models were adjusted by gender, age, body index mass (BMI), glucose, total cholesterol, HDL-C, LDL cholesterol, triglycerides, hypertension, T2DM, dyslipidemia, and smoking habit.

Linkage disequilibrium analysis

The linkage disequilibrium analysis between the Taq1B *A/G* and −971 *A/G* polymorphisms SNPs located in the CETP gene showed four common haplotypes (Table 4). One of them four showed significant differences between patients with CAD and healthy controls. The "*AG*" haplotype was associated with high risk of developing restenosis (OR = 1.28, 95% CI: 1.02-1.62, p = 0.031). In this study, we did not find any other haplotype associated because these SNPs are in strong evidence of recombination (D' = 0.47), which results in that not joint cosegregation of these polymorphisms in the cases and controls.

Functional prediction

According, with the *in silico* programs ESEfinder 3.0 and SNP function prediction, the functional prediction analysis showed that the presence of the *G* allele of the Taq1B *A/G* polymorphism produces a binding motif for the MAF transcription factor. The analysis also revealed that the *A* allele of the −971 *A/G* polymorphism generates binding motifs for SP3 transcription factor. This analysis suggests that Taq1B *A/G* and −971 *A/G* SNPs located in the CETP gene could be influence in the expression other molecules.

Discussion

In our study, we found that the *G* and *A* alleles of the *Taq1B A/G* and *−971 A/G* SNPs, respectively, were

Table 2. Baseline clinical characteristics of the studied individuals (patients with CAD and healthy controls)

Clinical characteristics		CAD patients (n [%]) (n = 219)	Healthy controls (n [%]) (n = 607)	p-value
		Median (percentile 25-75)	Median (percentile 25-75)	
Age (years)		59 [54-66]	53 [48-59]	<0.0001
BMI (kg/m^2)		26 [24.2-29.1]	28 [25.5-30.7]	<0.0001
Blood pressure (mmHg)	Systolic	120 [110-135]	115 [107-127]	<0.0001
	Diastolic	80 [70-80]	72 [67-78]	<0.0001
Glucose (mg/dl)		117 [94-159]	91 [84-98]	<0.0001
Total cholesterol (mg/dl)		161[130-196]	189 [165-209]	<0.0001
HDL-C (mg/dl)		40 [34-49]	42 [35-53]	0.077
LDL-C (mg/dl)		102 [70-135]	115 [95-134]	0.001
Triglycerides (mg/dl)		167 [120-212]	154 [113-210]	0.144
Gender, n (%)	Male	170 (78)	461 (76)	0.344
	Female	49 (22)	146 (24)	
Hypertension, n (%)	Yes	98 (45)	239 (39)	0.092
Type II diabetes mellitus, n (%)	Yes	105 (48)	55 (9)	<0.0001
Dyslipidemia, n (%)	Yes	176 (80)	459 (75)	0.087
Smoking, n (%)	Yes	134 (61)	139 (23)	<0.0001

Data are expressed as median and percentiles (25th-75th). p values were estimated using Mann–Whitney U-test continuous variables and Chi-square test for categorical values.

Table 3. Distribution of *CETP* polymorphisms in patients with CAD and healthy controls

		Genotype frequency		Allele frequency	Model	OR (95% CI)	*pC*
CETP Taq1B	*A5454-G* (rs708272)						
Control	*AA*	*AG*	*GG*	*A/G*			
(n = 604)	187 (0.309)	285 (0.471)	132 (0.218)	0.546/0.454	*Codominant*	1.56 (0.99-2.13)	0.093
					Dominant	1.48 (1.03-2.14)	0.032
CAD	52 (0.241)	109 (0.504)	55 (0.261)	0.493/0.507	*Recessive*	1.23 (0.85-1.78)	0.281
(n = 216)					*Overdominant*	1.18 (0.86-1.62)	0.310
					Log-additive	1.25 (1.00-1.56)	0.048
CETP -971 A/G	(rs4783961)						
Control	*GG*	*AG*	*AA*	*A/G*			
(n = 604)	138 (0.229)	310 (0.513)	156 (0.257)	0.514/0.486	*Codominant*	2.03 (1.20-3.43)	0.022
					Dominant	1.83 (1.15-2.89)	0.008
CAD					*Recessive*	1.43 (0.92-1.92)	0.121
(n = 218)	35 (0.161)	118 (0.541)	65 (0.298)	0.571/0.429	*Overdominant*	1.14 (0.80-1.61)	0.468
					Log-additive	1.39 (1.08-1.79)	0.011

The p-values were calculated by the logistic regression analysis, and ORs were adjusted for age, gender, blood pressure, BMI, glucose, total cholesterol, HDL-C, LDL-C, triglycerides, and smoking habit. CAD: coronary artery disease; OR: odds ratio; CI: confidence interval; pC: p-value.

Table 4. Frequencies (%) of haplotypes of the *CETP –971 A/G* and *CETP Taq1B A/G* polymorphisms in patients with CAD and healthy controls

–971 A/G	*Taq1B A/G*	CAD	Controls	OR	95% CI	pC
Haplotype		Hf	Hf			
G	*A*	0.290	0.340	0.79	0.62-1.01	0.062
A	*G*	0.365	0.310	1.28	1.02-1.62	0.031
A	*A*	0.203	0.205	0.99	0.75-1.30	0.961
G	*G*	0.142	0.145	0.96	0.70-1.32	0.831

The order of the polymorphisms in the haplotypes is according to the positions in the chromosome [*CETP -971 A/G (rs4783961)* and *CETP Taq1B A/G (rs708272)*].
Hf: haplotype frequency; CAD: coronary artery disease; pC: p-corrected.

associated with an increased risk of developing CAD, but not with restenosis after coronary stenting. As far as we know, our work is one of few studies that describe the association of the *Taq1B A/G* and *–971 A/G* SNPs with risk of developing restenosis. In the literature, the association of these polymorphisms with restenosis is controversial with positive and negative results. For example, in contrast with our results. Kaestner et al. reported that *Taq1B A/G* SNP not is associated with restenosis after coronary stenting[24]. In line with this data, Zee et al. reported that *Taq1B A/G* SNP not is associated with incidence of restenosis after PTCA[25]. Nonetheless, it has been shown that the G allele of the *Taq1B A/G* SNP increased the risk of developing cardiovascular diseases such as CAD, acute coronary syndrome (ACS), and myocardial infarction[14-16,26]. In addition, the analysis of the *–971 A/G* SNP showed that the A allele increased risk of developing CAD in our population. In contrast with these data, Wang et al., in a meta-analysis, reported that the *–971 A/G* SNP not is associated with myocardial infarction in Caucasian and Asian populations[14]. Nonetheless, the haplotype analysis showed that the "*AG*" haplotype conformed by *–971 A/G*, and *Taq1B A/G* SNPs increased the risk of developing restenosis, similarly to previous report[16]. In this context, the haplotype has –971 *A* and *Taq1B G* alleles, and both of them were associated independently with the disease. This finding corroborated the role of these two alleles in the genetic susceptibility to CAD whether they were analyzed independently or as haplotypes. Finally, in our study, the –971 *A/G* and *Taq1B A/G* polymorphisms were associated with the risk of developing CAD, but controversial with other population. We suggest that the association of these SNPs may be due cardiovascular risk factors that play an important role in the development of the CAD[27], as well as, to the ethnic origin of the study populations. In this context, our population presents a characteristic genetic background that differs from other populations[28-30]. Therefore, we considered that more studies with a greater number of individuals and with different ethnic origins are needed to explain the true role of *CETP* SNPs in the risk of developing CAD.

Moreover, using bioinformatics tools, we determined the potential effect of the polymorphisms associated with the developing of restenosis. The analysis of the *Taq1B A/G* polymorphism showed that the presence of the *G* allele produces a binding motif for the *MAF* transcription factor. The MAF transcription factor is a basic region leucine zipper (bZIP)-type that is essential for activation or repression of pro-inflammatory cytokines in T cells, NKT cells, and regulatory T cells that play an important role in the inflammatory process[31,32]. On the other hand, the analysis of the –971 *A/G* polymorphism also revealed that the *A* allele generates binding motifs for *SP3* transcription factor. *SP3* transcription factor regulates the expression of tumor necrosis factor-alpha pathway inhibitors of apoptosis proteins and nuclear factor kB[33]. In addition, the *SP3* transcription factor regulates *CETP* promoter activity and thus contributes significantly to variation in plasma CETP mass concentration[34,35]. Additional to this information, experimental studies have shown that *Taq1B A/G* and *–971 A/G* polymorphisms are associated with the CETP activity, and concentration of HDL-C levels[12,35]. However, in contrast with these data, He et al., in a meta-analysis study, reported that the serum HDL-C levels are not associated with instent restenosis or CAD[36]. Nonetheless, data in the literature proposed that the role of *CETP* SNPs may be more important on the HDL structure that rather of the HDL-C plasma levels; due the selective increase

or decrease of cholesterol associated to certain HDL subclasses, probably the result of an impaired metabolism of lipoproteins[9,37,38]. However, the precise mechanism by which CETP participates in the concentration and remodeling of HDL-C remains to be elucidated. Nonetheless, we think that future investigations are warranted to understand the contribution of these polymorphisms to HDLs metabolism.

Conclusion

We found that the *Taq1B A/G* and *–971 A/G* polymorphisms of the *CETP* gene are associated with an increased risk of developing CAD, but not with restenosis after coronary stenting. On the other hand, due to the number of individuals included in our study and the specific genetics characteristics of the Mexican population, we considered that additional studies in a larger number of individuals and in other populations could help to define the true role of these polymorphisms as marker risk or protection in the developing restenosis after coronary stenting.

Acknowledgments

The authors are grateful to the study participants. Institutional Review Board approval was obtained for all sample collections. The authors are grateful to the technicians Marva Arellano-Gonzalez and Silvestre Ramirez-Fuentes for their participation in the collection of samples and extraction of DNA.

Funding

This research was funded by Consejo Nacional de Ciencia y Tecnología (CONACyT), Mexico City, Mexico (Project *Fronteras de la Ciencia*-1958).

Conflicts of interest

The authors have declared that no competing interests exist.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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