CORRELATIONS BETWEEN THE PRESENCE OF SIGMOID INTERVENTRICAL SEPTUM AND INCREASED RELAPSE RISK OF STROKE IN HYPERTENSIVE PATIENTS

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CORRELATIONS BETWEEN THE PRESENCE OF SIGMOID INTERVENTRICAL SEPTUM AND INCREASED RELAPSE RISK OF STROKE IN HYPERTENSIVE PATIENTS (Abstract) Objectives: Comparison between cerebrovascular accident (CVA) relapse in hypertensive patients with sigmoid interventricular septum (SIS) and CVA relapse in hypertensive patients without SIS. Materials and methods: We selected 36 hypertensive patients, all of them complicated with previous CVA; 18 patients had SIS (Group A) and 18 patients didn’t have SIS (Group B). The utilized methods were the following: clinical examination, electrocardiogram, transthoracic echocardiogram, biochemical findings and complete blood count, performed every 3 months, during 2 years of observation. Another method, addressed for CVA relapse patients, were cerebral computed tomography or magnetic resonance imaging. The recommended treatment was administered according to the European therapeutic guidelines. Results: 6 (out of 18) patients with SIS presented a CVA relapse and only 1 (out of 18) patient without SIS revealed a CVA relapse. Conclusions: Our results support recent conclusions from another publications: patients with SIS (an apparently benign condition, which is a part of the cardiac modifications usually discovered in elderly people) have a higher cardiovascular risk for acute events, than the patients without SIS. Keywords: SEPTUM, HYPERTENSIVE, CEREBROVASCULAR

The physiological aging of the heart can reveal different aspects: myocardium atrophy, isolated amiloid deposits, mitral annulus calcification or the angulations of the interventricular septum to the ascending aorta (1). This last mentioned modification is known (in echocardiography) as sigmoid interventricular septum (SIS) and has been described in the medical literature since 1969 (2). Initially, SIS has been just a physiological variant of the heart aging. Afterwards, its occurrence has been explained as due to the ascending aorta dilation (in elderly people) and to the tilting of the aorta towards the interventricular septum. The basal portion of the interventricular septum is bulging into the left ventricular outflow tract (LVOT) and is becoming sigmoid-shaped, without significant clinical consequences (3). The same authors, Chan and Veinot, suggested the fact that the benign aspect of the SIS could have
hemodynamic consequences (the obstruction of LVOT) if the patient had left ventricular hypertrophy associated to SIS. A physiopathology impact could occur in some cases of heart aging. Several Japanese authors mentioned the age-related morphological changes of the inter-ventricular septum; a part of them had proven the fact that the thickening of basal portion of the interventricular septum was more significant in hypertensive patients than in normotensives, during follow-up spanning 10 years (4); other authors (5) remarked the basal portion of the interventricular septum hypertrophy (age-related) even in normotensives and no hypertrophy of the mid-ventricular portion. All these studies allowed a better understanding of the so-called “sigmoid interventricular septum” modification. A new concept about SIS developed during the last 10 years: a part of these patients could have dynamic obstruction into the left ventricular outflow tract, followed by hemodynamic consequences: a decreased coronary and/or cerebral perfusion pressure and an increased telediastolic left ventricular pressure. The clinical consequences generated by these hemodynamic changes consisted of: angina pectoris, lipothymia / syncope and dyspneea on effort. The treatment of the patients with SIS and dynamic obstruction in LVOT, using a medication which decreased the pressure gradient, became absolutely required. Clinical studies have proven the beneficial effect (decrease of the gradient and improvement of the symptoms) of the association between negative inotropic agents: betablockers and cibenzoline (6, 7) or betablockers and dysopiraime (8).

MATERIAL AND METHODS
The study included 36 patients (men: 60%; women 40%), aged between 65-79 years.

The inclusion criteria were: arterial hypertension (with an evolution of at least 10 years); ischemic stroke (past medical history); adherence to medical recommendations.

The exclusion criteria were: smoking or alcohol intake, at the beginning of the study; diabetes mellitus; association of severe medical diseases (neoplasia, severe heart/ renal/ respiratory/ liver failure).

The patients were monitored through the following methods (every 3 months, during 2 years): clinical examination, biochemical findings (serum creatinine, transaminases, glycemia, and lipid profile), complete blood count, electrocardiogram, transthoracic echocardiogram (we used a Fukuda Denshi UF-850 XTD echograph machine). Cerebral computed tomography or magnetic resonance imaging were performed only for the CVA relapse patients. We had 2 groups of patients, after echocardiography: group A- 18 patients with SIS and group B-18 patients. We selected (through echocardiography) these 18 patients with SIS, CVA and arterial hypertension, from 107 patients with arterial hypertension and previous CVA.

Clinical examination revealed the following: 1. angina pectoris (4 classes’ classification, according to the Cardiology Canadian Society); 2. dyspneea (4 classes classification, according to the New York Heart Association); 3. vertigo; 4. sensibility and/ or motility disorders (confirmed by neurological examination); 5. blood pressure values (clinostatic and orthostatic positions). The CVA relapse has been clinically suspected; neurological consultation and cerebral computed tomography/magnetic resonance imaging were required for CVA confirmation.

Medical treatment (for group A, with
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SIS) consisted of betablockers (Metoprolol succinate 50-200 mg/day), antiplatelet agents (Clopidogrel 75 mg/day), statins (Atorvastatin 40-80 mg/day or Rosuvastatin 20-40 mg/day), diuretic „thiazide-like”: Indapamide 0.625-1.5 mg/day, single or associated (with angiotensin converting enzyme inhibitors), into a fixed combination- Perindopril / Indapamide 2.5/ 0.625 mg or 5/1.5 mg, daily. Those patients with SIS and obstruction in LVOT received smaller doses of diuretics or fixed combination (for blood pressure control); this caution was necessary for the prevention of gradient increasing in LVOT, followed by redoubtable clinical consequences. We selected calcium channel blockers (Amlodipine 2.5-10 mg) and diuretics (Indapamide 0.625-1.5 mg/day) for group B- the hypertensive patients without SIS, according to European therapeutic guidelines in elderly hypertensive with CVA. We preferred beta blockers (Nebivolol 2.5-10 mg/day or Carvedilol 6.25-12.5 mg, twice daily) instead of calcium channel blockers, for those hypertensive with associated ischemic heart disease.

The patients without SIS and elevated blood pressure values, despite treatment with calcium channel blockers and diuretics, also received angiotensin converting enzyme inhibitors (Perindopril 2.5-10 mg/day) or sartans (Telmisartan 20-80 mg/day). All the patients without SIS (group B) received Clopidogrel 75 mg/day and statins (Atorvastatin 40-80 mg/day or Rosuvastatin 20-40 mg/day), considering previous CVA.

RESULTS

I. Group A. This group was formed by the following: group A₁ - 7(out of 18) patients with SIS, LVOT obstruction and cardiovascular symptoms; group A₂- 4(out of 18) patients with SIS, symptoms and without LVOT obstruction; group A₃ - 7 (out of 18) patients with SIS and without symptoms or LVOT obstruction. All those 7 patients of group A₁ had cardiovascular symptoms: IIIrd class angina pectoris (angina on minor efforts) and IIIrd class dyspnea (dyspnea on minor efforts). Group A₂ had the following symptoms (fig.1): IIIrd class angina pectoris-2 patients; IIrd class dyspnea-1 patient and IIIrd class angina pectoris plus dyspnea-1 patient. The patients of group A₃ had no cardiovascular symptoms, but they have SIS. All the 7 patients of group A₁ improved after 3 months treatment their effort tolerance (IIrd class instead of IIIrd class). The patients of groups A₂ and A₃ remained in the same situation concerning effort capacity.

II. Group B. This group was formed by the following: group B₁ (fig.2) -10 (out of 18) patients without SIS, had the following symptoms: IIIrd class angina pectoris-4 patients; IInd class angina pectoris - 2 patients; IIIrd class dyspnea-1 patient; IIIrd class dyspnea plus angina pectoris- 3 patients; group B₂-8(out of 18) patients without SIS and without cardiovascular symptoms. Five (out of 7) patients from group B₁ had a favorable evolution of cardiovascular symptoms (they passed from IIIrd class to IInd class). Concerning the 8(out of 18) patients of group B₂ we noticed the same clinical condition throughout the 2 years study.

About CVA relapse, we revealed the fact that 6 out of 18 patients (33%) with SIS (from group A) had a CVA relapse, during 2 years study. All these 6 patients had LVOT obstruction, suggesting a strong correlation between the presence of hemodynamic significant gradient and CVA.
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relapse risk. The CVA relapse rate was significantly reduced - 5% - (1 out of 18 patients) among the patients without SIS (group B).

![Fig.1. The symptoms of the patients with SIS and without obstruction in LVOT](image1)

Echocardiography revealed obstruction in LVOT (mild / moderate obstruction: LVOT gradient was between 25-52 mmHg), in all 7 patients of group A. All these 7 patients recorded a qualitative echocardiographic improvement after the treatment: the highest LVOT gradient was 34 mmHg (after 3 months), comparing with the highest gradient-52 mmHg (at the beginning of the study).

The biochemical findings revealed the following aspects: 1) 2 patients from the group A with SIS maintained (at 3 months revaluation) a lipid profile associated with high cardiovascular risk (total cholesterol≥230 mg/dl). These 2 patients required the addition of Fenofibrate 160 mg to the previous statin and they had a favorable evolution of cholesterol values (at 6 months revaluation).

![Fig. 2. The symptoms of the patients without SIS](image2)

They were part of the 6 patients group with the relapse of the CVA; 2) at the 3 months revaluations of the serum creatinine, renal dysfunction has been preciously revealed in 3 (out of 18) patients from group B without SIS (treated with Perindopril 10 mg). We stopped Perindopril administration for these patients; replacing that medication with betablockers (the patients also continued the diuretics and calcium channel blockers).

We haven’t discovered right or left renal artery stenosis at these patients (there was the possibility they had atherosclerotic stenosis of the small renal arteries, undetectable with echography).

Cerebral computed tomography and magnetic resonance imaging proved the CVA relapse in all 7 patients clinically suspected: 6 (out of 18)-33% from group A.
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and 1 (out of 18)-5% from group B.

DISCUSSION
The clinical studies have proven the fact that an apparent benign aspect of heart aging, like sigmoid interventricular septum, could precipitate severe obstruction in LVOT, under special circumstances. The hemodynamic worsening (vasoplegic syndrome determined significant gradient in LVOT) after lumbar anesthesia, in patients with SIS, was an example for this situation (9). Another clinical situation which could develop the aforementioned gradient was anemia associated with SIS; anemia could induce hyperkinesias (with powerful ventricular contractility) and could decrease blood flow volume, both of them leading to sudden increase of the LVOT gradient (10). Our study has related results with other publications (11, 12): an apparent physiological heart aging situation – SIS - could increase the risk for ischemic cardiovascular events (cerebral or myocardial) and medical intervention could decrease this risk.

CONCLUSIONS
Our study noticed that increasing LVOT gradient in SIS patients with LVOT obstruction lead to a higher relapse of CVA (33%- 6 from 18 patients) than in patients without SIS (5%-1 from 18 patients). Despite medical treatment which had benefits towards LVOT gradient, those 6 patients with LVOT obstruction unfortunately developed CVA relapse.

That means they had done some mistakes according life style and behavior: they had a sudden increasing in LVOT gradient, due to heavy efforts or psychological distress. Those patients who performed heavy efforts developed a sudden more powerful left ventricle contraction, so an increasing LVOT gradient and decreasing cerebral blood flow; therefore they made an ischemic CVA under these circumstances (medical treatment could not protect the patient because the effort was too strong).

Those patients who had a major psychological distress had a sudden catecholamines releasing, which provoked a more powerful contraction of left ventricle, followed by the same consequences as aforementioned heavy efforts.

After a detailed anamnesis, we discovered one of this etiology at all our patients with CVA relapse. Future studies, including more patients, are necessary to complete these observations.

REFERENCES
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**INTRAVASCULAR LARGE B-CELL LYMPHOMA**

Intravascular lymphoma was first described in 1959 by Pfleger and Tappeiner in Germany. It was described as a neoplasm of the vascular endothelium, due to intravascular growth of malignant cells, hence the initial name of the disease as “angioendotheliomatosis proliferans systemisata”. In 1986 Sheibani et al proved, via immunohistochemical investigation, that the cells of intravascular lymphoma were of lymphoid origin and described the disease as angiotropic (intravascular) large-cell lymphoma. In 2008, the World Health Organization defined intravascular large B-cell lymphoma (IVLBCl) as a type of extranodal large B-cell lymphoma where growth is restricted to the lumina of vessels, particularly capillaries. Intravascular large B-cell lymphoma is rare, occurring at an estimated frequency of less than 1 person per million. Two forms have been described: classical, also known as Western form, with a cutaneous variant; and an Asian form occurring more frequently in the Far East. Intravascular lymphoma is most frequently a disease of B lymphocytes, although rare cases of thymus-cell (T-cell) and natural killer–cell disease have been reported; the World Health Organization considers these cases to be a separate entity. Intravascular large B-cell lymphoma is aggressive, and has historically been a rapidly fatal malignancy when diagnosis and treatment is delayed. Intravascular large B-cell lymphoma is a rare type of extranodal large B-cell lymphoma. It tends to occur in elderly patients, occurs with only slight predilection for male sex, and is without known risk factors. Accurate diagnosis is elusive, requires strong clinical suspicion, and tissue sampling and microscopy of at least 1 of what is typically several disseminated lesions. Microscopy will demonstrate large B cells sequestered within the intravascular spaces; these cells inconsistently express several of the typical B-cell antigens, with CD79a, CD20, MUM1/IRF4, and CD19 being the most commonly expressed. With the exception of a cutaneous variant, IVLBCL is aggressive and carries a grim prognosis, although the prognosis has improved with recent introduction of rituximab to combination chemotherapy regimens. These anthracycline-based or CHOP-like regimens plus rituximab have resulted in improvement of clinical course, and prolonged remission and survival (Dennis E. Orwat.; Nicholas I. Batalis, Intravascular Large B-Cell Lymphoma, *Arch Pathol Lab Med.* 2012;136:333–338).

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