Unraveling of the Effect of Nodose Ganglion Degeneration on the Coronary Artery Vasospasm After Subarachnoid Hemorrhage: An Experimental Study

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BACKGROUND: **Cardiac arrest is a major life-threatening complication of subarachnoid hemorrhage (SAH). Although medullary cardiocirculatuar center injury and central sympathetic overactivity have been suspected of initiating coronary artery spasm-induced cardiac arrest, we aimed to elucidate the effects of vagal ischemia at the brainstem on coronary vasospasm and sudden death in SAH.**

METHODS: **Twenty-six rabbits were randomly divided into 3 groups. Control (n = 5); SHAM (n = 8), and SAH group (n = 13). Experimental SAH was applied by injecting homologous blood into the cisterna magna, and the SHAM group was injected with isotonic saline solution also in the cisterna magna., Twenty-one days after the injection, histopathologic changes of the neuron density of nodose ganglia, the vasospasm index values of the coronary arteries, and the electrocardiographic events were analyzed.**

RESULTS: **Increased vasospasm index of the coronary arteries and degenerated neuron density of nodose ganglion were significantly different between animals with SAH, control, and SHAM groups ($P < 0.005$). If neurons of the nodose ganglia are lesioned due to ischemic insult during SAH, the heart rhythm regulation by vagus afferent reflexes is disturbed.**

CONCLUSIONS: **We found that there is causal relationship between nodose ganglion degeneration and coronary vasospasm. Our finding could be the reason that many cardiac events occur in patients with SAH. Vagal pathway paralysis induced by indirect sympathetic overactivity may trigger coronary vasospasm and heart rhythm disturbances. Our findings will aid in the planning of future experimental studies and in determining the clinical relevance of such studies.**

INTRODUCTION

Subarachnoid hemorrhage (SAH) is one of the most important neurosurgical diseases.[1] It accounts for only 5% of stroke.[2] At the present time, neurosurgical practice is confronted by an explosion of technology,[3,4] but SAH caused by an aneurysm rupture is still a devastating condition that carries significant mortality.[5-8] In addition, there is significant morbidity among survivors, which still poses substantial challenges during the early phase of patient management.[9] Outcomes in patients with aneurysmal SAH need to improve.[6] A better understanding, identification, and management of modifiable risk factors for SAH are pivotal to reducing its incidence.[6] It would undoubtedly lead to better patient outcomes.[10] Myocardial injury is a known complication of aneurysmal SAH.[11] A high incidence of cardiac problems, particularly electrocardiographic (ECG) abnormalities, may be seen in patients with SAH. Toussaint et al[12] reviewed medical records of 305 consecutive patients with angiographically proven aneurysmal SAH treated at the Mayo Clinic between 1990 and 1997, and we found 11 patients (3.6%) who had 14 episodes of cardiac arrest. The exact pathomechanisms behind acute myocardial injury or neurogenic myocardial damage are incompletely understood.[13] Initial theories focused on the sustained stimulation of sympathetic nerve endings on cardiomyocytes, but

Key words
- Coronary artery vasospasm
- Nodose ganglion
- Subarachnoid hemorrhage

Abbreviations and Acronyms
ECG: Electrocardiographic
SAH: Subarachnoid hemorrhage
VSI: Vasospasm index

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recent data suggest that dysfunction of the parasympathetic nervous system may contribute to these processes.[14] Survivors of SAH may lead to impaired activity of vagal fibers. This reduced vagal activity may be one of the major pathophysiologic cause of morbidity and mortality of SAH. Although the role of ischemic neurodegeneration of the nodose ganglia on cardiac arrest afterg SAH has been studied by Aydin et al,[14] these investigators could not show the real cause cardiac arrest. In addition, the main roles of vagus network pathologies in the development of coronary artery spasm have not previously been reported. It is possible that during SAH, the neural mechanisms that generate the dangerous vasospasms of the main brain arteries may also cause spasm of coronary arteries and death. An understanding of the reason of spasm of coronary arteries and death is crucial in achieving low mortality and morbidity after SAH. This study aimed to investigate the role of ischemic nodose ganglion degeneration induced by SAH on coronary artery vasospasm and heart rhythm regularity.

METHODS

Twenty-six rabbits aged 2.0 years and weighing 3.5 ± 0.25 kg were studied. The study design was approved by the Committee on Animal Research of Erzurum Ataturk University. This study was carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Experiment

Animals were randomly divided into 3 groups: control ($n = 5$), SHAM group ($n = 8$), in which injections of 0.75 mL of serum saline were administered to the cisterna magna, and SAH group ($n = 13$), in which injections of 0.75 mL of arterial autologue blood were administered to the cisterna magna. Balanced injectable anesthesia was used to reduce pain and mortality. After inducing anesthesia with isoflurane by face mask, 0.2 mL/kg of an anesthetic combination (ketamine HCl, 150 mg/1.5 mL; xylazine HCl, 30 mg/1.5 mL; and distilled water, 1 mL) was subcutaneously injected before surgery. During the experiment, all animals were monitored for changes in ECGs, respiration patterns, and blood oxygen concentrations. All parameters were recorded by a camera and analyzed by physicians who did not know the experimental group to which the individual animals belonged (Figure 1). All the animals were followed for up to 21 days without any medical treatment and then sacrificed.

Tissue Processing

All of the hearts and nodose ganglia of the vagus nerves were removed bilaterally for histologic examination. They were kept in a 10% formalin solution for 7 days. Then, 1-μm tissue sections were stained with hematoxylin and eosin, Masson's trichrome staining, and terminal deoxynucleotidyl transferase dUTP nick end labeling assay.

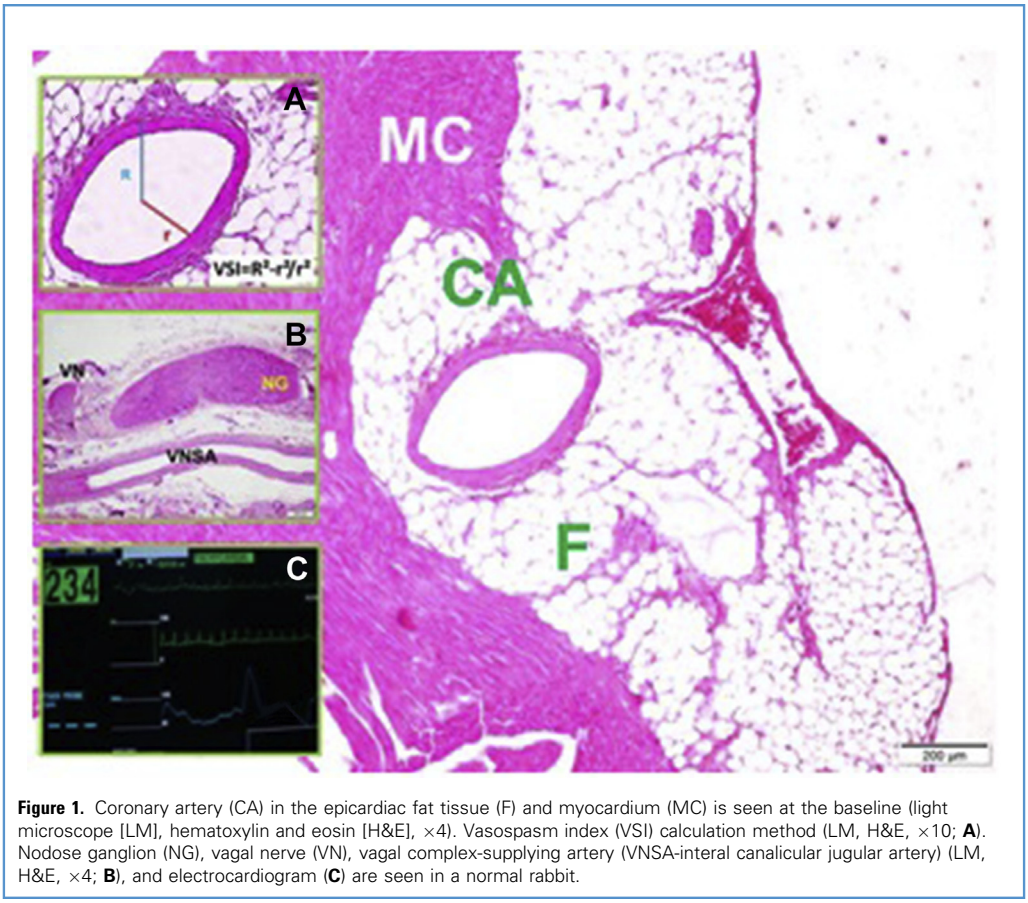

Figure 1. Coronary artery (CA) in the epicardiac fat tissue (F) and myocardium (MC) is seen at the baseline (light microscope [LM], hematoxylin and eosin [H&E], ×4). Vasospasm index (VSI) calculation method (LM, H&E, ×10; **A**). Nodose ganglion (NG), vagal nerve (VN), vagal complex-supplying artery (VNSA-interal canalicular jugular artery) (LM, H&E, ×4; **B**), and electrocardiogram (**C**) are seen in a normal rabbit.