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New determinants for casual peripheral mechanism of neurogenic lung edema in subarachnoid hemorrhage due to ischemic degeneration of vagal nerve, kidney and lung circuitry. Experimental study[1]

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Abstract

Purpose: To evaluate whether there is a relationship between renal artery vasospasm related low glomerular density or degeneration and neurogenic lung edema (NLE) following subarachnoid hemorrhage.
Methods: This study was conducted on 26 rabbits. A control group was formed of five animals, a SHAM group of 5 to which saline and a study group (n=16) injected with homologous blood into the sylvian cisterna. Numbers of degenerated axons of renal branches of vagal nerves, atrophic glomerulus numbers and NLE scores were recorded.
Results: Important vagal degeneration, severe renal artery vasospasm, intrarenal hemorrhage and glomerular atrophy observed in high score NLE detected animals. The mean degenerated axon density of vagal nerves (n/mm^2), atrophic glomerulus density (n/mm^3) and NLE scores of control, SHAM and study groups were estimated as 2.40±1.82, 2.20±1.30, 1.80±1.10, 8.00±2.24, 8.80±2.39, 4.40±1.14 and 154.38±13.61, 34.69±2.68 and 12.19±1.97 consecutively. Degenerated vagal axon, atrophic glomerulus and NLE scores are higher in study group than other groups and the differences are statistically meaningful ($p<0.001$).
Conclusion: Vagal complex degeneration based glomerular atrophy have important roles on NLE following SAH which has not been extensively mentioned in the literature.
Key words: Subarachnoid Hemorrhage. Renal Artery. Lung. Edema. Rabbits.

■ Introduction

Neurogenic lung edema (NLE) can be originated from vagosympathetic imbalance[1] following SAH. Vagal insufficiency and hypo-functioned hilar parasympathetic ganglia may be a causative role on the pathogenesis of NLE[2]. Vagal ischemia and cervical spinal network degenerations trigger respiratory disturbances because vagal ischemia also cause NLE by destroying heart functions. Cerebral fat embolism induced by SAH[3] could cause worsened prognosis of NLE because NLE has an important roles on systemic chylomicron embolism. SAH induced vagal lesions cause acute kidney injury[4]. SAH is prevalent causes of morbidity and mortality among dialysis patients. And even, chronic kidney disease is associated with higher stroke and SAH incidence[5]. Sodium retention related fulminant nephrotic edema arising from sympathetic over activity may aggravate NLE. Vagal micro-ganglia and plexus insufficiency around renal tissue[6] or increased sympathetic outflow cause renovascular hypertension[7]. Because the vagal stimulation prevents renal inflammation and renovascular pathologies. Interruption of vagal impulses inhibit hyperactive sympathetic receptors of kidneys[8] and renal sympathetic activity increase in vagotomised rats[9]. Although renal vasospasm is a dangerous complication of subarachnoid hemorrhage, nobody mentioned vagal insufficiency based neurogenic lung edema (NLE). The aim of this study was to elucidate whether there is a relationship between vagal ischemia induced renal artery vasospasm triggered glomerular degeneration and NLE following subarachnoid hemorrhage.

■ Methods

Animal husbandry and the study design followed the guidelines of the National Institutes of Health. The study plan was approved by the Ethic Committee of Ataturk University. All experimental protocols were conducted Pharmacology Laboratory, Ataturk University, School of Medicine, Erzurum.

This experimental study was conducted on 26 rabbits. Five rabbits (n=5) used to analyze the normal structure of the vagal nerve roots, lungs and kidney tissues. The remaining's (n=21) anaesthetized by subcutaneous injection of a mixture of ketamine hydrochloride (25 mg/kg), lidocain hydrochloride (15 mg/kg), and acepromasine (1mg/kg). After preparing the occipital region, five rabbits of (n=5) received an 1cc saline injection into the sylvian cisterna for SHAM group (n=5). SAH was produced by the injection of 0.5cc blood into sylvian cisterna taken from auricular arteries (n=16) once a day/three days periods. Animals followed-up two weeks then were sacrified. Their lungs, vagal nerve roots and kidneys were removed and preserved in 10% formalin solution for seven days. The specimens embedded in paraffin blocks and consecutive twenty sections of 5 µm were taken for the stereological examinations. Vagal nerve roots, kidney and lung tissues were stained with hematoxylene and eosin (H&E) and tunnel methods. All preparations were analysed by Stereological and cavaliery methods and data analysed by statistical methods. Histopathologically, cytoplasmic condensation, nuclear shrinking, cellular angulations and peri-cytoplasmic halo formation secondary to cytoplasmic regression and Tunnel staining positivity were considered as the criteria of epithelial degeneration in kidneys and lungs.

Physical dissector method was used to evaluate the numbers atrophic glomerulus numbers. Two dissector pairs were mounted on each slide. A counting frame was placed on consecutive section photographs on screen of PC for counting of neurons. The bottom and the left hand edges of the frame were excluded for exclusion lines together with the

extension lines. Other boundaries of the frame and the top-right corner were considered to be inclusion points and any particle which hit these lines or was located inside the frame counted as a dissector particle. Glomerules of kidneys were counted if they were visible in the reference section. Reference and look-up sections were reversed in order to double the number of dissector pairs without taking new sections. The average numerical density of glomerules (NvGN) per mm3 was estimated using the following formula: NvGN=ΣQN/txA

Where ΣQN is the total number of counted glomerules appearing only in the reference sections; t is the section thickness and A is the area of the counting frame. Cavalieri volume estimation method was used to obtain the total number of glomerules in each specimens. Total number of neurons was calculated by multiplication of the volume (mm^3) and numerical density of glomerules in each kidney were counted by stereological methods.

NLE scores were classified as: Normal-0, minimally edema-1, pulmonary artery vasospasm-2, alveolar hemorrhage-3, lymph node enlargement-4 and alveolar rupture-5, and that scores evaluated between 0-15. NLE scoring system is designed by ourselves according to clinical and neuropathological findings of neurogenic edema. Namely that scoring system was arranged by simple to complex histopathological findings of NLE[3].

To estimate atrophic glomerulus numbers, one hundred section was taken from each kidneys and normal/atrophic glomerulus numbers were estimated by Stereological methods. The relationship between the degenerated vagal axon, atrophic glomerulus and NLE scores were analyzed statistically. Statistical analysis was performed on IBM SPSS 20.0 (SPSS Inc., Chicago, Illinois, USA) software. The distribution of variables was evaluated for normality using the Shapiro-Wilk tests. Descriptive data were expressed as mean ± standard deviation. Normally, distributed data comprising continuous variables were analyzed using ANOVA test. Otherwise, the Kruskal-Wallis test was used. $P < 0.05$ was considered statistically significant.

■ Results

Two of 15 rabbits died within the second week, likely due to cardiorespiratory irregularities and new animals were restudied. Four animals in the study group died. In control group, the heart rate was 252±31 beats/min, the respiration rate was 24±4 breaths/min and the arterial oxygen saturation was 96±4%. Early phase of SAH, the heart rate decreased to 156±12 beats/min, the breathing rate was 13±3 breaths/min, and the oxygen saturation was 83±10%. Late phase of SAH, the pulse rate increased to 349±31 beats/min, while the respiration rate increased to 41±11 breaths/min with severe tachypnea and apneic variabilities. ST depression, ventricular extrasystols, bigeminal pulses, QRS separation, and fibrillations were observed in animals with SAH. Finally, decreased respiration amplitude, shortening of inspiration with prolonged expiration time, apnea-tachypnea attack, diaphragmatic breath and respiratory arrest observed in dead animals. Massive neurogenic lung edema detected in important glomerulus degeneration developed animals.

Important degenerative changes detected in vagal axons in severe hypertension detected animals. Severe renal artery vasospasm, intrarenal hemorrhage and renal glomerular degenerations observed in hypertensive rabbits. Normal blood pressure was estimated as 98±10/mmHg in normal rabbits, 105±12/mmHg in SHAM, 112±14/mmHg in middle (n=10), and >122±10/mmHg in severe glomerular degeneration detected animals (n=6). The mean degenerated axon

density of vagal nerves (n/mm^2), atrophic glomerulus density (n/mm^3) and NLE scores of control, SHAM and study groups were estimated as 2.40 ±1.82, 2.20±1.30, 1.80±1.10; 8.00±2,24 8.80±2.39, 4.40±1.14 and 154.38±13.61, 34.69±2.68 and 12.19±1.97 consecutively. Statistical analysis between the axonal degeneration, low density or atrophic glomerulus numbers and NLE scores were not meaningful in SHAM ($p>0.05$), but meaningful in study group ($p<0.001$). Numerical values are summarized in Table 1 and Figure 1.

Table 1 - Numerical results of study.

	Group A	Group B	Group C
Degenerated axon density of vagal nerves (n/mm^2)	3 (0-4)	8 (5-11)	153.50 (134-188)$^{\alpha, \beta}$
Atrophic glomerulus density (mm^3)	2 (1-4)	9 (6-12)	34 (32-42)$^{\alpha, \beta}$
NLE scores	1 (1-3)	4 (3-6)	12.50 (9-15)$^{\gamma, \beta}$

All values given median (minimum-maximum), Group A: Control Group, Group B: SHAM group, Group C: Study group, NLE: Neurogenic lung edema.
$^{\alpha}$ $p < 0.001$ between Group C and A, $^{\beta}$ $p < 0.001$ between Group C and B, $^{\gamma}$ $p < 0.001$ between Group C and A

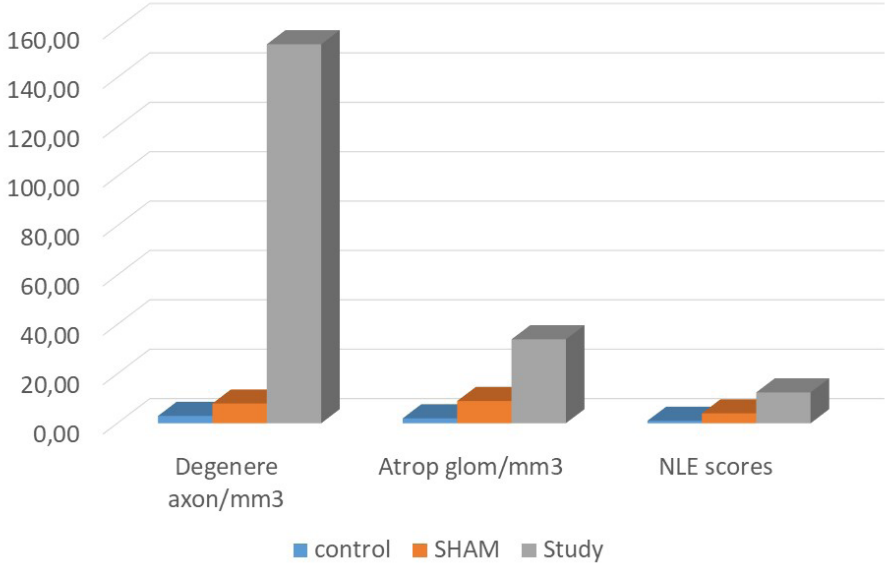

Figure 1 - Numerical results of study.

Histopathological findings were summarized as follows. Figure 2 shows histopathological appearance of renal arteries and glomerulus of kidneys in normal and atrophic glomerulus in SAH created rabbit. Histological representation of paranchymal renal arteries and normal glomerulus, renal branches of vagal nerves near the renal arteries and normal tubulus with normal glomerulus is seen in a normal rabbit in Figure 3.

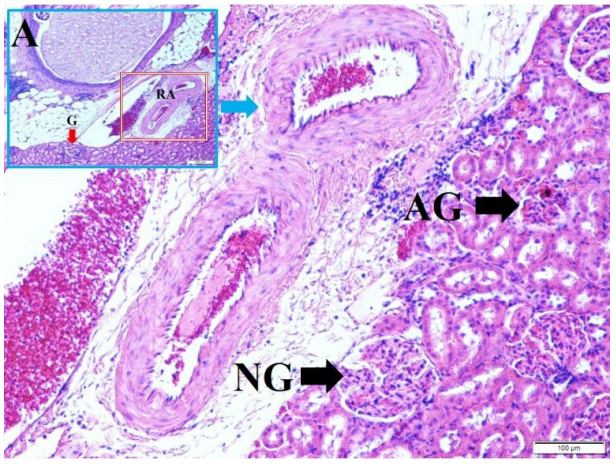

Figure 2 - Histopathological appearance of renal arteries (**RA**) and glomerulus of kidney (LM, H&E, x4/A); normal (**NG**) and atrophic glomerulus is seen in SAH created rabbit (LM, H&E, 10).

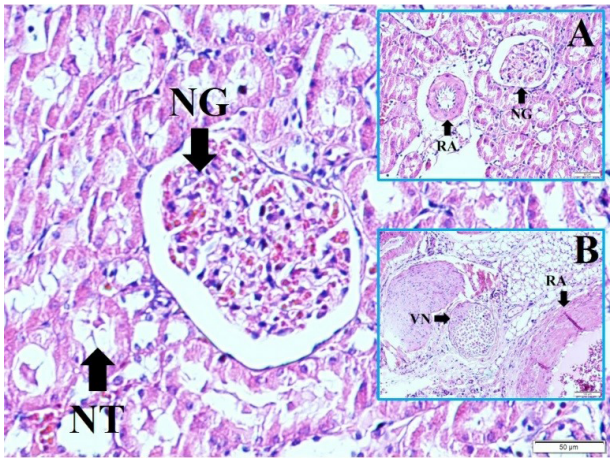

Figure 3 - Histological representation of paranchymal renal arteries (**RA**) and normal glomerulus (**NG**) (LM, M&E, x4/A), renal branches of vagal nerves (**VN**) near the renal arteries (**RA**) (LM, H&E, x4/B) and normal tubulus (**NT**) with normal glomerulus (**NG**) is seen in a normal rabbit (LM, H&E, x20/Base).

Figure 4 shows histological representation of paranchymal spastic renal arteries and atrophic glomerulus, renal branches of vagal nerves near the renal arteries with normal and degenerated axons and atrophic glomerulus with edematous tubules in a SAH created rabbit. Axon numbers estimation method is illustrated in renal branches of vagal nerves. Degenerated and normal axons were counted in per ¼ of all quadrants and multiplied by 4 (Fig. 5). Figure 6 shows glomerulus numbers estimation method is illustrated in renal tissues. Degenerated and normal glomeruluses were counted in per mm^3 of all consecutive four histological sections cutted with 5 micrometers. Histopathological appearances of NLE developed sample with spasm detected pulmonary artery, alveolar rupture, hemorrhage and enlarged lymph node of a SAH created animal (Fig. 6).

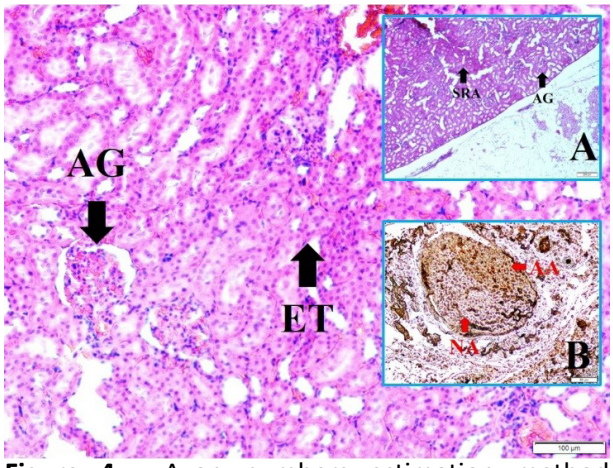

Figure 4 - Axon numbers estimation method is illustrated in renal branches of vagal nerves. Degenerated and normal axons were counted in per ¼ of all quadrants and multiplied by 4 (LM, H&E, x10/B).

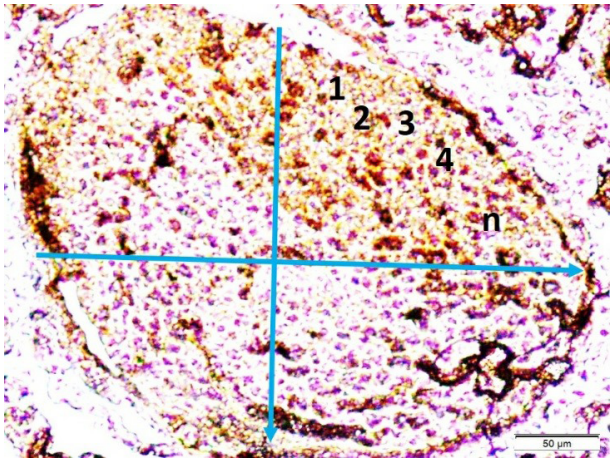

Figure 5 - Glomerulus numbers estimation method is illustrated in renal tissues. Degenerated and normal glomeruluses were counted in per mm^3 of all consequtive four histological sections cutted with 5 micrometers silices (LM, H&E, x10/4).

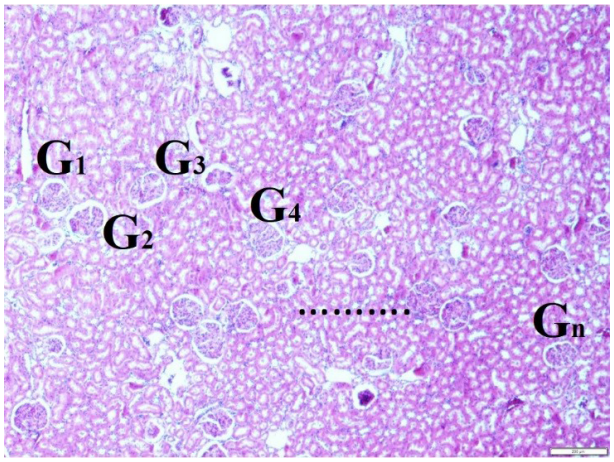

Figure 6 - Histopathological appearances of NLE developed sample with spasm detected pulmonary artery (**SPA**), alveolar rupture (**R**) (LM, H&E, x10/ Base), hemorrhage (**H**) (LM, H&E, x4/A) and enlarged lymph node (**LN**) (LM, H&E, x4/B) of a SAH created animal.

■ Discussion

A synopsis of study

Autonomic control of the lungs are maintained by cervical sympathetic-vagal network and cervicothoracic spinal nerves. Neurogenic lung edema (NLE) is known as a serious complication of SAH, but the rational neuronal mechanism of that over activity has not yet been understood. High neuron density of stellate ganglion may have important roots in sympathetic over activity-related NLE in SAH[1]. Cervical dorsal root ganglion degenerations result in cardiorespiratory disturbances[10]. Vagal ischemia may be a causative role on the pathogenesis of NLE. Degenerated vagal complex may be a causative factor in the lymph node infarct in SAH[11]. Failure hilar parasympathetic ganglia may be responsible for pulmonary vasospasm in lungs. SAH related NLE cause systemic chylomicron embolism[3] in kidneys and rely on renal insufficiency. Vagal ischemia originated renal vagal network degeneration increase in renal sympathetic over activity focused renal vasospasm / renal hypertension/glomerular injury/renal insufficiency induced NLE.

Vagus and renal innervation

Renal tissues are innervated by vagal nerves, sympathetic trunks and thoracolumbar somatosensitive fibers and renal functions are regulated by that neural network[12]. Vagal efferent and afferent preganglionic neurons are seen in the suprarenal ganglia. These vagal contacts may directly control the postganglionic outflow and modulate postganglionic vagal inputs which exert sympathetic outflow[13]. Vagal efferents terminated in micro ganglia and periarterial sympathetic named as renal plexuses and maintain the essentials roles of kidney. Parasympathetic innervation deficiency of the adrenal glands[6] should be considered as a factor for classical renovascular hypertension. Baroreflex dysfunction cause in renal failure by aortic vagal efferent nerve ischemia[14]. Cardiopulmonary reflexes and body fluid electrolyte imbalances controlling could not be regulated by vago-sympathetic network following SAH[15].

Increased sympathetic activity and reduced cardiac vagal tone aggravate hypertension, kidney disease, heart failure[7]. Efferent renal sympathetic nerve activity increase in vagotomised rats[9]. Impaired reflex control of heart rate is frequently disrupt via depressed baroreflex sensitivity following myocardial infarction[16]. Under appropriate conditions vagal afferents stimulate renal release of dopamine and produce a neurogenically mediated natriuresis[17].

Cervical vagotomy abolished the hemorrhage-induced inferior cardiac sympathetic activity and renovascular hypertension[18]. Interruption of the impulse by vagotomy result of inhibit suppression of the hyperactive sympathetic receptors on kidneys[8].

Prolonged ischemia during reperfusion are mediated by activation of vagal and sympathetic afferent endings on kidneys[19].

Vagotomy alters sympathetic outflow predominantly to the renal circulations. Sympathetic control of the kidney and spleen can be selectively maintained by sympathetic outflow[20]. Renal and adrenal sympathetic nerve activity cause acute renal hemorrhage secondary to inputs decreased vagal activity[21]. Activation of cardiac sympathetic afferent neurons can lead to alterations in excretion of water and electrolytes[22].

Baroreflex neural regulation of renal blood flow controls carotid sinus and vagus nerves[23]. Ischemia of carotid sinus baroreceptors contribute to deteriorated baroreceptor reflexes[24]. If carotid baroreflex arc lesioned; arterial pressure, heart rate and renal vascular conductance deteriorated[25]. Systemic hypoxia markedly potentiates the reflex renal constriction[26]. In our model, vagal ischemia based renovascular hypertension are discussed.

Subarachnoid hemorrhage renal disease relations

Intracerebral hemorrhage, cerebral infarction, and SAH remain a dangerous causes of morbidity and mortality among dialysis patients. SAH increases the incidence of acute kidney injury[4]. Acute kidney injury is common in critically ill patients and may contribute to poor outcome and renal functions can be disordered in SAH. Kidney transplantation recipients have a higher risk of SAH compared to the general population[27]. Isolated anterior spinal artery aneurysms may cause renal dysfunction in SAH patients[28]. Chronic kidney disease is associated with higher stroke and SAH incidence[5]. Hypertonic saline therapy is a risk factors for developing acute kidney injury following SAH[29]. Hyponatremia is common complication in neurosurgical patients and associated with significant morbidity and mortality. In our opinion, glomerulopathies may be an important factor in such cases. Hypokalemia is a common electrolyte disorder in the intensive care unit. Hyponatremia is often associated with, and worsens, the prognosis of severe aneurysmal SAH. Several sodium and water intake have been described in SAH[30]. Hyponatremia may be originated from SAH induced glomerular disease. Hyponatremia is frequently seen in neurosurgical patients and generally attributed to inappropriate secretion of antidiuretic hormone. According to this knowledge; we announced that disordered sodium metabolism should be regarded as renal diseases related NLE.

Based on our findings, we hypothesized that vagal ischemia induced by SAH rely on descendant degeneration renal vagal network and developed renal sympathetic overactivity and renal vasospasm cause renal hypertension, glomerular injury and renal insufficiency presented by body fluid collection and also NLE which has not been mentioned in the literature.

Limitations

If renal angiography, ultrasonography or other invasive procedures and biochemical analysis should be done the better results could be obtained.

The animals were divided into three group as five (n=5) for the control group, five for the SHAM group (n=5) and the remaining sixteen (n=16) for the study group. Many researchers consider five animals per group as adequate sample size, but after reviewing recently published papers of on this issue, it can come to the conclusion that this notion of five animals per group has a little scientific and statistical basis.

■ Conclusion

Vagal complex degeneration based glomerular atrophy have important roles on NLE following SAH.

■ References

1. Onen MR, Yilmaz I, Ramazanoglu L, Tanriverdi O, Aydin MD, Kanat A, Yolas C, Sipal S. Rational roots of sympathetic overactivity by neurogenic pulmonary edema modeling arising from sympathyco-vagal ımbalance in subarachnoid hemorrhage: an experimental study. World Neurosurg. 2016 Aug;92:463-70. PMID: 27132179.
2. Araz O, Aydin MD, Gundogdu B, Altas E, Cakir M, Calikoglu C, Atalay C, Gundogdu C. Preventive role of hilar parasympathetic ganglia on pulmonary artery vasospasm in subarachnoid hemorrhage: an experimental study. Turk Neurosurg. 2015;25(4):519-25. PMID: 26242326.
3. Aydin MD, Kotan D, Aydin N, Gundogdu C, Onder A, Akcay F. Mechanism of cerebral fat embolism in subarachnoid hemorrhage: an experimental study. Neuropathology. 2006 Dec;26(6):544-9. PMID: 17203591.
4. Kieninger M, Unbekannt D, Schneiker A, Sinner B, Bele S, Prasser C. Effect of hydroxyethyl starch solution on ıncidence of acute kidney ınjury in patients suffering from cerebral vasospasm following aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2017 Feb;26(1):34-40. PMID: 27059048.
5. Ovbiagele B. Chronic kidney disease and risk of death during hospitalization for stroke. J Neurol Sci. 2011 Feb 15;301(1-2):46-50. PMID: 21094955.
6. Berthoud HR, Powley TL. Characterization of vagal innervation to the rat celiac, suprarenal and mesenteric ganglia. J Auton Nerv Syst. 1993 Feb;42(2):153-69. PMID: 8450174.
7. Millar PJ, Floras JS. Statins and the autonomic nervous system. Clin Sci (Lond). 2014 Mar;126(6):401-15. PMID: 24274967.
8. Hiatt N, Hiatt JR. Vagal modulation of the insulin secretory response to KCl loading in nephrectomized dogs. Horm Metab Res. 1995 Feb;27(2):67-9. PMID: 7759059.
9. DiBona GF, Sawin LL. Reflex regulation of renal nerve activity in cardiac failure. Am J Physiol. 1994 Jan;266(1 Pt 2):R27-39. PMID: 8304550.
10. Kazdal H, Kanat A, Aydin MD, Yazar U, Guvercin AR, Calik M, Gundogdu B. Sudden death and cervical spine: a new contribution to pathogenesis for sudden death in critical care unit from subarachnoid hemorrhage; first report - An experimental study. J Craniovertebr Junction Spine. 2017 Jan-Mar;8(1):33-8. PMID: 28250634.
11. Atalay C, Gundogdu B, Aydin MD. Vagal ıschemia ınduced lung ımmune component ınfarct following subarachnoid hemorrhage: an experimental study. Turk Neurosurg. 2017;27(4):509-15. PMID: 27593821.
12. Thames MD, Yuih SN, Fortner CA, Brands DB. Control of lumbar sympathetic nerve traffic by vagal cardiopulmonary baroreflexes in renal hypertension. Circ Res. 1987 Oct;61(4 Pt 2):I72-5. PMID: 3652405.
13. Berthoud HR, Powley TL. Interaction between parasympathetic and sympathetic nerves in prevertebral ganglia: morphological evidence for vagal efferent innervation of ganglion cells in the rat. Microsc Res Tech. 1996 Sep 1;35(1):80-6. PMID: 8873061.
14. Salman IM, Phillips JK, Ameer OZ, Hildreth CM. Abnormal central control underlies impaired baroreflex control of heart rate and sympathetic nerve activity in female Lewis polycystic kidney rats. J Hypertens. 2015 Jul;33(7):1418-28. PMID: 26039532.
15. Veelken R, Leonard M, Stetter A, Hilgers KF, Mann JF, Reeh PW, Geiger H, Luft FC. Pulmonary serotonin 5-HT3-sensitive afferent fibers modulate renal sympathetic nerve activity in rats. Am J Physiol. 1997 Feb;272(2 Pt 2):H979-86. PMID: 9124462.
16. Jones CM, Quinn MS, Minisi AJ. Reflex control of sympathetic outflow and depressed baroreflex sensitivity following myocardial infarction. Auton Neurosci. 2008 Aug 18;141(1-2):46-53. PMID: 18554991.
17. Morgunov N, Baines AD. Vagal afferent activity and renal nerve release of dopamine. Can J Physiol Pharmacol. 1985 Jun;63(6):636-41. PMID: 4042002.
18. Tochihara M. Reflex control of cardiac sympathetic nerve activity in anesthetized rats. Hokkaido Igaku Zasshi. 1996 Mar;71(2):247-58. PMID: 8641679.
19. Ustinova EE, Schultz HD. Renal sympathetic nerve activity during cardiac ischemia and

reperfusion in rats. Am J Physiol. 1996 Oct;271(4 Pt 2):R1033-40. PMID: 8897997.
20. Weaver LC, Fry HK, Meckler RL. Differential renal and splenic nerve responses to vagal and spinal afferent inputs. Am J Physiol. 1984 Jan;246(1 Pt 2):R78-87. PMID: 6696104.
21. Dong XH, Pan JY, Zhan CY. Different changes in renal sympathetic nerve activity and adrenal sympathetic nerve activity produced by hemorrhage. Sheng Li Xue Bao. 1992 Oct;44(5):478-86. PMID: 1293764.
22. Meckler RL, Macklem LJ, Weaver LC. Excitation of cardiac sympathetic afferent nerves: effects on renal function. Am J Physiol. 1981 Nov;241(5):R267-70. PMID: 7304769.
23. Mitani Y, Hosomi H, Tateishi J, Iwasaki T. Flow-dependence of vasodilatory response in renal vascular bed to hemorrhage in dogs. Biomed Biochim Acta. 1987;46(6):487-98. PMID: 3675566.
24. Ohta H, Talman WT. Baroreceptors in the carotid sinus contribute to arterial baroreceptor reflexes in normotensive rats. Clin Exp Pharmacol Physiol Suppl. 1995 Dec;22(1):S62-3. PMID: 9072445.
25. McIlveen SA, Hayes SG, Kaufman MP. Both central command and exercise pressor reflex reset carotid sinus baroreflex. Am J Physiol Heart Circ Physiol. 2001 Apr;280(4):H1454-63. PMID: 11247754.
26. Pelletier CL, Shepherd JT. Effect of hypoxia on vascular responses to the carotid baroreflex. Am J Physiol. 1975 Jan;228(1):331-6. PMID: 1147025.
27. Sood MM, Garg AX, Bota SE, Marisiddappa L, McArthur E, Naylor KL, Kapral MK, Kim SJ, Lam NN, Molnar AO, Harel Z, Perl J, Knoll GA. Risk of major hemorrhage after kidney transplantation. Am J Nephrol. 2015;41(1):73-80. PMID: 25677869.
28. Seerangan G, Narayanan M. A rare case of subarachnoid hemorrhage due to rupture of ısolated anterior spinal artery aneurysm in a patient with polycystic kidney disease. Case Rep Nephrol Urol. 2012 Jul;2(2):108-12. PMID: 23197965.
29. Kumar AB, Shi Y, Shotwell MS, Richards J, Ehrenfeld JM. Hypernatremia is a significant risk factor for acute kidney injury after subarachnoid hemorrhage: a retrospective analysis. Neurocrit Care. 2015 Apr;22(2):184-91. PMID: 25231531.
30. Audibert G, Steinmann G, de Talance N, Laurens MH, Dao P, Baumann A, Longrois D, Mertes PM. Endocrine response after severe subarachnoid hemorrhage related to sodium and blood volume regulation. Anesth Analg. 2009 Jun;108(6):1922-8. PMID: 19448223.

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