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Impact of Obesity on Subarachnoid Hemorrhage-Induced Cerebral Vasospasm: An Experimental Rat Model

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ABSTRACT

AIM: To investigate the effect of obesity on the severity of cerebral vasospasm after subarachnoid hemorrhage.

MATERIAL and METHODS: In this study, six experimental groups, each consisting of 10 rats, were defined (60 rats in total). Groups 1 and 2 comprised rats with normal body weight, Groups 3 and 4 comprised obese rats, and Groups 5 and 6 comprised rats that returned to normal body weight after being obese. Rats in Groups 2, 4, and 6, represented the study groups, and experimental SAH was induced in them. Group 1, 3 and 5 was determined as the control group. Basilar artery lumen areas and wall thicknesses were measured and compared in all groups.

RESULTS: The luminal area of the basilar artery was significantly reduced in Groups 2, 4, and 6, than in Groups 1, 3, and 5, respectively. This indicated the development of vasospasm. No significant differences were found in the basilar artery luminal areas and wall thicknesses between Groups 1, 3, and 5. However, there were significant differences between Groups 2, 4, and 6. The basilar artery luminal area was significantly smaller in Group 4 than in Groups 2 and 6. There was no significant difference in basilar artery luminal areas between Groups 2 and 6.

CONCLUSION: This experimental study elucidated that the severity of vasospasm subsequent to subarachnoid hemorrhage escalated in the presence of obesity, and conversely, a return to normal body weight mitigated the severity of cerebral vasospasm. Prospective clinical investigations ought to scrutinize the correlation between obesity and vasospasm, emphasizing the necessity for vigilant monitoring of vasospasm post-SAH in obese patients.

KEYWORDS: Obesity, Cerebral vasospasm, Subarachnoid hemorrhage, Delayed cerebral ischemia

ABBREVIATIONS: CSF: Cerebrospinal fluid, **CV:** Cerebral vasospasm, **DCI:** Delayed cerebral ischemia, **eNOS:** Endothelial NO synthase, **ET-1:** Endothelin-1, **NO:** Nitric oxide, **SAH:** Subarachnoid hemorrhage

INTRODUCTION

Cerebral vasospasm (CV) is characterized by narrowing of the cerebral vessels, leading to a decrease in distal cerebral blood flow (21). It is one of the most common complications of subarachnoid hemorrhage (SAH) and is associated with poor clinical outcomes (7). Although 70% of patients with SAH experience angiographic vasospasm, only 30% of them develop neurological deficits (7,21). CV typically begins 3 days after SAH develops, peaks between days 8 and 11, and gradually resolves after the third week (10). CV can lead to delayed cerebral ischemia (DCI), which causes neurological deficits (26). Several retrospective studies have investi-

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gated the risk factors for DCI in patients with aneurysmal SAH (15,17,26). In these studies, various factors such as advanced age, increased body weight, hypertension, and hyperglycemia have been shown to increase the risk of DCI (15,17,26). The mechanism of SAH-induced CV has not been fully elucidated. However, the following factors are believed to contribute to its pathophysiology: activation of calcium channels, reduced production of nitric oxide (NO), constrictor effect of oxidative stress and free radicals on smooth muscles, and sympathetic activation (35). Obesity, characterized by increased fat accumulation, reportedly decreases endothelial NO synthase (eNOS) activity, which leads to reduce NO production, endothelial dysfunction, increased levels of vasoconstrictor endothelin-1 (ET-1), and heightened sympathetic activation (33). In addition, obesity is associated with potassium channel dysfunction in rats, which plays a role in the impairment of arterial vasodilation (6). Therefore, obesity disrupts vascular relaxation and renders blood vessels prone to vasoconstriction (33).

Determining CV risk factors and the resulting development of DCI will be useful in developing follow-up algorithms in SAH patients. In this study, the effect of obesity on CV was demonstrated in an experimental rat model.

MATERIAL and METHODS

This study received approval from the Local Ethics Committee (No: 2022-11-99; dated 25/05/2022), and all experimental procedures were carried out at animal laboratory. Animal handling and procedures adhered strictly to ethical standards as prescribed by the guidelines outlined in the "Guide for the Care and Use of Laboratory Animals (22). All rats were housed under optimal environmental conditions at a standard room temperature, an appropriate light and dark cycle (12 hours light and 12 hours dark), and an optimal humidity range (35%–45%), and in suitable cages. A total of 60 healthy male Sprague–Dawley rats (age 16 weeks) were included in the study. The body weight of each rat was measured and noted weekly under the same conditions and using the same device. The body lengths (Nasoanal distance) of the rats were measured and noted weekly. Using the body weights and nasoanal body lengths of the rats, the body mass indices were calculated using the Lee method (Lee index) (12,23). The Lee index is calculated as the cube root of the body weight (in grams) divided by the nasoanal length (in centimeters) and multiplied by 1000, which corresponds to the body mass index in humans (12). Results exceeding 310 indicated obesity in the rats (12).

Experimental Groups

In this study, six experimental groups were defined (Groups 1, 2, 3, 4, 5, and 6). Each group consisted of 10 rats. The rats in Groups 1 and 2 were provided with a normal amount of food and tap water for 8 weeks. The rats in these two groups were fed a standard-calorie balanced rat chow (containing approximately 10% fat, 20% protein, 65%–70% carbohydrates, and appropriate amounts of vitamins and minerals). At the end of 8 weeks, the Lee index values of the rats were consistent with normal body weight (Lee index < 310). The rats in Groups 3 and 4 were fed high-calorie rat chow (containing approximately 40%–50% fat, 30%–40% carbohydrates, 15%–20% protein, and appropriate amounts of minerals and vitamins) for 8 weeks. At the end of 8 weeks, the Lee index values of the rats were consistent with obesity (Lee index > 310). Unlike the rats in the Groups 1, 2, 3, and 4 that were followed for 8 weeks, the rats in Groups 5 and 6 were monitored for 16 weeks. The 16-week period was divided into two periods: the first 8 weeks and the second 8 weeks. During the initial 8 weeks, the rats were fed high-calorie rat chow. At the end of 8 weeks, the Lee index values of the rats were consistent with obesity (Lee index > 310). In the subsequent 8 weeks, the diet of the rats was altered; they were fed standard-calorie rat chow, and a normal-calorie feeding protocol was initiated. Furthermore, the feeding intervals of these rats were adjusted, and longer intervals were implemented. At the end of the second 8-week period, the rats had Lee index values consistent with normal body weight (Lee index < 310). Thus, this group consisted of rats that were obese at the end of the first 8 weeks but whose body weight returned to normal at the end of the 16th week observation period.

Procedures Applied to the Experimental Groups

At the end of the described durations and dietary protocols, the rats in Groups 1, 3, and 5 were euthanized using the high-dose carbon dioxide inhalation method, which is in compliance with the ethical standards of the animal laboratory. Groups 1, 3, and 5 were defined as control groups, and the rats were euthanized without inducing SAH. Immediately following the euthanasia, under surgical laboratory conditions, the brain hemispheres and brainstem structures of the rats were dissected as a single piece using appropriate surgical methods. Experimental SAH was induced in the rats in Groups 2, 4, and 6 (at the end of the 8th week for Groups 2 and 4, and at the end of the 16th week for Group 6). The rats were injected intraperitoneally with ketamine (100 mg/kg^2) and xylazine (10 mg/kg^2) to achieve anesthesia without compromising their respiration; spontaneous breathing was maintained. After positioning the anesthetized rats in the prone position, a 27-gauge needle was inserted via the median suboccipital area into the cisterna magna under sterile conditions. Subsequently, the tail was incised, and 0.3 mL of autologous blood was drawn from each rat using a heparinized insulin syringe. Thereafter, cerebrospinal fluid (CSF) was drawn from the subarachnoid space, mixed with autologous blood obtained from the tail incision, and injected into the cisterna magna. Thus, an experimental SAH model was created in the rats. The rats in which experimental SAH was induced (Figure 1), were observed for 7 days, allowing for the development of CV. At the end of the 7 days, the rats were euthanized using the high-dose carbon dioxide inhalation method. The same steps and appropriate dissection methods of the rat brains described for Groups 1, 3, and 5 were applied to the rats with SAH.

Histopathological Examination

All measurements were made by a histopathologist (N.A.) The single-piece brain was sectioned at the level of the pons, and the structure of the basilar artery was examined under a

light microscope (Figure 2). Sections stained with hematoxylin and eosin, which were prepared using paraffin blocks of the tissues, were scanned using a digital scanning and imaging system and digital images were generated. The luminal area and wall thickness of the basilar artery were measured using digital tissue images (Figure 3). H&E stained sections were scanned with 3D HISTECH, Panoramic P250 Flash 3 and Version Panoramic Scanner 3.0.2 and the luminal area and wall thickness measurements were made on the digitized images with SlideViewer 2.5 software.

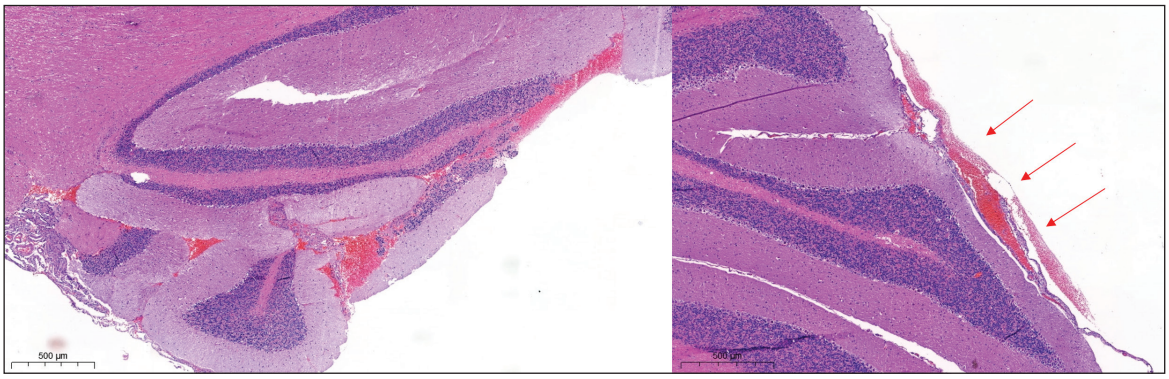

Figure 1: The hematoxylin and eosin-stained left and right figures show microscopic images of the cerebral tissue of rats with induced subarachnoid hemorrhage. Red arrows on the right image indicating subarachnoid hemorrhage beneath the arachnoid mater (Left: x28.3; Right: x30.1).

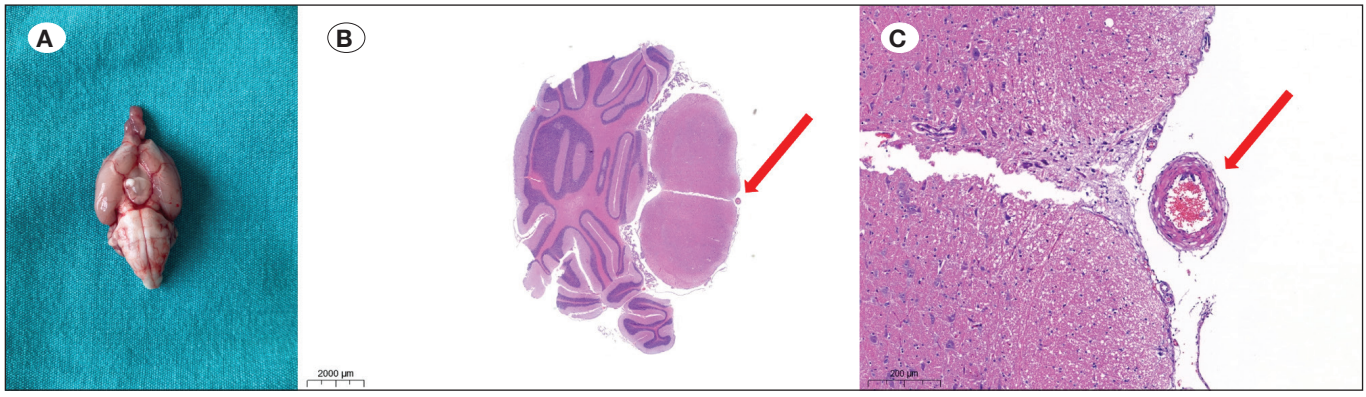

Figure 2: The structure of the basilar artery as seen in **A)** a fresh specimen, **B)** under a light microscope (hematoxylin and eosin-stained section, x3.6), and **C)** an enlarged view under a light microscope (x40.2). Red arrow indicates the basilar artery structure.

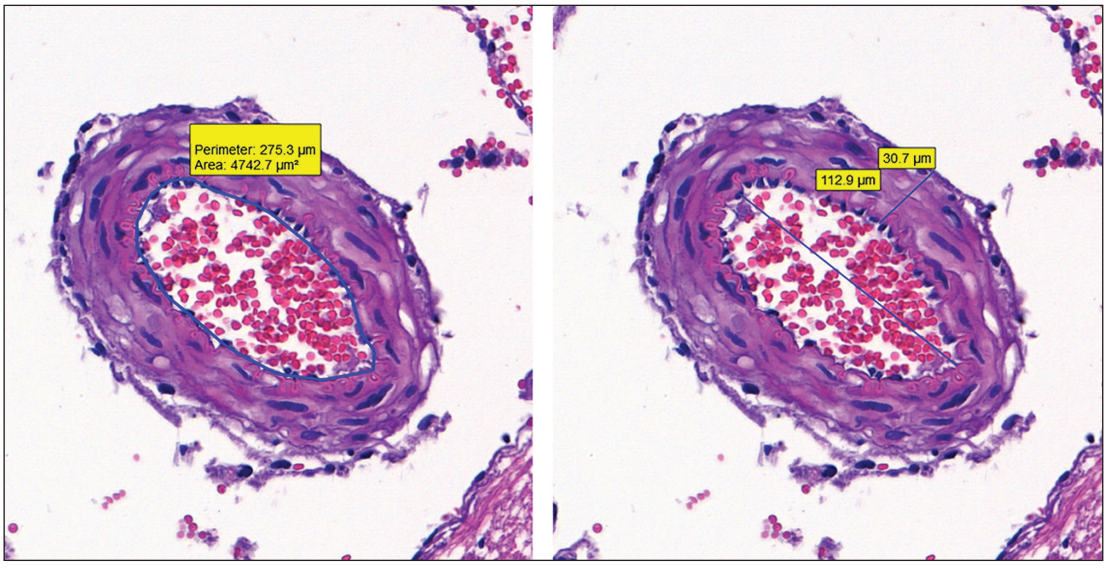

Figure 3: Measurement of the wall thickness and luminal area of the basilar artery using images obtained from digital tissue scans (Hematoxylin-Eosin, x48.7).

Statistical Analysis

Statistical analyses were conducted using SPSS (version 22.0; IBM, Armonk, NY, USA). The Mann–Whitney U–test, Kruskal–Wallis variance analysis, and Dunn test were used to evaluate the relationship between basilar artery luminal area and wall thickness among the groups. The results were interpreted at a p-value of <0.05 was considered statistically significant.

RESULTS

The study included 60 rats that were divided into six groups of 10 rats each. Groups 1 and 2 consisted of rats with normal body weight after 8 weeks (mean Lee index was 294.4 ± 6.7 and 291.6 ± 7.5, respectively). Groups 3 and 4 consisted of rats who were obese after 8 weeks (mean Lee index was 325 ± 5.7 and 327.4 ± 7.8, respectively). Groups 5 and 6 comprised rats who were obese after 8 weeks (mean Lee index was 324.5 ± 7.5 and 324.8 ± 6.9, respectively) and whose body weights were normal at the end of 16 weeks (mean Lee index was 298.2 ± 6.1 and 295.6 ± 5.7, respectively).

Comparison of Rats with Normal Body Weight

The basilar artery luminal area of the rats in Group 2 was significantly lower than that of the rats in Group 1 (p<0.001). This indicates that CV developed after SAH was induced in the rats with normal body weight, resulting in a significant reduction in arterial luminal area (mean luminal area in Groups 1 and 2 was 5032.9 ± 307.4 μm² and 4338 ± 400.6 μm², respectively). Evaluation of the basilar artery wall thickness of the rats in Groups 1 and 2 did not reveal a significant relationship (p=0.07). This indicates that the thickness of blood vessel walls did not significantly change after SAH and CV development in the rats with normal body weight (mean wall thickness in Groups 1 and 2 groups was 37.8 ± 4.4 μm and 41 ± 4.2 μm, respectively).

Comparison of Obese Rats

The basilar artery luminal area of the rats in Group 4 was significantly lower than that of the rats in Group 3 (p<0.001). This indicates that CV developed after SAH was induced in the obese rats, resulting in a significant reduction in arterial luminal area (mean luminal area in Groups 3 and 4 was 4930 ± 224.7 μm² and 3600.4 ± 465.6 μm², respectively). Evaluation of the basilar artery wall thickness of the rats in Groups 3 & 4 did not reveal a significant relationship (p=0.076). This indicates that the thickness of blood vessels walls did not significantly change in the obese rats after the development of SAH and CV (mean wall thickness in Groups 3 and 4 was 43.6 ± 7.7 μm and 50.1 ± 6.7 μm, respectively).

Comparison of Rats Whose Weight Reverted from Obese to Normal

The basilar artery luminal area of the rats in Group 6 was significantly lower than that of the rats in Group 5 (p=0.003). This indicates that the rats whose body weight returned to normal after being obese developed CV after SAH was induced, resulting in a significant decrease in the arterial luminal area (mean luminal area in Groups 5 and 6 was 4897.1 ± 265.3 μm² and 4333.3 ± 344.1 μm², respectively). Evaluation of the basal artery wall thicknesses of the rats in Groups 5 and 6 did not reveal a significant relationship (p=0.104). This indicates that in rats reverting to normal body weight after a history of obesity, the thickness of the vessel wall did not significantly change following the development of SAH and vasospasm (mean vessel wall thickness in Groups 5 and 6 was 39.9 ± 4.6 μm and 43 ± 4.9 μm, respectively).

Comparison of the Control Groups

Comparison of the basilar artery luminal areas and wall thicknesses of the rats in Groups 1, 3, and 5 did not reveal a significant relationship (p=0.508 and p=0.131, respectively). This indicates that the basilar artery luminal areas and wall thicknesses were similar among the rats in the three groups.

Comparison of the Study Groups in Which Experimental Sah was Induced

Comparison of the basilar artery luminal area of Groups 2, 4, and 6 revealed a significant relationship (p=0.003). The basilar artery luminal area was significantly smaller in Group 4 than in Group 2 (p=0.010). This indicates that following the development of SAH, the basilar artery diameter significantly reduced in obese rats than in rats with normal body weight. This implies that obesity is more closely associated with severe CV following the development of SAH than normal body weight. The basilar artery luminal area was significantly smaller in Group 4 than in the Group 6 (p=0.009). This indicates that following the development of SAH, the basilar artery diameter significantly reduced in obese rats than in rats with a normal body weight after being obese. This implies that the effects of obesity on CV severity in the rats were not permanent and that the CV severity can be reduced by reducing the body weight to normal. There was no significant difference between Groups 2 and 6 in terms of the basilar artery luminal area (p=1.000). This indicates that the rats whose body weight returned to normal after being obese demonstrated similar results to rats with a normal body weight in terms of CV severity following SAH, implying that the adverse effects of obesity on CV severity are not permanent. Comparison of the basilar artery wall thickness between Groups 2, 4, and 6 demonstrated a significant relationship (p=0.013). The basilar artery wall thickness was significantly more in Group 4 than in Group 2 (p=0.012). This indicates that the basilar artery wall thickness following the development of SAH was higher in obese rats than in rats with a normal weight.

DISCUSSION

SAH is a neurological emergency that most commonly occurs non-traumatically because of the rupture of a cerebral aneurysm. Cerebral aneurysms typically present as saccular or berry types and are more commonly observed in individuals over the age of 30, particularly in the anterior communicating artery and middle cerebral artery (31). Non-traumatic SAH constitutes 3%–5% of all stroke types and is associated with a mortality rate of up to 50% (11,20). CV, which progresses with the narrowing of the cerebral arteries, and DCI, resulting from perfusion impairment in cerebral tissues, are the most

critical complications that occur several days after SAH develops (5). Although advances in treatment of aneurysms have reduced mortality rates associated with SAH, the management of CV should not be overlooked to prevent the associated mortality and morbidity. This is because two–thirds of individuals with SAH develop CV, and its pathophysiology is a highly complex process (28). Numerous studies have aimed to elucidate the mechanism of SAH-induced CV (30). The blood accumulating in the subarachnoid space dissolves and breaks down over time. As a result, the accumulation of ferritin and oxyhemoglobin induces the development of CV (3). Furthermore, when oxyhemoglobin comes into contact with methemoglobin, superoxide is released, triggering lipid peroxidation and CV. Moreover, oxyhemoglobin directly inhibits vascular relaxation, with previous studies having demonstrated that an intrathecal injection of oxyhemoglobin induces CV (2). There is a correlation between the volume of hemorrhage and the severity of CV (19). Another effect of the accumulation of blood in the subarachnoid space is the disruption of cerebral autoregulation because of changes in the pressure on the arterial wall. CV increases with the disruption of cerebral autoregulation (18). Vasoconstriction due to SAH-induced sympathetic activation, activation of protein kinase C due to endothelial damage, and release of various mediators such as serotonin, catecholamines, thromboxane A2, potassium, prostaglandins, endothelin, and angiotensin, which directly cause vascular spasm, contribute to the development of CV (34). A decrease in NO synthesis is also involved in the pathophysiology of CV, and alterations in calcium levels in astroglial cells occur because of the activation of calcium channels (28,35).

Obesity is a well-defined condition that is associated with an increase in mortality and morbidity. However, recent studies suggest that obese individuals may have a greater resilience to diseases and acute medical conditions than individuals with a normal weight, leading to the concept of an obesity paradox (27). Several studies have investigated the relationship between obesity and clinical outcomes following SAH. Platz et al. stated in their clinical study that, although worse clinical outcomes are predicted for obese patients, obesity is not an independent predictor of poor clinical outcomes after SAH and is a negligible factor compared to aneurysm size, patient age, or the amount of bleeding (25). In a retrospective study involving 305 patients with SAH, Hughes et al. reported that as the body mass index increased, short-term and long-term mortality rates decreased. Therefore, they concluded that obesity reduces mortality in patients with SAH (13). Conducted in a retrospective study involving 406 patients with SAH, Damodara et al. demonstrated that body mass index is an important predictor of the outcome of patients with SAH. In their study, overweight patients exhibited significantly lower mortality rates than patients with a normal weight (4). However, the obese patients experienced worse clinical outcomes than patients with a normal weight. Elliott et al. carried out a study in patients with non-traumatic SAH to investigate the effects of morbid obesity on the clinical outcomes of patients. They demonstrated that the mortality rates were lower in patients with SAH who were morbidly obese than patients with a normal weight (9). Rautalin et al. conducted an extensive systematic review of 177 relevant articles. They emphasized that there are no definitive conclusions regarding the obesity paradox concept and highlighted the need for more detailed and advanced studies (27). Currently, the development of CV following SAH poses a significant risk of mortality and morbidity (16). CV has been identified as the primary cause of poor clinical outcomes following SAH (16). Rumalla et al., in their study involving 8346 patients, investigated the risk factors for CV. They found that tobacco and cocaine use, anemia, hypovolemia, hypotension, hyponatremia, hypokalemia, leukocytosis, younger age, female sex, and clinical severity of SAH (Hunt and Hess grade ≥2) were associated with the risk for CV (29). Rautalin et al. examined risk factors for DCI following SAH. They determined that hypertension before admission, advanced age, male sex, and obesity were associated with an increased risk for DCI and may be linked to poor clinical outcomes (26). Several studies indicate that obesity decreases the amount of vasodilator agents in blood vessels and increase the amount of vasoconstrictor agents (26,31,33,36). Because of obesity-induced endothelial dysfunction, both eNOS activity and NO levels decrease. Furthermore, a high-fat diet leads to an increase in caveolin-1 levels, which negatively regulate NO synthesis, resulting in decreased levels of the vasodilator agent NO in obesity (31,33). Obesity is also associated with an increase in the activation of endothelin-1, a potent vasoconstrictor agent, which leads to the impairment of vascular wall relaxation (36). Moreover, studies conducted on patients with systemic sclerosis, a disease progressing with vasospasm and microvascular involvement, demonstrate that vascular wall relaxation tolerance decreases in obese patients due to endothelial dysfunction (1).

Studies linking vasospasm with impaired blood glucose levels and diabetes mellitus, which are components of metabolic syndrome directly associated with obesity, demonstrate that impaired glycemic control is a risk factor for the development of CV (8). Studies investigating the effects of insulin resistance on the vascular wall indicate a direct relationship between vascular contractility and insulin resistance (24). Researches demonstrating that insulin resistance induced in rats impairs vascular reactions following SAH also support this hypothesis (14).

Considering the reported impacts of obesity, a pandemic disease with an increasing prevalence worldwide, we conducted this study to investigate the influence of obesity on the severity of CV, a leading cause of mortality and morbidity following SAH. We aimed to clarify the ambiguity in the literature regarding the impact of obesity on the clinical outcomes of SAH and to directly demonstrate its effect on the severity of CV, which is the most common complication of SAH with adverse clinical outcomes.

Our study results indicate that the rats in the group in which experimental SAH was induced exhibited narrower basal artery lumens than rats in the control groups. This indicates the development of CV following SAH. Furthermore, the narrowing of the basal artery lumen was more pronounced in obese rats than in the rats in other groups, indicating that

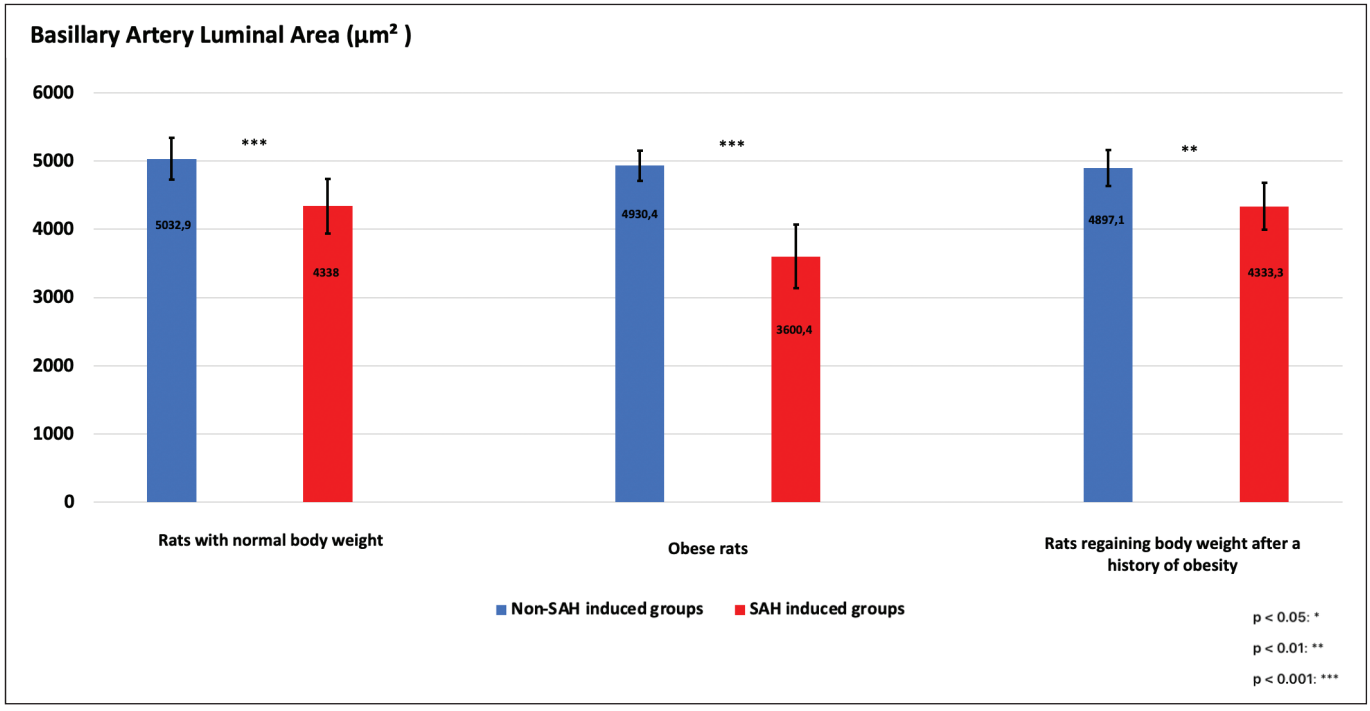

Figure 4: The graph illustrates the mean luminal areas of the basilar artery across different groups, with standard deviations represented by error bars. Blue columns represent the basilar artery luminal area in the control groups (SAH not induced), and red columns represent the basilar artery luminal area in the experiment groups (SAH induced). The luminal area was reduced after SAH induction for all the groups. The magnitude of this reduction was larger for the obese rats compared to other groups. The significance levels are indicated by asterisks on the bar graphs. The Mann-Whitney U test was used for statistical analysis.

obese individuals may exhibit a more severe CV (Figure 4). These findings imply that obesity may intensify CV and have a negative impact on the outcomes of patients with SAH. Another finding of our study was that the CV severity in rats whose body weight returned to normal after being obese was similar to that in rats with a normal body weight. This indicates that the negative effects of obesity are not permanent and can reversed after controlling the weight. However, obesity in this experimental study was induced over a period of 2 months and reversed over another 2 months. Therefore, the results may vary in rats with chronic obesity.

CONCLUSION

Obesity might have an impact on the degree of CV that occurs after SAH, and the process of CV may be exacerbated in the presence of obesity. However, return of the body weight from obese to normal values may decrease the risk of severe CV. This study, to the best of our knowledge, is the first experimental investigation that directly explores the relationship between obesity and the severity of CV.

Declarations

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Availability of data and materials: Available from the corresponding author on request.

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AUTHORSHIP CONTRIBUTION

Study conception and design: BCA, ID
Data collection: BCA, ID
Analysis and interpretation of results: BCA, ID
Draft manuscript preparation: BCA, EG, MCK
Critical revision of the article: BCA, EG, MCK, ID
Other (study supervision, fundings, materials, etc...): BCA, EG, MCK, NA, CCE
All authors (BCA, EG, MCK, NA, CCE, ID) reviewed the results and approved the final version of the manuscript.

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