

ORIGINAL RESEARCH



Cerebral blood flow in type II diabetes mellitus patients with impaired awareness of hypoglycemia: a cross-sectional study

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Abstract

Cerebral blood flow is maintained and regulated through various homeostatic mechanisms. It is maintained even during hypoglycemia in patients with type 1 diabetes mellitus, but appears to increase in those with impaired awareness of hypoglycemia. However, experiments are lacking to clarify these findings. Thus, this study was conducted to investigate whether cerebral blood flow increases in type 2 diabetes mellitus patients with impaired awareness of hypoglycemia by using Doppler sonography. This was a cross-sectional study conducted from July 2021 to June 2022 in the emergency department (ED) of Inje University Busan Paik Hospital, Busan, South Korea. Patients with type 2 diabetes with complaints of various symptoms of hypoglycemia (defined as blood glucose level <60 mg/dL) were evaluated for this study after obtaining their informed consent. First, we assessed each patient's awareness of hypoglycemia using the Gold method. Cerebral blood flow was then measured on Doppler sonography. The primary outcome was blood flow in both internal carotid arteries, and secondary outcomes included the diameter and time-averaged maximum velocity of both internal carotid arteries. A total of 132 patients were enrolled in the study, but 11 patients were excluded from analysis. Hypoglycemia was associated with increased cerebral blood flow in those with impaired awareness of hypoglycemia, but this association was not observed in other groups. The blood flow in the left internal carotid artery was significantly higher compared to the right side, perhaps due to the anatomical differences between the two arteries. The increased cerebral blood flow could be due to an adaptive response to hypoglycemia to enhance nutrient supply to the brain. However, given that this was a cross-sectional study, causality could not be determined. Thus, as in type 1 diabetes mellitus, hypoglycemia is associated with an increased cerebral blood flow in type 2 diabetes mellitus as well.

Keywords

Hypoglycemia; Cerebral blood flow; Diabetes mellitus

1. Introduction

Cerebral blood flow (CBF) is maintained and regulated through various homeostatic mechanisms [1]. Such mechanisms can be divided into four different categories: myogenic, neurogenic, metabolic and endothelial [1]. These ensure that CBF stays within a normal range regardless of the patient's condition. According to one study, CBF can be measured indirectly by measuring the blood flow and velocity in the internal carotid arteries [2]. This demonstrated that CBF is related to cardiac output which in turn is directly related to the blood flow and velocity in the internal carotid arteries [2]. In patients with type 1 diabetes mellitus (DM), CBF is maintained even during hypoglycemia. However, in those with impaired awareness of hypoglycemia (IAH), CBF

appears to increase [3]. IAH is defined as “a phenomenon whereby patients have no symptoms or vague symptoms of hypoglycemia” [4]. It increases the risk of severe hypoglycemia six times compared with normal awareness of hypoglycemia (NAH) in type 1 DM [5]. Furthermore, hypoglycemia is known as a cause of “dead in bed” syndrome, which is the “leading cause of death in people under 40 years of age with Type I DM” [5]. Alkhatatbeh *et al.* [6] claimed that an increased frequency of hypoglycemia may lead to an increase in the prevalence of IAH and ultimately to the development of severe hypoglycemia.

Therefore, this clearly shows the need to formulate methods to diagnose IAH in diabetic patients to prevent severe hypoglycemia. In addition, considering the importance of IAH in general, more attention must be paid to diabetic patients who

do not exhibit typical symptoms of hypoglycemia. As such, if patients visiting the emergency department with hypoglycemia are screened for IAH, those found with IAH could immediately receive continuous blood glucose level monitoring to prevent severe hypoglycemia. Thus, CBF measurement could be a valuable tool for assessing the hypoglycemic awareness of hypoglycemic patients. However, because recent studies on CBF rely on magnetic resonance imaging (MRI) to measure CBF, and MRI requires intravenous injection of contrast media and is expensive for most patients, Doppler sonography was used in this study to indirectly measure CBF based on the internal carotid artery (ICA) flow [7]. In addition, owing to the general lack of experiments regarding CBF in patients with type 2 DM, this study focused on investigating whether type 2 DM patients with IAH would show a similar increase in CBF compared with those with type 1 DM.

The aim of this study was to investigate whether CBF increases in type 2 DM patients with IAH by using Doppler sonography. The primary outcome was blood flow in both internal carotid arteries, and the secondary outcomes included the diameter and time-averaged maximum velocity of both internal carotid arteries.

2. Materials and methods

2.1 Study design and setting

In total, 132 subjects were recruited and gave written informed consent. After exclusion of 11 patients, there were 121 patients that were analyzed for this study (diabetic group, $n = 61$; healthy group, $n = 60$). Of 61 cases in the diabetic group, 27 were type 2 DM with IAH, and 34 were type 2 DM and NAH (normal awareness of hypoglycemia) (Fig. 1). In this study, hypoglycemia was defined as a blood glucose level <60

mg/dL. None of the subjects who participated in the study used medication other than insulin. The state of awareness of hypoglycemia of each subject was determined using the Gold method [8]. The Gold method relies on a questionnaire that poses the question “Do you know when your episodes of hypoglycemia are commencing?” [8]. The subject then scores their response to the question on a 7-point Likert scale, where 1 represents “always aware” and 7 represents “never aware” [8]. On this scale, a score of ≥ 4 indicated IAH [8]. Subjects with type 1 DM were obviously excluded from the study, and factors that may affect internal carotid artery flow (*i.e.*, ICA stenosis or thrombosis, congenital heart disease or valvular heart disease) were excluded from the study [3, 9]. In addition, each patient’s body mass index (BMI) was calculated because it affects CBF [3]. Furthermore, because hypercapnia and hypoxia increase CBF, subjects with partial pressure of oxygen (PaO_2) of <75 mm Hg or end-tidal CO_2 (ETCO_2) of >45 mm Hg were excluded from the analysis [10, 11].

2.2 Selection of participants

Subjects with hypoglycemia due to type 2 DM were recruited for the study from July 2021 to June 2022 at the emergency department of Inje University Paik Hospital in Busan, South Korea. Those willing to participate were asked to give their informed consent after the study purpose, method and possible complications that may occur during the experiment were explained to them. If they were physically unable to give consent, members of their immediate family were asked to sign the consent form on their behalf. In addition, it was ensured that they did not have any underlying medical conditions that require an exclusion from this study based on the criteria given above. Blood samples were collected intravenously for the measurement of PaO_2 and PaCO_2 .

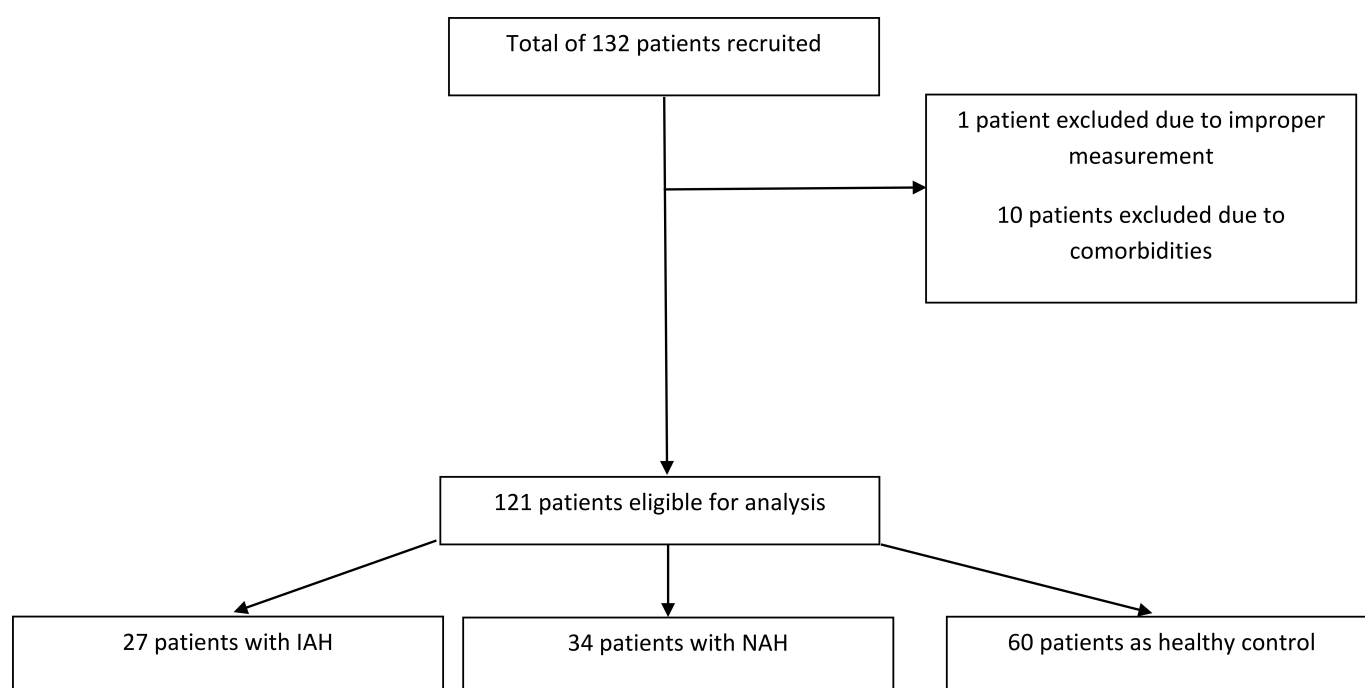


FIGURE 1. CONSORT diagram illustrating how the overall experiment was conducted. IAH, impaired awareness of hypoglycemia; NAH, normal awareness of hypoglycemia.

2.3 Measurements

For each subject, the time averaged maximum velocity and vessel diameter of both internal carotid arteries were measured to determine the blood flow using the following equation [12]:

$$\text{Blood flow} = 60 \times \pi \times \left(\frac{\text{Diameter}}{2} \right)^2 \times \frac{\text{Time averaged maximum blood velocity}}{2}$$

The internal carotid artery was evaluated at least 1.5 cm distal to its bifurcation at 5–10 MHz (ACUSON NX3, Siemens) in a longitudinal view with the head turned in either direction [12]. At a stable angle of ≤ 60 degrees, the angle-corrected time-averaged maximum velocity was measured on pulsed-wave Doppler sonography, and the vessel diameter was determined using edge detection software (Supplementary material) [12].

2.4 Outcomes

The primary outcome was blood flow in both internal carotid arteries, and the secondary outcomes included the diameter and time-averaged maximum velocity of both internal carotid arteries.

2.5 Statistical analysis

The within group differences in CBF between the subjects with IAH and NAH were determined using a two-sided Student *t*-test. Between-group differences were determined using one-way analysis of variance (ANOVA), Welch ANOVA, and Bonferroni/Games-Howell multiple comparison tests (IBM SPSS 27 (Armonk, NY, USA)). Statistical significance was set at $p < 0.05$.

3. Results

In total, 132 subjects were recruited and gave written informed consent from July 2021 to June 2022. However, one patient was excluded from analysis because of improper measurement (the external carotid artery was measured instead of the internal carotid artery), and 10 patients were excluded because of comorbidities that could affect CBF. Hence, only 121 subjects were included in the study (Fig. 1). The case group included 61 patients, whereas the control group included 60 patients. Of the 61 type 2 DM cases, 27 had IAH, and 34 had NAH. In addition, 60 non-diabetic healthy controls were included in the study (Fig. 1). The baseline characteristics were similar between the two groups (Table 1). The mean age was 63.2 years in the IAH group, and 68.7 years in the NAH group. On the other hand, the mean age of the healthy controls was 62.8 years. The sex distribution was relatively even between the IAH and healthy control groups; however, the NAH group appeared to be heavily skewed toward males (Table 1). The mean body mass index (BMI) values in the IAH, NAH, and healthy controls were 22.5, 23.4 and 24.2 kg/m², respectively. Moreover, the mean blood glucose levels in the IAH and NAH groups were 32.2 and 37.2 mg/dL, respectively (Table 1).

Lastly, the mean Gold score was 4.4 in the IAH group and 2.9 in the NAH group (Table 1). Furthermore, the one-way ANOVA and two-sided Student *t*-test revealed that the mean BMI and Gold score significantly differed between the three groups ($p = 0.015$); however, the mean age and blood glucose level were not significantly different ($p = 0.306$).

As expected, the blood flow in the right internal carotid artery in the IAH group was approximately 20% greater than that in the NAH group and 19% greater than that in the healthy control group (Fig. 2 and Table 2). Furthermore, the blood flow in the left internal carotid artery in the IAH group was roughly 14% greater than that in the NAH group, and the percentage increase between the IAH and the healthy control groups was 22% (Fig. 3 and Table 2). A 19% increase in blood velocity was found in the left internal carotid artery compared with the right internal carotid artery (Fig. 4). In addition, an approximately 6% increase in diameter was found in the left internal carotid artery diameter compared with the right internal carotid artery (Fig. 5). Lastly, a 26% increase in the left internal carotid artery flow was observed compared with the right internal carotid artery (Fig. 6).

In Table 2, the mean time-averaged maximum velocity (TAVmax) in the right internal carotid artery was significantly different between the three groups (type 2 DM with IAH vs. type 2 DM with NAH and healthy controls: 22.9 ± 2.5 , versus 21.4 ± 1.8 and 21.3 ± 1.8 cm/s, respectively). Similarly, the mean TAVmax in the left internal carotid artery was also significantly different between the type 2 DM with IAH group and the type 2 DM with NAH and healthy control groups (26.7 ± 2.9 vs. 25.5 ± 1.9 and 25.7 ± 1.6 cm/s, respectively). In addition, the mean diameters of the right and left internal carotid artery were significantly different across the three groups (7.2 ± 0.5 mm vs. 6.4 ± 0.5 , 6.5 ± 0.2 mm, respectively, in the right internal carotid artery, and 7.7 ± 0.6 mm vs. 7.1 ± 0.5 and 6.6 ± 0.4 mm, respectively, in the left internal carotid artery) (Table 2). The mean right internal carotid artery flow between IAH, NAH and control group was significantly different between the groups (7738.7 ± 701.1 mL/min vs. 6470.4 ± 543.1 and 6504.0 ± 690.3 mL/min, respectively). The mean left internal carotid artery flow was also significantly different between the three groups (9731.2 ± 1331.8 mL/min vs. 8565.5 ± 869.8 and 7955.6 ± 644.3 mL/min, respectively; Table 2).

4. Discussion

The idea of IAH was first suggested in 1991 by Gerich *et al.* [13]. Since then, many studies have investigated the impact of IAH on CBF during hypoglycemia. A study by de Galan *et al.* [14] demonstrated that theophylline improved counter-regulatory responses and decreased CBF in patients with IAH, which implies that theophylline can be used to improve the perception of hypoglycemia to ultimately prevent severe hypoglycemia [14]. Weigers *et al.* [3] concluded that changes in CBF during hypoglycemia may contribute to the development of IAH. Moreover, according to Nwokolo *et al.* [15], hypoglycemia in patients with type 1 DM induced increases in global CBF. However, no significant difference was found between the IAH group and NAH groups [15].

TABLE 1. Baseline characteristics of the study participants.

Variable	Type 2 DM IAH n = 27	Type 2 DM NAH n = 34	Healthy Controls n = 60	p-value
Age (yr)	63.2 ± 14.1	68.7 ± 14.4	62.8 ± 10.3	0.141
Sex (male/female)	16/11	22/12	29/31	NA
Body mass index (kg/m ²)	22.5 ± 2.9	23.4 ± 4.7	24.2 ± 2.6	0.083
Blood glucose level (mg/dL)	32.2 ± 11.8	37.2 ± 13.0	NA	0.130
Gold score	4.4 ± 0.5	2.9 ± 0.3	NA	<0.001

Data are presented as mean ± SD using ANOVA. F, female; M, male; Type 2 DM IAH, type 2 diabetes with impaired awareness of hypoglycemia; Type 2 DM NAH, type 2 diabetes with normal awareness of hypoglycemia; N/A, not applicable.

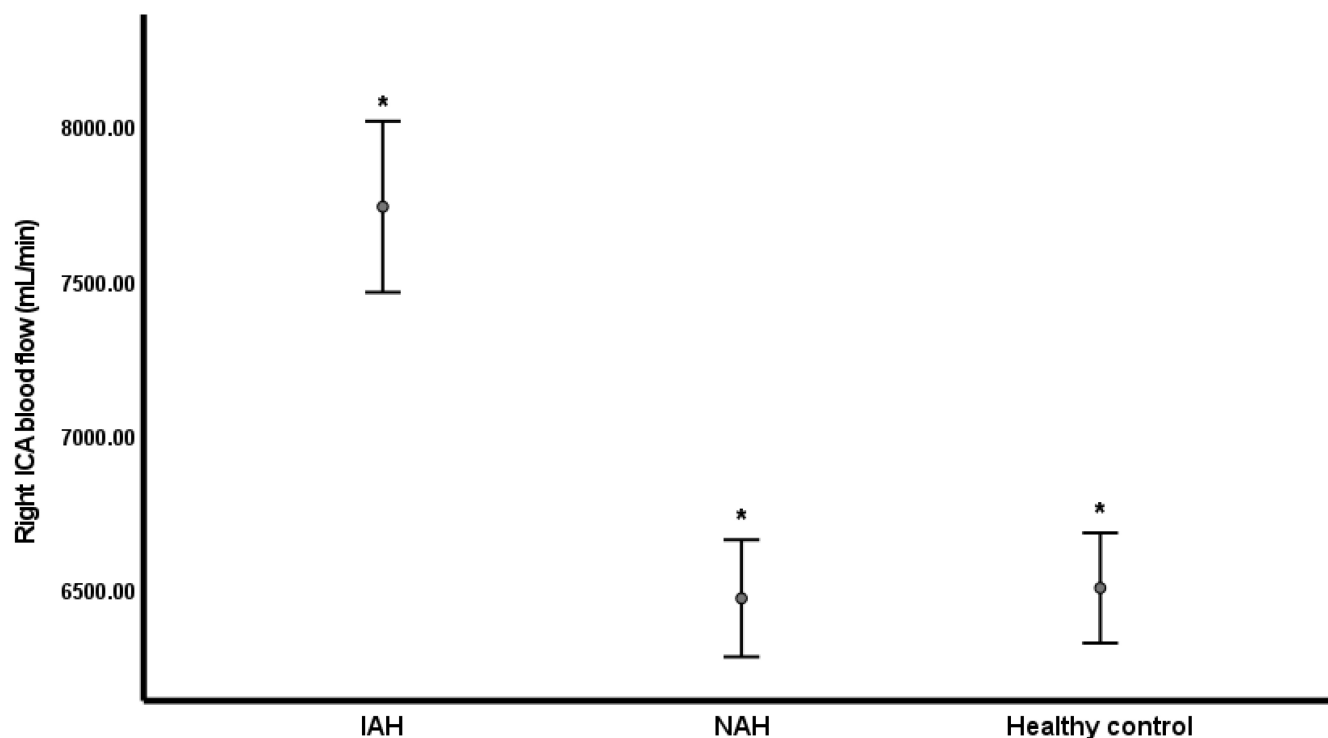


FIGURE 2. Hypoglycemia-induced changes in right ICA flow in the IAH group. The right ICA flow in the IAH, NAH and healthy control groups are represented as 95% confidence intervals obtained using ANOVA. IAH, impaired awareness of hypoglycemia; NAH, normal awareness of hypoglycemia; ICA, internal carotid artery; ANOVA, analysis of variance. * $p < 0.05$ for the IAH group compared with the NAH and healthy control groups.

TABLE 2. Hypoglycemia-induced changes in ICA flow in the IAH, NAH and healthy control groups.

Variable	Type 2 DM IAH n = 27	Type 2 DM NAH n = 34	Healthy controls n = 60	p-value
TAVmax (Rt.) (cm/s)	22.9 ± 2.5	21.4 ± 1.8	21.3 ± 1.8	0.001
TAVmax (Lt.) (cm/s)	26.7 ± 2.9	25.5 ± 1.9	25.7 ± 1.6	0.042
ICA diameter (Rt.) (mm)	7.2 ± 0.5	6.4 ± 0.5	6.5 ± 0.2	0.001
ICA diameter (Lt.) (mm)	7.7 ± 0.6	7.1 ± 0.5	6.6 ± 0.4	0.001
ICA flow (Rt.) (mL/min)	7738.7 ± 701.1	6470.4 ± 543.1	6504.0 ± 690.3	0.001
ICA flow (Lt.) (mL/min)	9731.2 ± 1331.8	8565.5 ± 869.8	7955.6 ± 644.3	0.001

Data are presented as mean ± SD using ANOVA. TAVmax, time-averaged maximum velocity; ICA, internal carotid artery; Type 2 DM IAH, type 2 diabetes with impaired awareness of hypoglycemia; Type 2 DM NAH, type 2 diabetes with normal awareness of hypoglycemia.

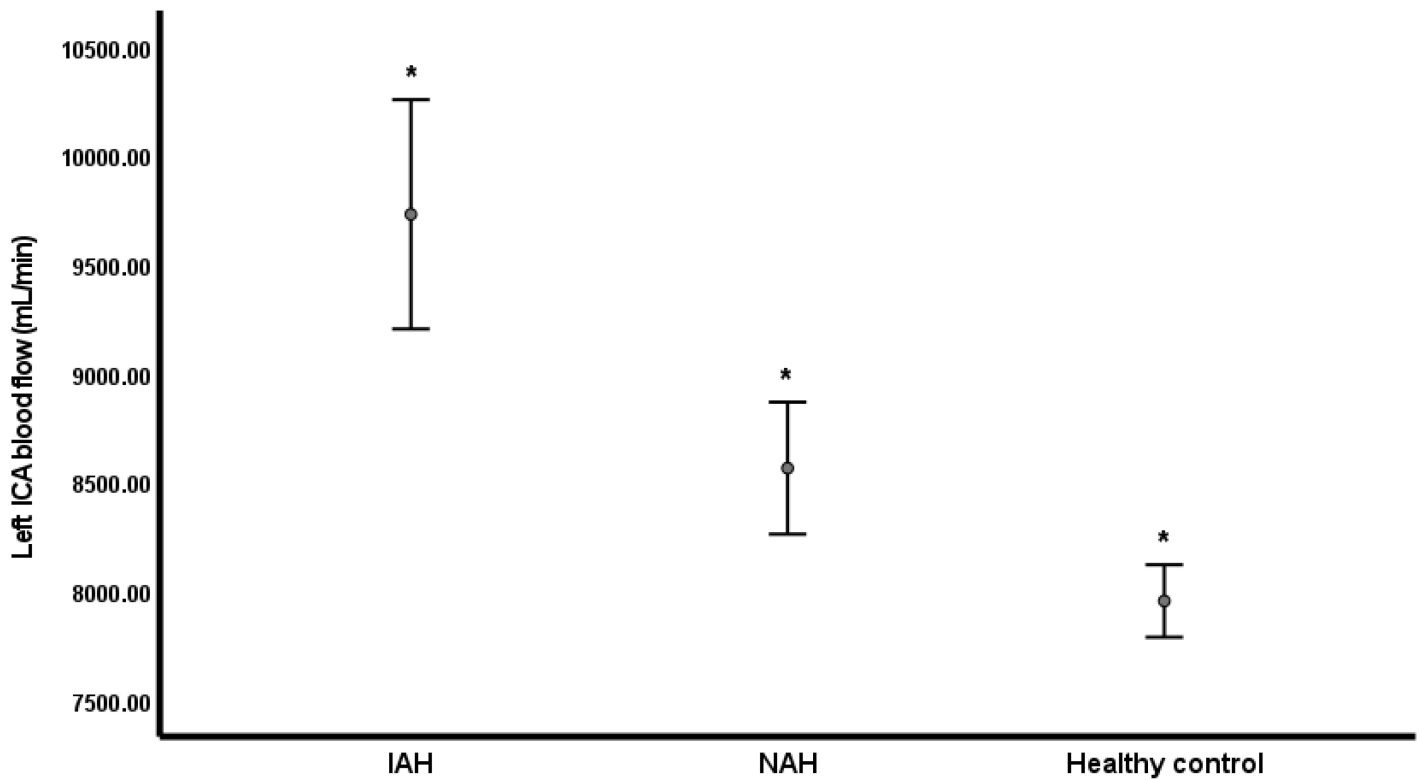


FIGURE 3. Hypoglycemia-induced changes in left ICA flow in the IAH group. The left ICA flow in the IAH, NAH and healthy control groups are represented as 95% confidence intervals obtained using ANOVA. IAH, impaired awareness of hypoglycemia; NAH, normal awareness of hypoglycemia; ICA, internal carotid artery; ANOVA, analysis of variance. $*p < 0.05$ for the IAH group compared with the NAH and healthy control groups.

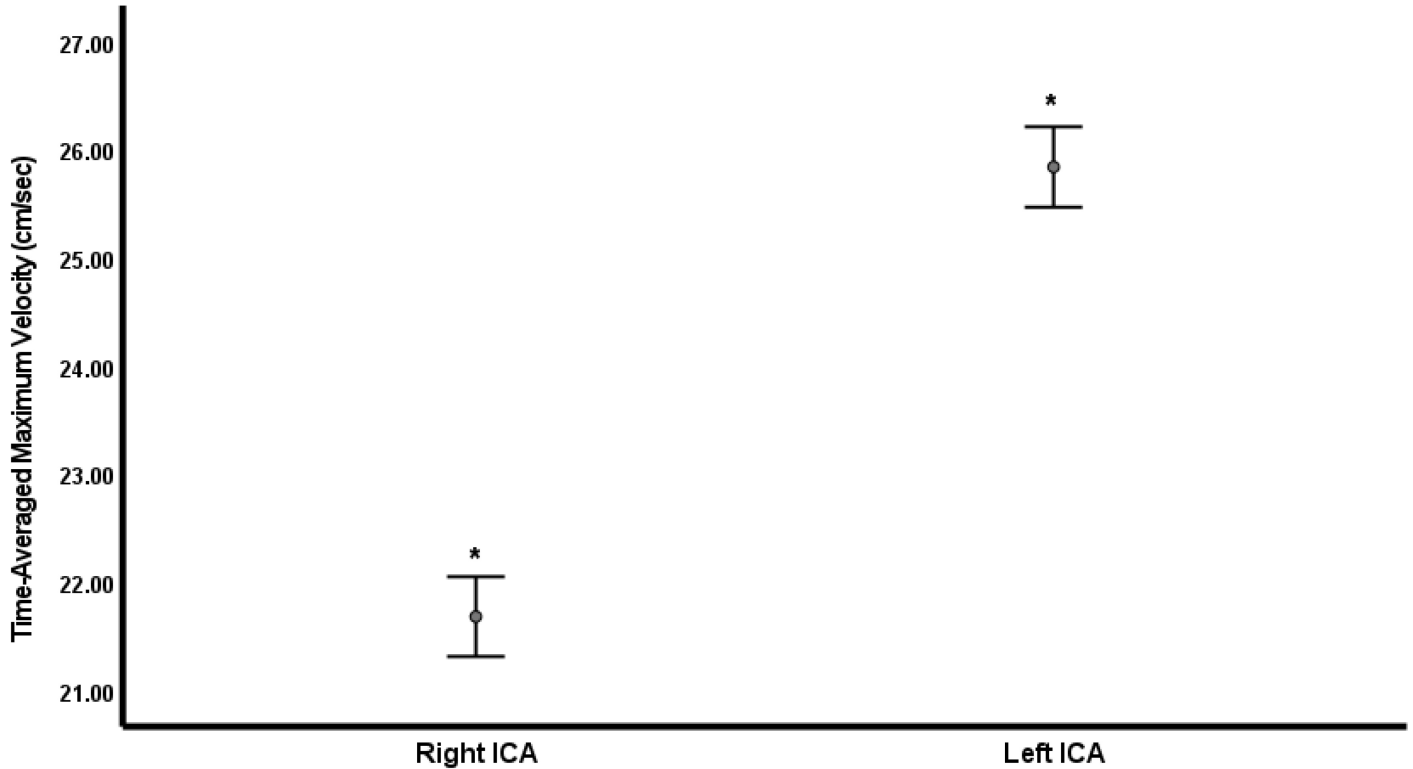


FIGURE 4. Hypoglycemia-induced changes in the time-averaged maximum velocity of the left and right ICA. The blood flow velocity in both ICAs is represented as a 95% confidence interval obtained using ANOVA. ICA, internal carotid artery; ANOVA, analysis of variance. $*p < 0.05$ for the left ICA compared with the right ICA.

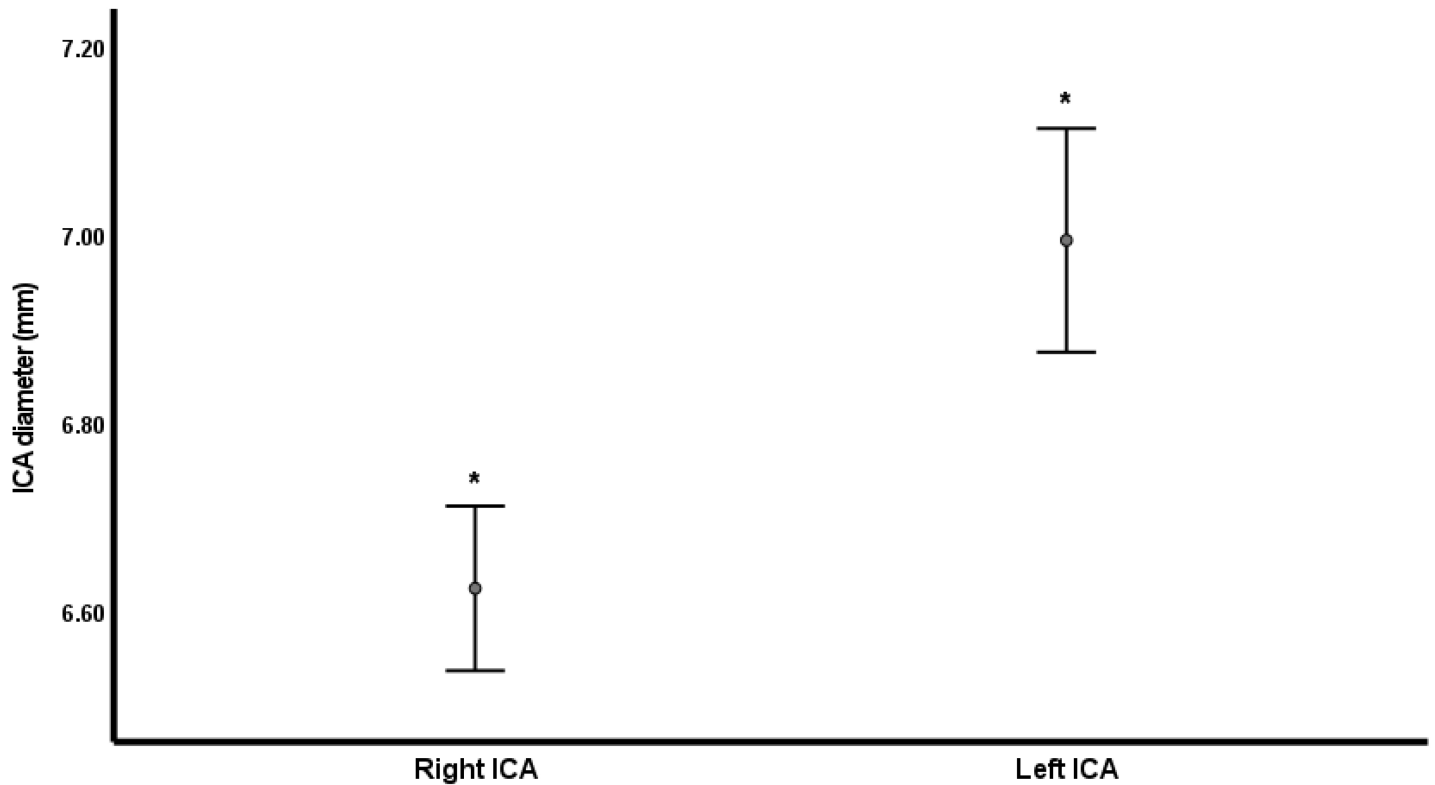


FIGURE 5. Hypoglycemia-induced changes in the vessel diameters of both left and right ICAs. The vessel diameters of the two ICAs are represented as 95% confidence intervals obtained using ANOVA. ICA, internal carotid artery; ANOVA, analysis of variance. $*p < 0.05$ for the left ICA compared with the right ICA.

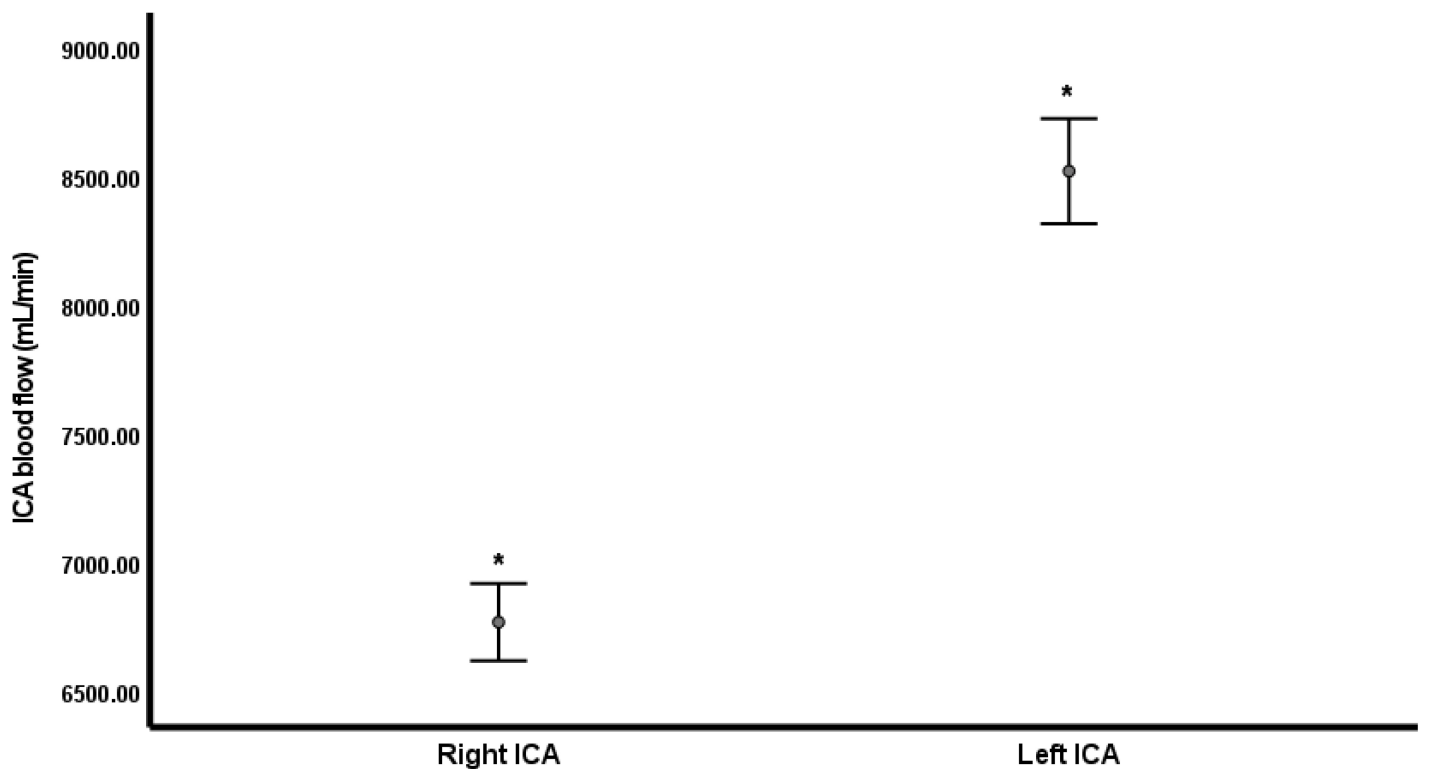


FIGURE 6. Hypoglycemia-induced changes in the right and left ICAs. Blood flow in both ICAs is represented as a 95% confidence interval obtained using ANOVA. ICA, internal carotid artery; ANOVA, analysis of variance. $*p < 0.05$ for the left ICA compared with the right ICA.

In our study, we relied on Doppler sonography to determine whether increased CBF is associated with hypoglycemia in type 2 DM patients with IAH. On the basis of previous experiments, it has been established that CBF increases in response to hypoglycemia in type 1 DM patients with IAH [3]. Our study suggests that IAH is related to increased internal carotid artery blood flow, which in turn is associated with increased CBF [16]. This is based on the finding that only the IAH group showed a significant increase in internal carotid artery flow compared with the NAH and control groups. In addition, the internal carotid artery flow, which is directly related to TAVmax and vessel diameter, was clearly higher in the left internal carotid artery than in the right internal carotid artery. Such difference could be attributed to the anatomical difference between the left and right internal carotid arteries, with the left internal carotid artery arising from the aortic arch, and the right internal carotid artery arising from the brachiocephalic trunk [16]. This could result in greater hemodynamic stress on the left side, thus increasing blood flow [16]. Weigers *et al.* [3] demonstrated an 8% increase in CBF in type 1 DM patients with IAH during hypoglycemia and a 5% increase in CBF in type 1 DM patients with NAH [3]. Similarly, our study showed that the IAH group had 20% and 19% increases in CBF compared with the NAH and healthy control groups, which is somewhat consistent with the findings by Weigers *et al.* [3]. However, because we could not measure the CBF of the diabetic patients during euglycemia in this study, whether the change in CBF occurred suddenly in response to hypoglycemia or chronically over time remains unclear. The use of a euglycemic-hypoglycemic glucose clamp could have helped in this regard [3]. In addition, an experiment by Nwokolo *et al.* [15] indicated that CBF increased globally in NAH and IAH groups in response to hypoglycemia; however, no significant difference in CBF was found between the groups. This could be attributed to the different sample sizes between the two experiments.

Nonetheless, the increase in internal carotid artery flow could be due to an “altered threshold,” where the increase in blood flow is due to a response to recurrent hypoglycemia [3]. This may be a “neuroprotective response to prior hypoglycemia,” as the supply of glucose and other nutrients may be enhanced as a result [3]. In the context of our study, this means that the patients with IAH might have had increased CBF because they had experienced hypoglycemia prior to this study and their brain metabolism had been altered as a result. This is achieved by the suppression of the counterregulatory responses that normally occur in response to hypoglycemia [3].

Moreover, it was quite surprising how so many patients with type 2 DM that visited the emergency department with general weakness were later found to have hypoglycemia. In addition, most of them claimed that they had never experienced an episode of hypoglycemia before; in other words, they were likely to have IAH. As such, it is imperative to screen diabetic patients for IAH, as these patients are significantly at a higher risk of developing hypoglycemia that could ultimately lead to “dead in bed” syndrome [5]. It is our hope that the findings of this study could be utilized to screen for higher risk individuals and ultimately formulate new guidelines for the management of patients with IAH.

5. Limitations

First, this was a single-center study with a relatively short data collection period and small sample size. Other studies with multicenter trials, larger sample sizes, and a longer follow-up period will likely produce more reliable findings. Second, because we primarily relied on Doppler sonography to measure CBF, other studies aimed at reproducing the same results may yield different results instead due to the operator-dependent nature of sonography in general. Third, because this is a cross-sectional study, any causal relationship between CBF and hypoglycemia could not be explained. Thus, future research should rely on randomized controlled trials or case-control studies to determine causality. Fourth, because the patients' blood glucose levels were taken prior to Doppler sonography, initial blood glucose level and the blood glucose level during CBF measurement may be discrepant, possibly altering the results. A second measurement of blood glucose levels during Doppler sonography would have led to more reliable findings. Fifth, even though our study aimed to account for internal carotid artery-related diseases that affect CBF, we could not exclude patients with atherosclerosis because atherosclerosis often remains undiagnosed until it causes disorders such as myocardial infarction or cerebral infarction. Lastly, our control group consisted of healthy individuals; in other words, they were not hypoglycemic during the CBF measurement, unlike those in the other groups. Therefore, utilizing equipment such as euglycemic-hypoglycemic glucose clamps or having the patients undergo overnight fasting prior to Doppler sonography would have enhanced the overall quality of this study. Furthermore, using other methods such as MRI to measure CBF would confirm our findings. MRI scans would also allow researchers to identify the exact location of a change in CBF in the brain during hypoglycemia in patients with IAH. In addition, duplicating similar results by chemically altering CBF using substances such as theophylline would also strengthen our findings.

6. Conclusions

Our study demonstrated that CBF increases are associated with hypoglycemia in type 2 DM patients with IAH. Furthermore, the blood flow in the left internal carotid artery appeared to be significantly greater than that in the right internal carotid artery. This suggests that similar to type 1 DM, recurrent hypoglycemia in type 2 DM induces IAH as an adaptive response. Thus, diabetic patients with increased CBF can be considered to have IAH and require strict monitoring to prevent severe hypoglycemia in the future.

ABBREVIATIONS

CBF, cerebral blood flow; ICA, internal carotid artery; IAH, impaired awareness of hypoglycemia; NAH, normal awareness of hypoglycemia; MRI, magnetic resonance imaging; DM, diabetes mellitus; TAVmax, time-averaged maximum velocity; ANOVA, analysis of variance; BMI, body mass index.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

KH and JKY—designed the study with inputs from YWK, JHK and JGJ. KH—was responsible for the collection and analysis of Doppler measurements with assistance from DSK and YDJ. KH—recruited the patients and performed the cerebral blood flow measurements. YWK, JHK, YSY—contributed to the drafting of the manuscript. All authors discussed the results and implications and commented on the manuscript at all stages. All authors approved the final version of the manuscript. All authors contributed equally to this work.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by and conducted in accordance with the ethical standards of the institutional review board of the Inje University Busan Paik Hospital (BPIRB 2021-11-066-008). We collected signed informed consent forms from all participants in this study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at <https://oss.signavitae.com/mre-signavitae/article/1765982299405336576/attachment/Supplementary%20material.docx>.

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