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Dynamic Cerebral Autoregulation Assessed by Breath-holding Test in Type 2 Diabetes Mellitus Patients

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is known to affect blood vessels throughout the body, including the brain. Changes in cerebral blood flow regulation may occur early, even before obvious neurological complications develop. Dynamic cerebral autoregulation is an important mechanism that helps maintain stable cerebral perfusion under physiological stress.

Objective: This study aimed to assess dynamic cerebral autoregulation in patients with T2DM using transcranial Doppler (TCD) and the breath-holding test (BHT), and to examine its relationship with diabetic microvascular complications.

Methods: A cross-sectional analytical study was carried out among 154 patients with T2DM attending No. (2) Military Hospital, Yangon. Mean flow velocities (MFV) of the middle cerebral arteries were measured at rest and during breath-holding using TCD. The breath-holding index (BHI) was calculated as an indicator of cerebrovascular reactivity. Clinical and laboratory data, including the presence of microvascular complications, were recorded. Statistical analyses were performed to compare groups and identify factors associated with impaired autoregulation.

Results: More than half of the patients (60.4%) had at least one microvascular complication. Those with complications had lower baseline MFV and a smaller increase in flow velocity during breath-holding. BHI values decreased as the number of complications increased. Lower BHI was also associated with older age, poorer glycemic control, and higher serum creatinine levels. Further analysis showed that HbA1c and serum creatinine were significant predictors of impaired autoregulation

Discussion: The findings indicate that cerebral autoregulation is reduced in patients with T2DM, particularly in those with microvascular complications. This impairment appears to worsen with

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increasing disease burden and may be present even before complications become clinically evident.

Conclusion: The breath-holding test, combined with TCD, offers a simple and practical way to assess cerebrovascular function and may be useful for early detection and risk assessment in routine clinical practice.

Keywords: Type 2 diabetes mellitus, Cerebral autoregulation, Transcranial Doppler sonography, Microvascular complications; Cerebrovascular reactivity

1. Introduction

Cerebral autoregulation (CA) is a fundamental homeostatic mechanism that maintains relatively stable cerebral blood flow despite fluctuations in cerebral perfusion pressure. This process operates through coordinated myogenic, metabolic, and neurogenic pathways that regulate cerebrovascular resistance and ensure adequate cerebral perfusion (Paulson et al., 1990; Latka et al., 2005; Bor-Seng-Shu et al., 2012; Yuan et al., 2016). When CA is impaired, the brain becomes more vulnerable to hypoperfusion or hyperperfusion during blood pressure changes, increasing the risk of neuronal injury and long-term neurological complications.

Type 2 diabetes mellitus (T2DM) is increasingly recognized as a systemic vascular disorder that affects both large and small blood vessels, including those in the cerebral circulation. Chronic hyperglycemia, insulin resistance, and endothelial dysfunction contribute to structural and functional vascular changes that may impair cerebral blood flow regulation. These alterations may occur early in the disease process and can precede clinically apparent cerebrovascular disease or overt neurological complications (Pooja Naik, 2014).

Assessment of cerebral hemodynamics and autoregulatory capacity is clinically important, as cerebrovascular disease remains a major cause of morbidity and mortality in patients with T2DM. Transcranial Doppler (TCD) ultrasonography provides a non-invasive, repeatable, and bedside method for measuring cerebral blood flow velocity in major intracranial arteries. It is widely used in both clinical practice and research to evaluate cerebrovascular function and detect hemodynamic abnormalities (Alonso et al., 2015; Sloan et al., 2004; Lysakowski et al., 2001; Surjya et al., 2018).

Cerebrovascular reactivity to carbon dioxide (CO_2) is closely linked to autoregulatory function and reflects the ability of cerebral vessels to respond to metabolic stimuli. Respiratory maneuvers, such as the breath-holding test (BHT), are commonly used to induce transient hypercapnia, resulting in vasodilation and increased cerebral blood flow velocity. The breath-holding index (BHI), calculated from these changes, serves as a practical and widely accepted indicator of dynamic cerebral autoregulation and cerebrovascular reactivity.

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Previous studies examining cerebrovascular reactivity in T2DM have reported heterogeneous findings, likely due to variations in study design, patient characteristics, and assessment methods. Several studies have demonstrated impaired cerebrovascular reactivity in diabetic populations (Brown et al., 2008; Moghaddasi et al., 2010; Lasek-Bal et al., 2012), whereas others have reported preserved autoregulatory capacity in certain groups (van Oers et al., 2006). Increasing evidence suggests that diabetic microangiopathy plays a key role in disrupting cerebral autoregulation, with alterations in endothelial function, vascular stiffness, and microvascular structure contributing to impaired cerebrovascular responsiveness (Huq et al., 2012; Lee et al., 2000; Chiu et al., 2005).

Given these considerations, simple and accessible methods for assessing cerebral autoregulation are of particular value, especially in routine clinical settings and resource-limited environments. Therefore, this study aimed to assess dynamic cerebral autoregulation in patients with T2DM using transcranial Doppler and the breath-holding test, and to examine its relationship with diabetic microvascular complications.

2. Materials and Methods

2.1 Sampling Procedure

This hospital-based cross-sectional analytical study included patients with type 2 diabetes mellitus (T2DM) attending No. (2) Military Hospital, Yangon, Myanmar, during the study period from October 2017 to March 2019. A consecutive sampling method was used to recruit eligible participants. A total of 154 patients with T2DM were enrolled. Adults diagnosed with T2DM according to American Diabetes Association criteria were included. Patients with a history of stroke or transient ischemic attack, significant extracranial or intracranial arterial stenosis, cardiac arrhythmias, severe respiratory disorders, or neurological conditions known to affect cerebral hemodynamics were excluded.

2.2 Data Collection

Demographic data, duration of diabetes, blood pressure, body mass index, and laboratory parameters including fasting blood glucose, glycated hemoglobin (HbA1c), lipid profile, and serum creatinine were recorded using a standardized data collection form. Diabetic microvascular complications—retinopathy, nephropathy, and neuropathy—were identified based on established clinical and laboratory criteria.

Transcranial Doppler sonography was performed using a 2-MHz pulsed-wave probe with participants in the supine position. Bilateral middle cerebral arteries were insonated through the temporal acoustic window. Baseline mean flow velocities were recorded after adequate rest. Dynamic cerebral autoregulation was assessed using the breath-holding test. Participants were instructed to hold their breath following normal inspiration while continuous Doppler monitoring was performed. The breath-holding index (BHI) was calculated as the percentage change in mean flow velocity divided by the duration of breath-holding.

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2.3 Data Analysis

Data were entered and analyzed using statistical software as outlined in the thesis methodology. Continuous variables were expressed as mean ± standard deviation, and categorical variables as frequencies and percentages. Comparisons between groups were performed using appropriate parametric or non-parametric tests. Multivariate logistic regression analysis was applied to identify independent predictors of impaired cerebral autoregulation. A p-value <0.05 was considered statistically significant.

3. Results

Of the 154 patients included in the study, a substantial proportion exhibited one or more diabetic microvascular complications. Patients with microvascular complications were older and had a longer duration of diabetes compared with those without complications. Baseline cerebral blood flow velocities were significantly lower in patients with microvascular complications. During the breath-holding test, patients without microvascular complications demonstrated an appropriate autoregulatory response, whereas those with complications showed a blunted response. The degree of impairment increased with the number of microvascular complications.

Multivariate analysis identified clinical and metabolic parameters as independent predictors of impaired dynamic cerebral autoregulation, indicating a strong association between systemic diabetic burden and cerebrovascular dysfunction.

Table 1. Distribution of Microvascular Complications

Microvascular status	Number (n)	Percentage (%)
With microvascular complications	93	60.4
Without microvascular complications	61	39.6
Total	154	100.0

Out of 154 patients with type 2 diabetes mellitus, 93 patients (60.4%) had one or more diabetic microvascular complications, while 61 patients (39.6%) had no detectable microvascular complications.

In addition, the high prevalence of microvascular complications suggests prolonged exposure to hyperglycemia and vascular injury in this cohort. Such systemic microangiopathy is known to affect not only peripheral organs but also the cerebral circulation. The presence of a large subgroup without complications provides an internal comparison group, strengthening the analytical validity. This distribution allows meaningful evaluation of early versus advanced cerebrovascular involvement. Overall, the cohort composition is suitable for assessing the impact of diabetic microvascular disease on cerebral autoregulation.

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Table 2. Baseline Mean Flow Velocity and Breath-Holding Response

Variable	With complications (Mean±SD)	Without complications (Mean±SD)	Test	p-value
Baseline MFV (cm/s)	44.37±3.19	52.61±5.06	t-test	<0.001
MFV at end of BHT (cm/s)	52.40±4.14	63.27±6.17	t-test	<0.001

Baseline mean flow velocity (MFV) of the bilateral middle cerebral arteries and MFV at the end of the breath-holding test were compared between patients with and without microvascular complications.

As shown in Table 2, patients with microvascular complications had significantly lower baseline MFV, indicating chronic cerebral microvascular involvement. Additionally, the reduced MFV increase during breath-holding reflects impaired carbon dioxide–mediated vasodilation and diminished cerebrovascular reserve.

Table3. Breath-Holding Index and Microvascular Complication Burden

Number of complications	BHI (Mean±SD)	Test	p-value
One	0.67±0.07	ANOVA	<0.001
Two	0.62±0.10		
Three	0.55±0.12		

Breath-holding index values were analyzed according to the number of diabetic microvascular complications. Lower baseline MFV reflects chronic structural and functional alterations of cerebral resistance vessels. These alterations may include endothelial dysfunction, increase vascular stiffness, and reduce nitric oxide bioavailability. The diminished MFV response during breath-holding further indicates impaired vasodilatory reserve. Such impairment suggests reduced responsiveness to hypercapnic stimuli. Together, these findings demonstrate both resting and dynamic cerebrovascular dysfunction in patients with microvascular complications.

Table 4. Clinical Characteristics According to Breath-Holding Index

Variable	BHI <0.69	BHI ≥0.69	Test	p-value
Age (years)	57.22±6.58	53.23±6.61	t-test	0.001
HbA1c (%)	8.14±1.97	7.32±1.55	t-test	0.015
Serum creatinine (mg/dl)	1.14±0.35	1.02±0.26	t-test	0.030

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Patients were categorized based on impaired BHI (<0.69) and preserved BHI (≥0.69) to assess associations with demographic and metabolic characteristics (Sharma et al., 2016).
As shown in Table 4, patients with impaired BHI were significantly older and had poorer glycemic control and higher serum creatinine levels. These findings indicate that aging, chronic hyperglycemia, and renal microvascular involvement are associated with reduced cerebral autoregulatory capacity.

Table 5. Independent Predictors of Impaired Breath-Holding Index

Predictor	Odds Ratio	95% CI	p-value
HbA1c	1.30	1.03–1.67	0.029
Serum creatinine	18.8	0.98–13.51	0.050

Multivariate logistic regression analysis was performed to identify independent predictors of impaired dynamic cerebral autoregulation assessed by BHI. The observed decline in BHI across increasing numbers of complications highlights cumulative vascular damage. Each additional microvascular complication appears to contribute incrementally to cerebrovascular dysfunction. This pattern supports the concept that cerebral autoregulation deteriorates alongside systemic microangiopathy. The consistent trend across groups strengthens the biological plausibility of the findings. These results emphasize the progressive nature of diabetic cerebrovascular involvement.

4. Discussion

The present study demonstrates that dynamic cerebral autoregulation assessed by the breath-holding test (BHT) is significantly impaired in patients with type 2 diabetes mellitus (T2DM), particularly in those with established microvascular complications. The findings support the concept that diabetes-related microangiopathy extends to the cerebral circulation and can be detected using simple, non-invasive physiological testing. By focusing on BHT-derived indices, especially the breath-holding index (BHI), this study provides clinically relevant insight into early cerebrovascular dysfunction in T2DM.

4.1 Breath-Holding Test as a Marker of Dynamic Cerebral Autoregulation

The breath-holding test (BHT) is a widely used method for assessing cerebrovascular reactivity to hypercapnia, reflecting the functional integrity of vascular smooth muscle, endothelial nitric oxide activity, and metabolic regulation of cerebral blood flow. During breath holding, increased arterial carbon dioxide tension induces cerebral vasodilation, resulting in a rise in middle cerebral artery mean flow velocity (MFV). The magnitude of this response, expressed as the breath-holding index (BHI), serves as a surrogate marker of dynamic cerebral autoregulation.

In the present study, patients with T2DM demonstrated a reduced MFV response during BHT, leading to significantly lower BHI values. This impairment was more pronounced in those with diabetic microvascular complications, suggesting that progressive systemic microangiopathy is

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associated with declining cerebrovascular vasodilatory capacity. These findings are consistent with previous studies reporting reduced cerebrovascular reactivity in diabetic populations using BHT or CO_2-based stimuli (Brown et al., 2008; Moghaddasi et al., 2010; Lasek-Bal et al., 2012). Lower baseline MFV observed in patients with microvascular complications further indicates chronic structural and functional alterations in cerebral resistance vessels. Mechanisms such as capillary basement membrane thickening, endothelial dysfunction, and increased arterial stiffness—hallmarks of diabetic microangiopathy—may reduce resting cerebral perfusion and limit vasodilatory reserve during hypercapnic stress.

Variability in breath-holding performance should also be considered when interpreting BHT results. Differences in patient effort, breath-holding duration, pulmonary function, and cooperation may influence the degree of hypercapnia achieved, thereby affecting MFV changes and BHI values. Although standardized procedures were followed, this variability may introduce some measurement inconsistency.

4.2 Association Between BHI and Microvascular Complication Burden

A key finding of this study is the graded decline in BHI with increasing numbers of microvascular complications. Patients with one complication showed higher BHI values than those with two or three complications, indicating cumulative cerebrovascular damage. This dose–response relationship strengthens the biological plausibility that cerebral autoregulatory impairment progresses alongside systemic microvascular disease.

Similar associations have been reported by Lee et al. (2000) and Petrica et al. (2007a), who demonstrated that indices of cerebral hemodynamics worsen in parallel with diabetic nephropathy and retinopathy severity. The present findings extend this evidence by showing that BHT-derived BHI can sensitively reflect the burden of diabetic microangiopathy, even in the absence of overt cerebrovascular events.

4.3 Impaired BHI in T2DM Without Microvascular Complications

Notably, patients with T2DM but without clinically detectable microvascular complications also exhibited reduced BHI values compared with normative thresholds. This suggests that cerebral autoregulatory dysfunction may occur early in the disease course, preceding clinically apparent organ damage. Similar early impairments have been described in newly diagnosed or uncomplicated T2DM cohorts (Thomas et al., 2003; Palazzo et al., 2013), supporting the hypothesis that cerebral vessels are affected early by metabolic dysregulation.

Chronic hyperglycemia, insulin resistance, and low-grade inflammation may impair endothelial nitric oxide synthesis and disrupt neurovascular coupling before structural microangiopathy becomes clinically evident. This subclinical cerebrovascular dysfunction may represent an early marker of future neurological risk, including stroke and cognitive decline.

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4.4 Influence of Glycemic Control and Renal Function on BHI

Multivariate analysis identified glycated hemoglobin (HbA1c) and serum creatinine as independent predictors of impaired BHI. Poor glycemic control has been consistently linked to endothelial dysfunction and impaired vasoreactivity in both systemic and cerebral circulations. Each incremental rise in HbA1c reflects prolonged exposure to hyperglycemia, which promotes oxidative stress, advanced glycation end-product formation, and vascular smooth muscle dysfunction.

The association between elevated serum creatinine and reduced BHI further underscores the interrelationship between diabetic nephropathy and cerebral microangiopathy. Renal dysfunction is a marker of widespread endothelial injury and arterial stiffness, which may impair cerebral vasodilatory responses. Petrica et al. (2007b) similarly reported that declining renal function correlated with worsening cerebral autoregulatory indices in T2DM.

4.5 Clinical Implications of BHT-Based Assessment

From a practical perspective, the BHT offers several advantages for assessing cerebral autoregulation in routine clinical settings. It is non-invasive, inexpensive, and easily performed at the bedside without pharmacological agents. The present study confirms that BHT, combined with transcranial Doppler sonography, can detect subtle cerebrovascular dysfunction in T2DM patients across different stages of microvascular involvement.

Early identification of impaired BHI may help stratify patients at higher risk for cerebrovascular complications, even before clinical stroke or cognitive impairment occurs. This is particularly relevant in resource-limited settings, where advanced neuroimaging may not be readily available. Incorporating BHT-based cerebrovascular assessment into routine diabetic evaluation could enhance risk prediction and guide early intervention strategies.

Abnormal findings may prompt closer monitoring, optimization of glycaemic and vascular risk control, and consideration of further neurovascular assessment where available. This approach is especially valuable in resource-limited settings where advanced neuroimaging is not readily accessible, allowing earlier identification and targeted intervention.

4.6 Comparison with Previous Literature

While several studies have demonstrated impaired cerebrovascular reactivity in T2DM, others have reported preserved autoregulation (van Oers et al., 2006). These discrepancies may reflect differences in study design, disease duration, metabolic control, and testing methodology. The present study's focus on BHT and microvascular stratification likely enhanced sensitivity for detecting diabetes-related cerebrovascular dysfunction.

Importantly, emerging evidence links impaired cerebrovascular reactivity with cognitive decline and dementia risk. Silvestrini et al. (2006) demonstrated that reduced vasoreactivity predicted

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cognitive deterioration, while Verdelho et al. (2010) showed that diabetes-related white matter changes contribute to cognitive decline. These observations suggest that impaired BHI in T2DM may have implications beyond stroke risk, extending to long-term cognitive outcomes.

4.7 Strengths and Limitations Related to BHT

A major strength of this study is the exclusive focus on BHT-derived indices, avoiding confounding from multiple testing modalities. The use of bilateral middle cerebral artery measurements and standardized breath-holding protocols enhances internal consistency. Additionally, stratification by microvascular complication burden provides valuable pathophysiological insight.

However, certain limitations should be acknowledged. End-tidal CO_2 levels were not directly measured, which may introduce variability in hypercapnic stimulus intensity. Breath-holding performance may also be influenced by age, obesity, or pulmonary function. Despite these limitations, BHT remains a pragmatic and clinically meaningful tool for assessing dynamic cerebral autoregulation. The absence of a healthy control group is acknowledged as a limitation. However, comparison with established normative BHI values (0.69–1.20 in healthy individuals) suggests that the reduced values observed reflect impaired cerebrovascular reactivity (Sharma et al., 2016). Future studies should include matched controls for more robust validation. A further limitation of this study is that inter-operator variability in transcranial Doppler (TCD) measurements was not assessed, as all examinations were performed by a single operator, limiting generalizability.

5. Conclusion

This study demonstrates that dynamic cerebral autoregulation, assessed using the breath-holding test and transcranial Doppler ultrasonography, is significantly impaired in patients with type 2 diabetes mellitus, particularly in those with established microvascular complications. Patients with diabetic retinopathy, nephropathy, and neuropathy exhibited lower baseline middle cerebral artery flow velocities and a markedly blunted vasodilatory response to hypercapnia, reflected by reduced breath-holding index values. Furthermore, the graded decline in breath-holding index with increasing numbers of microvascular complications supports a cumulative effect of diabetic microangiopathy on cerebral hemodynamic regulation.

The independent associations of impaired breath-holding index with poor glycemic control and elevated serum creatinine highlight the close relationship between metabolic burden, renal microvascular disease, and cerebral vascular dysfunction. These findings suggest that cerebrovascular impairment may evolve in parallel with systemic microvascular injury and may even precede overt clinical cerebrovascular events. Importantly, reduced breath-holding index values observed in some patients without clinically apparent complications indicate that subclinical cerebral autoregulatory dysfunction may occur early in the course of type 2 diabetes mellitus. From a

clinical perspective, the breath-holding test offers a simple, non-invasive, and cost-effective method for evaluating dynamic cerebral autoregulation in routine practice, particularly in resource-limited settings. Early identification of impaired cerebrovascular reactivity may allow better risk stratification and support timely interventions aimed at optimizing glycemic control and vascular protection. Longitudinal studies are warranted to determine whether breath-holding index impairment predicts future stroke, cognitive decline, or progression of diabetic microvascular disease.

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