Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Ultrasound Evaluation of the Effect of Impaired Vascular Dilation Function in Diabetic Patients on the Vasodilatory Effect of Nitroglycerin During the Perioperative Period – A Prospective Trial Cohort Study

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Background: Diabetes mellitus (DM) is associated with vascular endothelial dysfunction, which may impair perioperative responsiveness to vasoactive drugs such as nitroglycerin.

Objective: This study aimed to assess vasodilatory dysfunction in diabetic patients using high-resolution ultrasound, compare their nitroglycerin response with non-diabetics during anesthesia emergence, and evaluate how endothelial impairment affects nitroglycerin-mediated vasodilation to guide personalized dosing.

Methods: This prospective cohort study compared 40 non-diabetic (Group A) and 40 diabetic patients (Group B). Preoperative brachial artery ultrasound assessed flow-mediated dilation (FMD) and nitroglycerin-induced dilation (NID). Following extubation, the total nitroglycerin dose required to restore blood pressure to baseline was recorded as the primary endpoint. Secondary endpoints comprised FMD and NID values, ED_{50}/ED_{90} of nitroglycerin, and perioperative hemodynamic changes.

Results: Compared with Group A, the nitroglycerin dose was significantly higher in Group B (48.47±5.11 μg vs 39.74±4.15 μg; mean difference: 8.73 μg, 95% CI: 6.82–10.64; P<0.001). Group B showed significantly lower FMD (3.68±1.70% vs 8.45±1.77%; mean difference: −4.77%, 95% CI: −5.65 to −3.89; P<0.001) and NID (5.07±2.63% vs 9.15±2.99%; mean difference: −4.08%, 95% CI: −5.27 to −2.89; P<0.001). Both FMD and NID correlated negatively with nitroglycerin dose (r=−0.653 and r=−0.610, respectively; both P<0.001). Diabetic patients required higher effective doses (ED_{50}: 0.292[0.268–0.316] vs 0.272[0.250–0.294]μg/kg/min; ED_{90}: 0.329[0.302–0.356] vs 0.312[0.288–0.336] μg/kg/min). Multivariate analysis identified higher HbA1c and lower FMD/NID as independent predictors of increased nitroglycerin requirement.

Conclusion: This prospective cohort study demonstrated that impaired vascular endothelial function in diabetic patients significantly reduced sensitivity to nitroglycerin perioperatively. This was manifested by the requirement for higher nitroglycerin doses to achieve target baseline blood pressure levels during hemodynamic management following extubation. These findings suggest that preoperative vascular ultrasound may provide an individualized nitroglycerin dosing framework for diabetic patients.

Keywords: diabetes, nitroglycerin, flow-mediated vasodilation, FMD, nitroglycerin-induced vasodilation, NID, vasodilatory dysfunction

Introduction

Diabetes mellitus (DM) is a major global metabolic disorder, with its prevalence having increased significantly over the past decade.[1] Beyond chronic hyperglycemia, DM is associated with extensive microvascular and macrovascular complications,

Received: 19 June 2025
Accepted: 19 November 2025
Published: 27 November 2025

including diabetic nephropathy, retinopathy, peripheral neuropathy, and cardiovascular disease.[2,3] Cardiovascular complications represent the leading cause of mortality among diabetic patients, accounting for over 50% of diabetes-related deaths.[4] Diabetic cardiovascular dysfunction is primarily characterized by impaired vasodilation, abnormal vascular smooth muscle function, and autonomic nervous system dysregulation.[5] These pathophysiological alterations increase the perioperative anesthesia risk for diabetic patients. Clinical observations indicate impaired hemodynamic stability perioperatively in these patients, manifested as significant blood pressure fluctuations and an elevated incidence of arrhythmias, contributing to an increased risk of postoperative cardiovascular and cerebrovascular complications.[6]

Nitroglycerin, a potent vasodilator, exerts its effects by releasing nitric oxide (NO), which activates the soluble guanylyl cyclase (sGC)-cyclic guanosine monophosphate (cGMP) signaling pathway. This activation leads to vasodilation, reduced cardiac preload, and decreased myocardial oxygen consumption.[7,8] Consequently, nitroglycerin is widely employed for perioperative hypertension management.[9] However, in diabetic patients, the efficacy of nitroglycerin is compromised by a cascade of events rooted in endothelial dysfunction. Insulin resistance and chronic hyperglycemia promote oxidative stress, which in turn disrupts the normal function of endothelial nitric oxide synthase (eNOS) and accelerates the degradation of nitric oxide (NO).[10–13] This results in a critical deficit of bioactive NO, thereby attenuating the vasodilatory signal triggered by nitroglycerin. Currently, the specific impact of diabetic vascular endothelial dysfunction on the perioperative vasodilatory efficacy of nitroglycerin has not been fully elucidated. This knowledge gap hinders anesthesiologists' ability to precisely tailor nitroglycerin dosing regimens for diabetic patients.

In recent years, high-resolution ultrasound technology has gained increasing application in perioperative care. Ultrasound assessment of vascular dilation function, particularly brachial artery flow-mediated dilation (FMD) and nitroglycerin-induced dilation (NID), has emerged as an important tool for evaluating endothelium-dependent and endothelium-independent vasodilatory functions, respectively.[14,15] Studies indicate that combining FMD and NID provides a more accurate assessment of vasodilatory function and offers greater clinical value compared to FMD alone.[16] Combining these assessment techniques offers a novel methodology. This approach can better investigate how vascular dysfunction in perioperative diabetic patients affects their response to vasoactive drugs. Furthermore, it may provide a critical basis for elucidating the individualized application of vasoactive drugs during the perioperative period.

Therefore, this study aims to: (1) quantitatively assess the degree of vasodilation function in diabetic patients using high-resolution ultrasound; (2) compare perioperative nitroglycerin-induced vasodilation responses between diabetic and non-diabetic patients during general anesthesia emergence/extubation; and (3) analyze the influence of impaired vasodilation function on nitroglycerin-induced vasodilation. The ultimate goal is to provide a scientific basis for developing individualized nitroglycerin dosing regimens for diabetic patients in the perioperative setting.

Methods and Materials

Study Design and Ethics

This study is a single-center, prospective, experimental cohort study. Received ethical approval from the Institutional Review Board of Sir Run Run Hospital Affiliated to Nanjing Medical University (2024-SR-050; August 28,2024). This study has been registered with the Chinese Clinical Trials Registry (ChiCTR2500099965). All participants received written informed consent. The study procedures adhered to the ethical standards set by the Human Research Ethics Committee (Institutional or Regional) and the Declaration of Helsinki (1975, revised in 2013). This clinical trial was conducted from December 2024 to March 2025.

Participants

Inclusion criteria include patients aged 18–65 years, with American Society of Anesthesiologists (ASA) physical condition grade II to III, who were scheduled to undergo selective radical resection of gastrointestinal tumors. The trial group consisted of diabetic patients (Group B) who had a history of diabetes for more than 5 years and were receiving oral hypoglycemic drugs or insulin treatment. The control group consisted of non-diabetic patients (Group A). All patients received the same anesthesia and surgical procedures. Exclusion criteria included: (I) moderate to severe hypertension and cardiovascular and cerebrovascular diseases; (II) History of smoking; (III) Peripheral vascular disease; (IV) Hyperlipidemia; (V) Severe preoperative arrhythmia or cardiac insufficiency; (VI) Allergy or contraindications to nitroglycerin drugs; (VII) Preoperative hemodynamic disturbances or electrolyte imbalances;(VIII) Liver and kidney insufficiency.

Ultrasound Assessment of Brachial Artery Function

Blood-Mediated Vasodilation Function (FMD) Assessment

All measurements were taken after the patient was transferred to the preoperative waiting area. Patients need to rest for at least 15 minutes before the examination and avoid caffeine or tobacco intake within the previous 24 hours. A high-resolution ultrasound diagnostic instrument (Mindray, Te 7, China) with a linear array probe (frequency 7.5–10 MHz) was used for the FMD test. The patient was in a supine position with the right upper arm abducted 15–25° and the palm facing upwards. The probe was placed 10–15 cm above the elbow joint and is probing along the longitudinal axis of the brachial artery to obtain the clearest images of the anterior and posterior walls of the artery. Measure the anterior-posterior diameter (D_0) between the intima of the brachial artery at the end of ventricular diastole, then wrap a compression cuff around the forearm, pressurize to 250 mmHg and maintain for 5 minutes, and then measure the inner diameter (D_1) of the brachial artery again within 60–90 seconds after rapid deflation. The formula for FMD is: FMD (%) = $(D_1 - D_0)/D_0 \times 100\%$. FMD≥6% indicates normal endothelium-dependent vasodilation function, and <6% indicates impaired function.[17,18]

Nitroglycerin-Induced Vasodilation Function (NID) Assessment

After the FMD measurement was completed, the patient rested for 15 minutes, followed by sublingual administration of nitroglycerin 0.4 mg. Four minutes later, the brachial artery inner diameter (D_2) was measured again. Nitroglycerin-induced vasodilation function (NID) is calculated by the formula: NID (%) = $(D_2 - D_0)/D_0 \times 100\%$. NID is used to assess non-endothelial-dependent diastolic function of vascular smooth muscle.[19]

To ensure the accuracy of the measurements, the ultrasound probe avoided compression of the artery. Three anteroposterior diameter parameters of the brachial artery were measured at each marker point, and the average values were recorded. All ultrasound measurements were conducted by an experienced anesthesiologist who had received more than 3 months of dedicated vascular ultrasound training and had completed over 100 such measurements. This assessor was blinded to the patients' group assignments throughout the study. To ensure effective blinding, a separate research coordinator, who was not involved in the ultrasound assessments, managed all aspects of patient enrollment and group allocation. The ultrasound assessor only had access to de-identified study codes during both data acquisition and analysis (Figure 1).

Anesthesia Management and Interventions

After the patient was admitted to the room, electrocardiogram (ECG), pulse oxygen saturation (SPO_2), non-invasive blood pressure (NIBP), and invasive arterial blood pressure (IABP) monitoring are connected. After establishing an intravenous access, hemodynamic parameters at admission (T0) and immediately after tracheal intubation (T_1) were accurately recorded based on IABP monitoring data. Anesthesia was induced by intravenous injection of midazolam (0.05 mg/kg), sufentanil (0.3–0.6 μg/kg), rocuronium (0.6 mg/kg), and propofol (1.0–1.5 mg/kg). Mechanical ventilation was performed after tracheal intubation, with volume control mode. Tidal volume (VT) was set at 6–8 mL/kg, respiratory rate (RR) at 12 breaths/min, inhalation oxygen concentration (FiO_2) at 60%, inhalation-exhalation ratio (I:E) at 1:2, and positive end-expiratory pressure (PEEP) at 5 cmH_2O. Maintain the end-expiratory carbon dioxide partial pressure ($PETCO_2$) between 35 and 45 mmHg.

Anesthesia was maintained by continuous intravenous pumping of 1% propofol (4–6 mg/kg/h), remifentanil (0.1–-0.3 μg/kg/min), and rocuronium (10–12 μg/kg/min). No inhalation anesthetic drugs were used during the operation. The depth of anesthesia was monitored by electroencephalogram bispectral index (BIS), and the BIS value was maintained between 25 and 50. During the operation, the mean arterial pressure (MAP) fluctuation was strictly controlled to no more than 20% of the baseline value based on the IABP monitoring data,[20] and patients were kept warm with a blanket to maintain body temperature at 36.0–37.0°C.

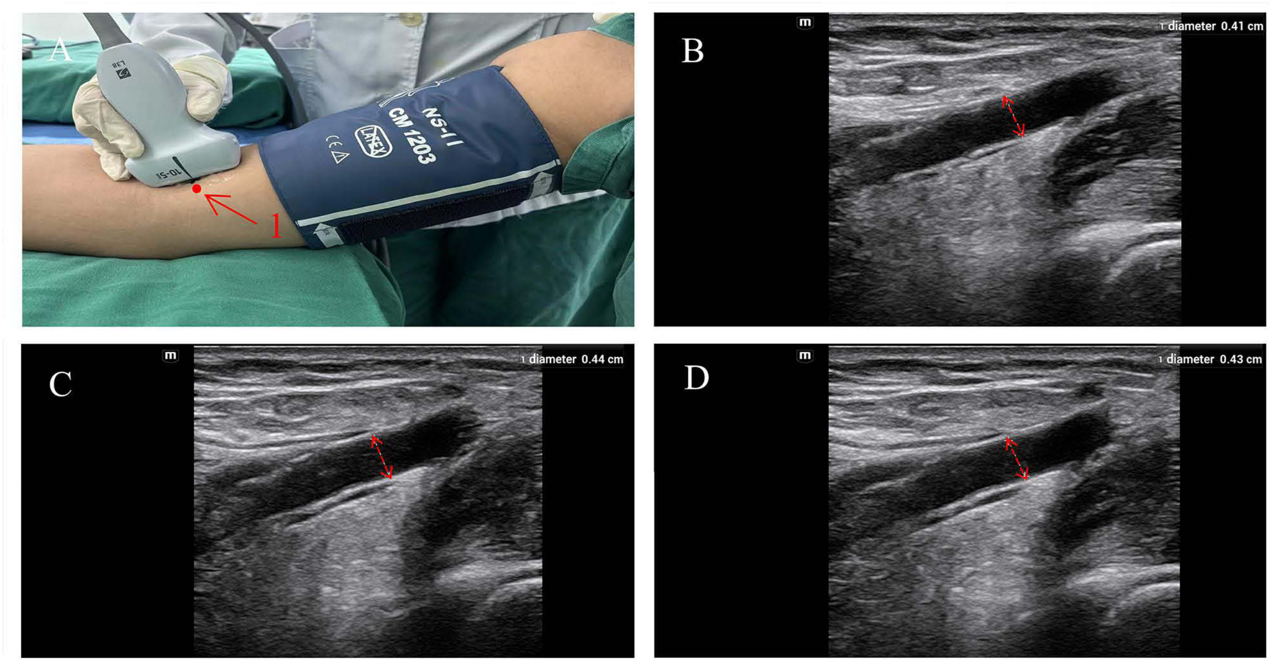

Figure 1 Ultrasound assessment of brachial artery vasodilatory function. (**A**) Representative ultrasound images obtained during the flow-mediated dilation (FMD) and nitroglycerin-induced dilation (NID) trials. (**B**) Baseline brachial artery diameter measurement. (**C**) Brachial artery diameter measurement after the FMD test. (**D**) Brachial artery diameter measurement after the NID test.

Notes: The red circle (spot 1) in panel A indicates the marker point for diameter measurement. The red arrows in panels B, C, and D indicate the anterior and posterior walls of the brachial artery between which the lumen diameter was measured.

Abbreviations: FMD, flow-mediated dilation; NID, nitroglycerin-induced dilation.

After the operation, the patient was transferred to the Post-Anesthesia Care Unit (PACU, T_2). Extubation indications include recovery of consciousness, presence of swallowing reflex, tidal volume ≥6 mL/kg, SPO_2≥95% at 5 minutes off the ventilator. After meeting the extubation criteria, extubation (T_3) was performe.[21] After extubation, if the patient developed hypertension (IABP showed systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or an increase in blood pressure exceeding baseline by more than 30%, administer intravenous nitroglycerin (0.001% concentration, at a rate of 0.3–1.0 μg/kg/min) to bring the blood pressure back to baseline (T_0) within 3 minutes.[22,23] Record the total dose of nitroglycerin infusion. If the patient has hypotension (IABP shows MAP<60 mmHg), stop pumping nitroglycerin and inject 100 μg of phenylephrine intravenously; If nitroglycerin fails to effectively control blood pressure, other vasoactive drugs (such as sodium nitroprusside) are used instead. Patients whose blood pressure returns to normal immediately after extubation do not require intervention and are excluded. Postoperative hemodynamic parameters and vital signs of the patients were continued to be recorded through the IABP monitoring system, including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), and SPO_2 at 1 minute (T_4), 3 minutes (T_5), 5 minutes (T_6), and 10 minutes (T_7) post-administration.

Statistical Analysis

Data analysis was conducted in this study using SPSS 25.0 software. Before the formal study began, a pre-experiment involving 20 patients (10 per group) was conducted to verify the feasibility of the study protocol. The results showed a statistically significant difference in the nitroglycerin dose between the diabetic and non-diabetic groups (38.48 ± 2.53 μg vs 36.62 ± 2.48 μg, $P < 0.05$). Based on these data, a sample size calculation was performed using PASS 21.0 software for an independent-sample *t*-test. With $\alpha = 0.05$ and $\beta = 0.1$ (power = 90%), a minimum of 40 patients per group (80 in total) was required for the final analysis. To account for an estimated 20% dropout rate, we planned to enroll 100 patients (50 per group). The actual dropout rate was 20%, resulting in 80 patients completing the study, which matched the initial calculation requirement. A post-hoc power analysis using the observed effect size (Cohen's d = 1.88) confirmed that the final analysis achieved a power greater than 99%, well above the conventional threshold.

In the formal study, the measurement data were first evaluated by the Shapiro–Wilk test to determine if they conformed to the normal distribution. Data that conform to the normal distribution are expressed as Mean ± standard deviation (Mean ± SD), and independent sample t-tests are used for comparison between groups; For data that were not normally distributed, the median (interquartile range, IQR) was expressed, and the Mann–Whitney *U*-test was used for comparison between groups. Categorical data were expressed as percentages (%), and comparisons between groups were performed using the chi-square test or Fisher's exact probability method. Correlation analysis used the Pearson correlation coefficient to evaluate the relationship between brachial artery flow-mediated vasodilation (FMD) and nitroglycerin-mediated vasodilation (NID) with the dose of nitroglycerin infusion.

In this study, logarithmic transformed dose-effect analysis was used to precisely quantify nitroglycerin sensitivity between the non-diabetic patient group (Group A) and the diabetic patient group (Group B). First, the total dose of nitroglycerin (μg) for each patient was standardized to individualized pumping rate (μg/kg/min) based on body weight (kg) and pumping time (min), and log10 conversion was performed on all dose data. Based on the converted data, the probit regression model was used to fit the dose-response curve, yielding $logED_{50}$ and $logED_{90}$ values along with their 95% confidence intervals (ED_{50} was defined as the dose threshold for restoring blood pressure to baseline in 50% of patients, and ED_{90} as the dose threshold for achieving target blood pressure in 90% of patients). The results were converted to the original units (μg/kg/min) by antilogarithmic transformation (10^x), and the degree of change in nitroglycerin sensitivity in diabetic patients was evaluated by comparing the differences in $logED_{50}$ and $logED_{90}$ between the two groups. In addition, univariate and multivariate logistic regression analyses were used to investigate the independent risk factors for nitroglycerin dose. In the univariate analysis, variables such as fasting blood glucose, glycated hemoglobin, FMD, and NID were included; In the multivariate analysis, stepwise regression was used to screen for significant variables.

For all statistical analyses, $P<0.05$ was considered statistically significant.

Result

A total of 112 patients were recruited for this study during the study period from November 2024 to March 2025. 12 patients were excluded according to established exclusion criteria, resulting in 100 patients enrolled in the study. During the study, a total of 20 patients failed to complete the study. Among them, 5 patients withdrew due to their inability to complete the FMD or NID tests, 4 patients withdrew due to unplanned ICU admissions, 7 patients withdrew because they did not exhibit a hypertensive response after extubation, and another 4 patients withdrew because they failed to reduce their blood pressure to baseline levels. As a result, a total of 80 patients completed the study, with 40 diabetic patients and 40 non-diabetic patients included in the final data analysis, as shown in Figure 2.

Preoperative Characteristics

As shown in Table 1, there were no significant differences between group A and group B in baseline data such as age, BMI, gender, ASA grade, and proportion of mild hypertension ($P > 0.05$). There were significant differences in fasting blood glucose and glycated hemoglobin (HbA1c) levels between the two groups ($P < 0.05$).

Surgical Data

As shown in Table 2, there were no significant differences between the diabetic patient group and the non-diabetic patient group in terms of operation duration, anesthesia duration, type of surgery, blood loss, and the volume of crystalloid fluid, colloid fluid, red blood cell suspension, and plasma infusion ($P > 0.05$).

Comparison of FMD, NID, and Nitroglycerin Infusion Dose Between the Two Groups

As shown in Table 3, this study compared brachial artery flow-mediated vasodilation (FMD), nitroglycerin-induced vasodilation (NID), and total nitroglycerin infusion dose between the non-diabetic group (Group A) and the diabetic group (Group B). The results showed that the FMD in group B was 3.68±1.70%, which was significantly lower than that

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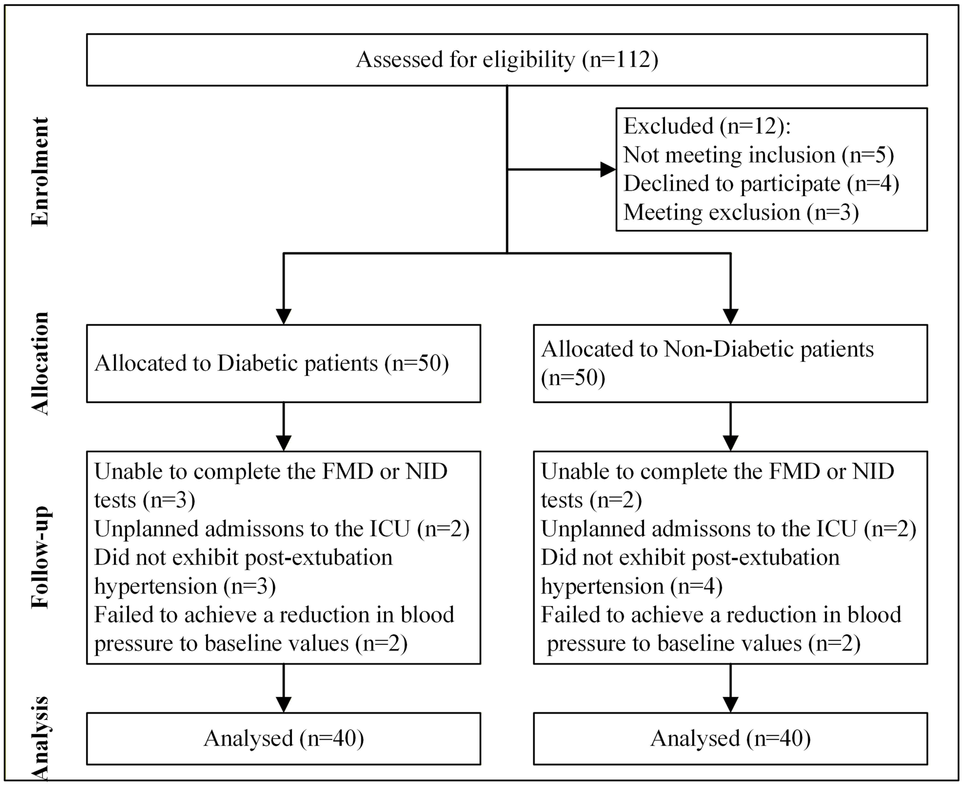

Figure 2 CONSORT showing flow of patients.

in group A at 8.45±1.77% (t=10.65, P<0.001). The NID of group B was 5.07±2.63%, which was also significantly lower than that of group A at 9.15±2.99% (t=5.63, P<0.001). In terms of nitroglycerin usage, group B was significantly higher than group A with a infusion dose of 48.47±5.11 µg vs 39.74±4.15 µg (t=−7.26, P<0.001). There was no significant

Table 1 Baseline Demographic Between Two Groups

Variables	Group A (n=40)	Group B (n=40)	P
Age (y)	54.38±4.9	52.83±4.32	0.14
BMI (kg/m^2)	24.92±2.74	26.28±3.01	0.17
Gender, n(%)			0.45
Male	28 (70.0%)	31 (77.5%)	
Female	12 (30.0%)	9 (22.5%)	
ASA			0.49
I	2	1	
II	18	22	
III	16	21	
Hypertension, (%)	13 (32.5%)	19 (47.5%)	0.17
Course of diabetes (year)	–	6.68±1.7	–
Fasting blood glucose (mmol/L)	5.57±0.64	5.87±0.52	0.02
Total cholesterol (mmol/l)	5.14±0.28	5.17±0.27	0.67
Triglyceride (mmol/L)	1.45±0.14	1.48±0.16	0.39
HDL (mmol/L)	1.30±0.77	1.32±0.74	0.51
LDL (mmol/L)	2.93±0.22	2.97±0.14	0.30
HbA1c (%)	5.78±0.22	6.84±0.42	0.001

Notes: Values are presented as mean ± SD, or number (percentage).
Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; HbA1c, Glycated hemoglobin.

Table 2 Clinical Characteristics and Outcomes of the Patients Among the Two Groups

Variables	Group A (n=40)	Group B (n=40)	P
Operation duration (h)	175 (155.00, 195.00)	185 (156.25, 198.75)	0.616
Anesthesia duration (h)	150 (130.00, 170.00)	160 (131.25, 170.00)	0.547
Surgical type, (%)			1.0
Endoscopic surgery	30 (0.75)	32 (0.8)	
Open surgery	10 (0.25)	8 (0.2)	
Blood loss (mL)	100.00 (62.50, 200.00)	125.00 (50.00, 187.50)	0.633
Fluid infusion			
Crystalloid (mL)	2000.00 (1500.00, 2000.00)	2000.00 (1500.00, 2000.00)	1.00
Colloidal solution (mL)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.957
Red cell concentrated (u)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.975
Plasma (mL)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.992

Note: Data are median (interquartile range).

Table 3 Comparison of FMD, NID, and Nitroglycerin Infusion Dose Between the Two Groups

Group	n	Basal Diameter (mm)	FMD (%)	NID (%)	Nitroglycerin (ug)
Group A	40	0.44±0.03 (0.43–0.45)	8.45±1.77 (7.86–9.04)	9.15±2.99 (8.18–10.13)	39.74±4.15 (38.39–41.05)
Group B	40	0.45±0.03 (0.44–0.46)	3.68±1.70 (3.11–4.25)	5.07±2.63 (4.21–5.95)	48.47±5.11 (46.82–50.15)
t		−1.29	10.65	5.63	−7.26
p		0.203	< 0.001	< 0.001	< 0.001

Note: Values are presented as mean ± SD (95% confidence interval).
Abbreviations: FMD, flow-mediated vasodilation; NID, nitroglycerin-induced vasodilation.

difference in baseline brachial artery diameter between the two groups (Group A: 0.44±0.03 mm, Group B: 0.45 ±0.03 mm, t=−1.29, P=0.203).

Comparison of Hemodynamic Parameters at Different Time Points Between the Two Groups

As shown in Figure 3, this study also compared hemodynamic parameters of the two groups of patients at different time points, including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse oxygen saturation (SPO_2), and heart rate (HR). The results showed no significant differences in SBP, DBP, MAP, SPO_2, and HR between the two groups at T_0 (at admission), T_2 (after PACU admission), T_4 (1 minute after administration), T_5 (3 minutes after administration), T_6 (5 minutes after administration), and T_7 (10 minutes after administration) (P>0.05). However, differences were observed between the groups at T_1 (immediate after intubation) and T_3 (immediate after extubation): at T_1, Group B's DBP (83.97±5.29 mmHg vs A: 80.63±5.23 mmHg) and MAP (113.81±4.61 mmHg vs A: 110.67±4.19 mmHg) were significantly higher than those in Group A; at T_3, Group B's DBP (87.80±4.61 mmHg vs A: 86.83±5.36 mmHg) and MAP (118.84±4.14 mmHg vs A: 117.12±4.03 mmHg) also showed the same trend. These results suggest that hemodynamic fluctuations were more significant in diabetic patients at the moment of intubation and extubation, especially in terms of diastolic blood pressure and mean arterial pressure. (Figure 3)

Correlation Between FMD, NID, and Nitroglycerin Dose

The correlation analysis used the Pearson correlation coefficient to evaluate the relationship between brachial artery flow-mediated vasodilation (FMD) and nitroglycerin-induced vasodilation (NID) with the dose of nitroglycerin infusion. The results showed a significant negative correlation between FMD and nitroglycerin injection dose (r=−0.653, P<0.001),

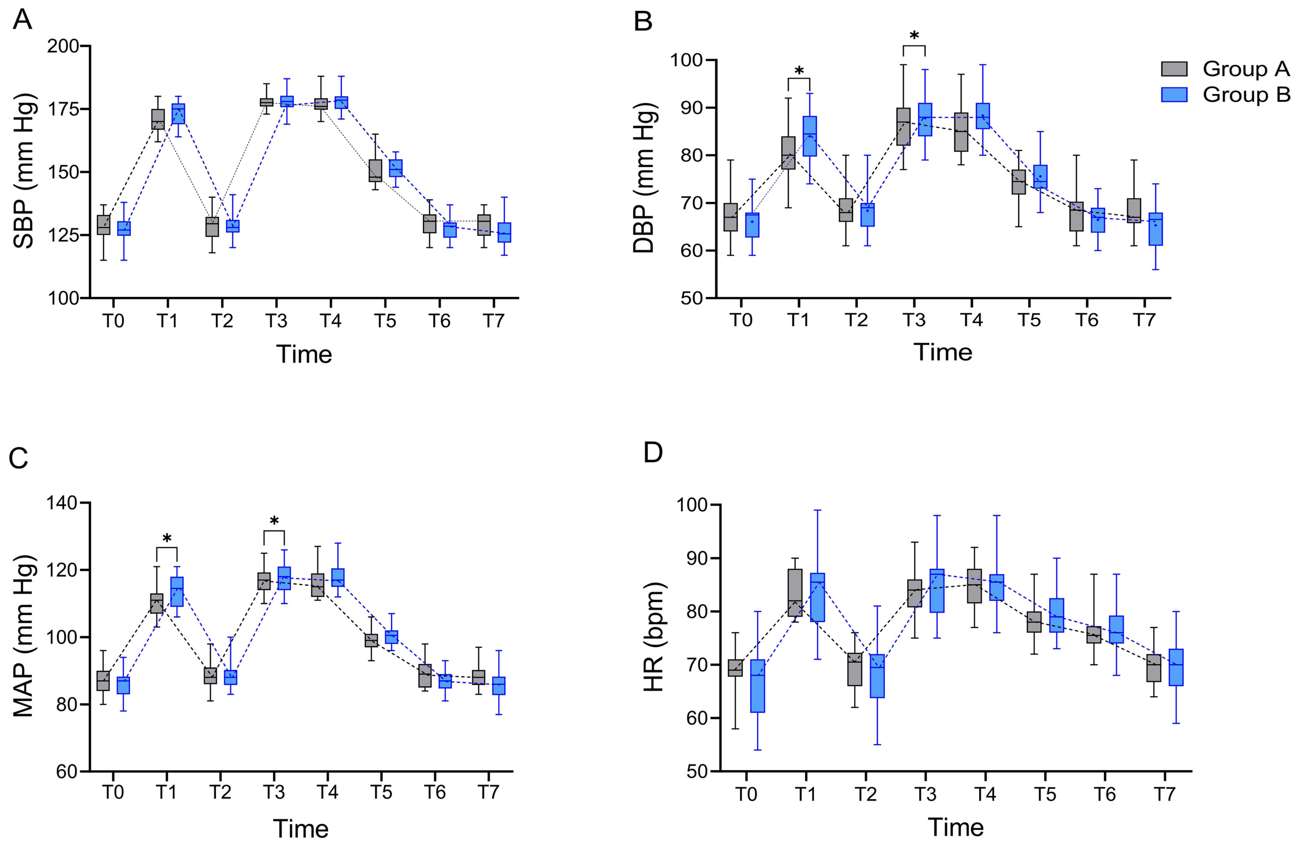

Figure 3 Comparison of hemodynamic parameters at different time points between the two groups. (**A**) Systolic blood pressure (SBP). (**B**) Diastolic blood pressure (DBP). (**C**) Mean arterial pressure (MAP). (**D**) Heart rate (HR).

Notes: Data are presented as mean ± SD. T0, at admission; T1, immediate after intubation; T2, after PACU admission; T3, immediate after extubation; T4-T7, 1, 3, 5, and 10 minutes after nitroglycerin administration. The sample size for each group at each time point is as follows: T0 (Group (A) n=48, Group (B) n=47), T1 (Group (A) n=48, Group (B) n=47), T2 (Group (A) n=46, Group (B) n=45), T3 (Group (A) n=42, Group (B) n=42), T4 (Group (A) n=42, Group (B) n=42), T5 (Group (A) n=40, Group (B) n=40), T6 (Group (A) n=40, Group (B) n=40), T7 (Group (A) n=40, Group (B) n=40).

Abbreviations: SD, standard deviation; PACU, post-anesthesia care unit.

indicating that the worse the vascular endothelium-dependent dilation function, the higher the nitroglycerin dose required. Similarly, NID was significantly negatively correlated with the dose of nitroglycerin (r=−0.610, P<0.001), suggesting that impaired non-endothelial-dependent dilation of vascular smooth muscle also increases the demand for nitroglycerin. (Figure 4)

Dose Response Curve of Nitroglycerin Infusion in Reducing Blood Pressure

The dose-response relationship of nitroglycerin was evaluated by probit regression analysis with logarithmic transformation, as shown in Figure 5. The results showed that $\log ED_{50}$ in group A (non-diabetic group) was −0.565, corresponding to the original dose of 0.272 (0.250–0.294) µg/kg/min (95% CI: −0.602 to −0.531); The $\log ED_{50}$ for group B (diabetes group) was −0.535, corresponding to the original dose of 0.292 (0.268–0.316) µg/kg/min (95% CI: −0.572 to −0.500). In terms of the effective dose at 90%, the $\log ED_{90}$ in group A was −0.506, equivalent to the original dose of 0.312 (0.288–0.336) µg/kg/min (95% CI: −0.540 to −0.473); $\log ED_{90}$ in group B was −0.483, corresponding to the original dose of 0.329 (0.302–0.356) µg/kg/min (95% CI: −0.520 to −0.448). All dose parameters were obtained by antilogarithmic transformation (10^x). These results suggest that the dose of nitroglycerin required to achieve the same antihypertensive effect in diabetic patients is significantly higher than that in non-diabetic patients, suggesting that diabetic patients are less sensitive to nitroglycerin. This finding provides an important dose reference for individualized administration of nitroglycerin in diabetic patients during the perioperative period. (Figure 5)

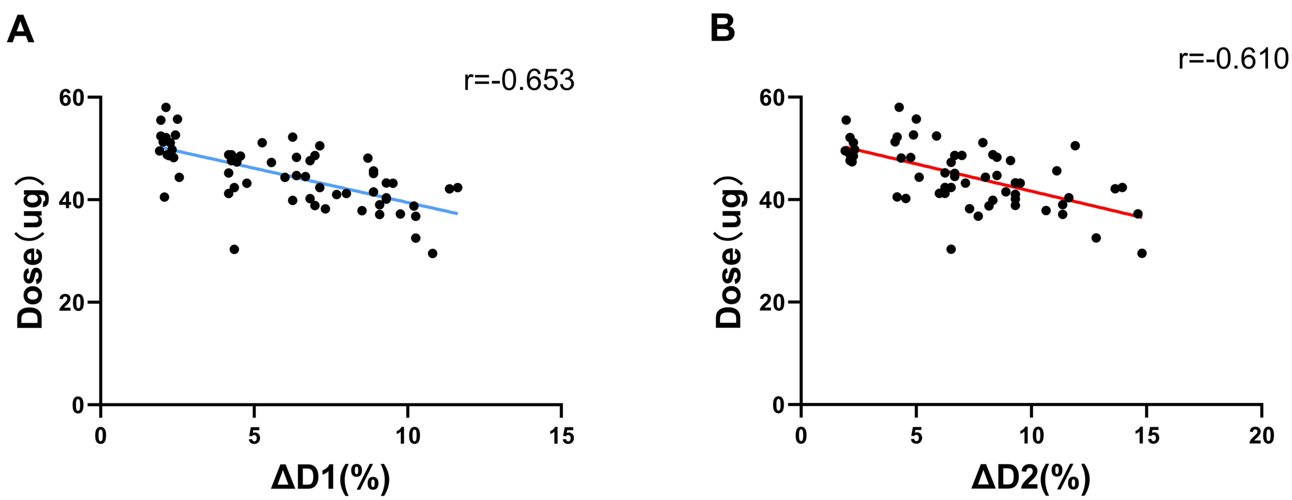

Figure 4 Correlation between vascular dilation function and the nitroglycerin dose required. (**A**) Correlation between flow-mediated dilation (FMD) and nitroglycerin dose. (**B**) Correlation between nitroglycerin-induced dilation (NID) and nitroglycerin dose.

Notes: ΔD1 represents the FMD-mediated diameter change (%); ΔD2 represents the NID-mediated diameter change (%). The analysis included all 80 patients who completed the study and were included in the final analysis (Group (A) n=40; Group (B) n=40).

Abbreviations: FMD, flow-mediated dilation; NID, nitroglycerin-induced dilation.

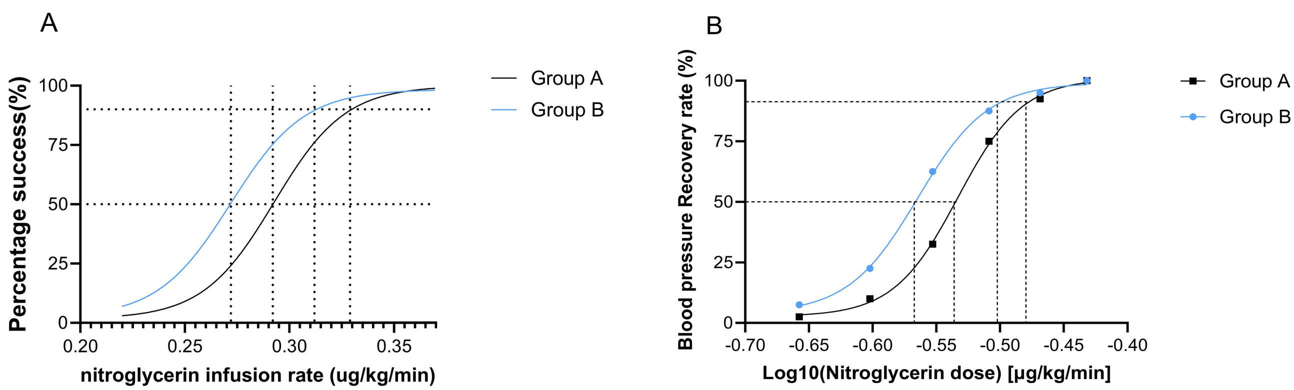

Figure 5 Dose-response curves of nitroglycerin for blood pressure reduction. (**A**) Observed dose-effect curves showing the success rate of blood pressure restoration across different nitroglycerin infusion rates for Group A (non-diabetic) and Group B (diabetic). (**B**) Corresponding probit regression curves with logarithmic transformation of the dose.

Notes: The curves were fitted using probit regression based on data from all 80 patients included in the final analysis (Group (A) n=40; Group (B) n=40).

Abbreviations: ED_{50}, effective dose 50%; ED_{90}, effective dose 90%.

Results of Logistic Regression Analysis to Predict the Dose of Nitroglycerin

To explore the independent risk factors influencing nitroglycerin dose, we conducted both univariate and multivariate logistic regression analyses. Univariate analysis showed that fasting blood glucose, glycated hemoglobin, FMD and NID were all significantly associated with nitroglycerin dose ($P < 0.05$). However, due to significant multicollinearity between fasting blood glucose and HbA1c (VIF >5), fasting glucose was excluded from the final multivariate model to ensure stability. The final multivariate analysis identified HbA1c (OR=1.320, 95% CI: 1.090–1.600, P=0.048), FMD (OR=0.673, 95% CI: 0.491–0.923, P=0.045) and NID (OR=0.812, 95% CI: 0.671–0.985, P=0.027) as independent predictors of nitroglycerin dose as shown in Table 4. These results suggest that preoperative assessment of glycemic status (as reflected by HbA1c) and vascular function (FMD and NID) could help predict the dose requirement of nitroglycerin.

Table 4 Results of logistic regression analysis to predict the dose of nitroglycerin

Parameter	Univariate Analysis		Multivariate Analysis	
	P	OR (95% CI)	P	OR (95% CI)
Fasting blood glucose (mmol/L)	< 0.001	1.112 (1.001–1.225)	—	—
HbA1c (%)	< 0.001	1.450 (1.280–1.650)	0.048	1.320 (1.090–1.600)
Total cholesterol (mmol/l)	0.900	1.018 (0.752–1.378)	—	—
Triglyceride (mmol/L)	0.350	0.847 (0.602–1.195)	—	—
HLDL (mmol/L)	0.737	0.948 (0.702–1.281)	—	—
LDL (mmol/L)	0.668	1.078 (0.762–1.525)	—	—
FMD (%)	< 0.001	0.307 (0.141–0.499)	0.045	0.673 (0.491–0.923)
NID (%)	< 0.001	0.306 (0.138–0.515)	0.027	0.812 (0.671–0.985)

Note: Dashes (—) indicate that the variable was not included in the multivariate model.
Abbreviations: HbA1c, Glycated hemoglobin; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; FMD, flow-mediated vasodilation; NID, nitroglycerin-induced vasodilation; OR, odds ratio; CI, confidence interval.

Discussion

To our knowledge, few prospective cohort studies have employed high-resolution ultrasound to assess how vasodilatory impairment affects nitroglycerin efficacy perioperatively. To address this gap, we conducted a controlled study involving 80 patients undergoing gastrointestinal tumor surgery (40 diabetic, 40 non-diabetic). We systematically assessed brachial artery flow-mediated dilation (FMD) and nitroglycerin-induced dilation (NID) to investigate intergroup differences in nitroglycerin dose-response. The results demonstrated significantly lower FMD and NID values in diabetic patients compared to non-diabetic patients (FMD: 3.68 ± 1.70% vs 8.45 ± 1.77%; NID: 5.07 ± 2.63% vs 9.15 ± 2.99%), indicating substantial impairment in both vascular endothelial function and smooth muscle function. Furthermore, the average perioperative intravenous nitroglycerin dose required was significantly higher in the diabetic group (48.47 ± 5.11 μg vs 39.74 ± 4.15 μg; representing a 22.0% increase), suggesting that diabetic patients require approximately 8.73 μg more nitroglycerin to achieve comparable vasodilation. FMD and NID also exhibited significant negative correlations with the nitroglycerin dose (r = −0.653 and r = −0.610, respectively). Dose-response curve analysis revealed significantly higher ED_{50} and ED_{90} values in the diabetic group (0.292 μg/kg/min and 0.329 μg/kg/min) versus the non-diabetic group (0.272 μg/kg/min and 0.312 μg/kg/min), confirming reduced nitroglycerin sensitivity in diabetes. Multivariate logistic regression analysis identified glycated hemoglobin (HbA1c), FMD, and NID as independent predictors of nitroglycerin dose requirement. Collectively, these findings indicate that metabolic status and vascular dysfunction in diabetic patients are key determinants of nitroglycerin dosing. This study provides important clinical evidence supporting the individualized perioperative administration of nitroglycerin in diabetic patients.

Association Between Vascular Endothelial Dysfunction in Diabetic Patients and Nitroglycerin Efficacy

This study demonstrated significantly reduced flow-mediated dilation (FMD) and nitroglycerin-mediated dilation (NMD) in diabetic patients, indicating substantial impairment of vasodilatory function. Nitroglycerin, functioning as a nitric oxide (NO) donor, induces vasodilation via NO metabolism and subsequent activation of the soluble guanylyl cyclase (sGC)-cyclic guanosine monophosphate (cGMP) signaling pathway.[7,8,24,25] Consequently, diabetes-associated endothelial dysfunction—characterized by diminished NO synthesis and bioavailability—may alter both pharmacokinetic and pharmacodynamic responses to nitroglycerin.[10,22,26] Dose-response analysis revealed significantly elevated ED_{50} and ED_{90} values in diabetic patients, confirming reduced nitroglycerin sensitivity and necessitating higher doses to achieve target antihypertensive effects. Furthermore, significantly lower NID values in diabetic patients suggest concomitant impairment of vascular smooth muscle function. This finding aligns with evidence from Les et al demonstrating impaired vascular smooth muscle cell function in diabetes.[27] Collectively, these results indicate that dual impairment of endothelial and smooth muscle function constitutes a primary mechanism underlying attenuated nitroglycerin efficacy in diabetic patients.

Perioperative Hemodynamic Management and Individualized Nitroglycerin Therapy

Hemodynamic instability during the perioperative period represents a major challenge in anesthetic management for diabetic patients. Studies indicate that precision pharmacotherapy tailored to individual patient characteristics significantly reduces perioperative complications.[28,29] This investigation observed more pronounced hemodynamic fluctuations—particularly in diastolic and mean arterial pressure—immediately following intubation and extubation in diabetic patients, indicating an increased requirement for vasoactive support. Preoperative assessment of brachial artery flow-mediated dilation (FMD) and nitroglycerin-induced dilation (NID) serves as a valuable predictor of nitroglycerin sensitivity in this population, thus enabling optimization of dosing strategies. For instance, patients exhibiting lower FMD and NID values may benefit from initiating nitroglycerin at higher doses than typically used. For those with a suboptimal response, switching to or combining with an alternative vasodilator is a rational subsequent strategy. For example, sodium nitroprusside, typically administered at 0.3–0.5 μg/kg/min, provides rapid and potent afterload reduction, which may be particularly suited for managing acute hypertensive crises.[30] Conversely, nicardipine, infused at 1–5 mg/h, offers a more predictable and steady hemodynamic effect with a favorable cerebral vascular profile, making it an excellent option for cases where tight and stable blood pressure control is paramount, such as in patients with known cardiovascular comorbidity.[31,32] This step-wise and scenario-based approach can help anesthesiologists tailor vasodilator therapy more effectively.

Perioperative Vascular Function Assessment Using High-Resolution Ultrasound Technology

Recent advancements in ultrasound imaging, particularly the widespread adoption of high-frequency linear array transducers, have significantly improved vascular lumen measurement accuracy, enabling detection of subtle diameter changes.[14] The real-time, dynamic capabilities of ultrasound further facilitate continuous perioperative vascular function monitoring, providing anesthesiologists with immediate hemodynamic data.[33] While transcranial Doppler (TCD) ultrasound is well-established for cerebral blood flow monitoring,[34] this study extends ultrasound application to peripheral vascular function assessment. We employed brachial artery flow-mediated dilation (FMD) and nitroglycerin-induced dilation (NID) techniques to comprehensively quantify vasodilatory function in diabetic patients. Results confirmed significant vasodilatory impairment in this population, evidenced by reduced FMD and NID values—consistent with prior literature.[35] Crucially, this impairment correlates strongly with perioperative hemodynamic instability, particularly during general anesthesia induction and emergence, where diabetic patients exhibit heightened susceptibility to blood pressure fluctuations and adverse cardiovascular events.[6,33,36]

This study was designed with rigorous attention to scientific validity, reproducibility, and clinical applicability to ensure robust and generalizable findings. First, all patients received standardized anesthetic and surgical protocols to minimize protocol-related confounding. Second, total intravenous anesthesia (TIVA) was employed exclusively to eliminate potential confounding effects of volatile anesthetics (eg, sevoflurane or isoflurane) on vascular function.[37] Existing evidence indicates volatile agents may interfere with nitroglycerin efficacy via modulation of endothelium-dependent vasodilation, whereas TIVA provides superior hemodynamic stability and minimizes vascular interference.[38] Third, nitroglycerin was selected as the study agent due to its well-characterized mechanism as a nitric oxide donor and its established role in perioperative hypertension management. The administered dose range (0.3–1.0 μg/kg/min) strictly adhered to clinical guidelines,[23] with no adverse events (eg, hypotension, headache, or tachycardia) observed, confirming its safety profile and controllability. Finally, all ultrasound measurements were performed by experienced, blinded assessors, with triplicate measurements averaged at each anatomical landmark to ensure data accuracy and reproducibility.

However, this study has several limitations that should be considered. First, its single-center design and relatively small sample size may limit the generalizability of our findings. While the sample was sufficient to detect statistically significant differences and was supported by a post-hoc power analysis, a larger, multicenter cohort would enhance the statistical robustness and external validity of the results across diverse clinical settings. Second, to isolate the effect of diabetes on vascular function, we employed strict exclusion criteria, such as the exclusion of patients with hypertension, documented vascular disease, or dyslipidemia. This strategy was crucial for enhancing internal validity and strengthening the causal inference between diabetes-related endothelial dysfunction and the observed blunted response to nitroglycerin. However, it consequently may limit the applicability of our findings, as they are most directly relevant to diabetic patients

 https://doi.org/10.2147/DDDT.S548145

without these common comorbidities and may not fully represent the therapeutic response in the broader, more clinically complex diabetic population. Third, the evaluation was confined to the perioperative vasodilatory effects of nitroglycerin. The efficacy and dosing implications for other commonly used vasoactive agents (eg, sodium nitroprusside, nicardipine) in diabetic patients remain to be elucidated in future studies. Finally, the lack of long-term prognostic follow-up represents another constraint. Our study was designed to assess immediate perioperative hemodynamic responses, therefore, the relationship between the preoperative vascular function assessments and long-term cardiovascular outcomes in this patient population remains an important area for future investigation.

Consequently, future studies should prioritize multicenter collaborations with larger sample sizes, encompass patients with a broader range of comorbidities, and incorporate long-term follow-up to both validate the broader applicability of our conclusions and explore their prognostic significance.

Conclusion

This study employed high-resolution vascular ultrasound to assess perioperative vasodilatory function in diabetic patients. The findings revealed that vascular endothelial dysfunction significantly reduced sensitivity to nitroglycerin, as evidenced by a higher required dose of nitroglycerin. Although derived from a single-center cohort and limited by its sample size, these findings suggest that in diabetic patients with significantly impaired vasodilatory function, clinical administration of nitroglycerin may necessitate dose adjustment or consideration of combination therapy with other vasoactive agents to maintain hemodynamic stability. Preoperative ultrasound assessment of vascular function may serve as a preliminary predictive tool for nitroglycerin reactivity, potentially aiding in the tailored application of vasoactive drugs during the perioperative period.

Data Sharing Statement

Deidentified individual participant data will be provided. The data supporting this study are available from the corresponding author (Jianhua He, hejianhua_73@163.com) upon reasonable request.

Ethical Approval

The study protocol was found to comply with the ethical principles outlined by the National Health Commission's "Regulations on Ethical Review of Biomedical Research Involving Humans" (2023), the WMA Declaration of Helsinki, and the CIOMS International Ethical Guidelines for Biomedical Research Involving Humans. The project was approvedby the ethics committee with the reference number 2024-SR-050.

Consent for Publication

All named authors agreed to submit the manuscript for publication.

Acknowledgments

We would like to thank all the doctors, nurses, technicians, and patients involved in this study for their cooperation.

Funding

This work was supported by the Research subject Jiangsu Association for Science and Technology (JSKXKT2023040) and the Medical Science and Technology Research Project of China Medical Education Association (2024KTM023).

Disclosure

The authors report no conflicts of interest in this work.

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