Effects of Thoracic Epidural Anesthesia on Flow and Endothelium of Internal Thoracic Artery in Coronary Artery Bypass Graft Surgery

Ismihan Selen Onan, MD,* Burak Onan, MD,* Askın Ali Korkmaz, MD,* Levent Oklu, MD,† Levent Kilickan, MD,† Suheyla Gonca, MD,‡ Hakki Dalcik, MD,‡ and Ilhan Sanisoglu, MD*

Objectives: **The internal thoracic artery (ITA) is the preferred conduit for coronary artery bypass graft (CABG) surgery. The authors investigated whether thoracic epidural anesthesia (TEA) as an adjunct to general anesthesia (GA) can increase the blood flow of the ITA.**

Design: **A prospective randomized study.**

Setting: **A university hospital.**

Participants: **Patients with ischemic heart disease.**

Interventions: **Thirty patients scheduled for elective CABG surgery were randomized to receive either GA (n = 15) or GA + TEA (n = 15) after receiving institutional review board approval. Demographics showed similarity between the groups. The epidural catheter was inserted in the thoracic region between T1 and T5 levels. In the GA + TEA group, the patients received a 20-mg bolus of 0.25% bupivacaine through epidural catheters 1 hour before surgery, and this was followed by the infusion (20 mg/h) of 0.25% bupivacaine. In all patients, ITA free blood flow was measured before cardiopulmonary bypass and without the administration of any vasodilatory agent. A short segment of ITA was excised for histologic examination; immunocytochemistry analysis was performed using antirabbit polyclonal VEGF antibody, rabbit polyclonal inducible nitric oxide synthase (i-NOS) antibody, and adenosine anti-A2B receptor antibody. The immunoreactivity rates then were evaluated.**

Main Results: **The mean ITA free flow in the GA + TEA group was significantly higher than in the GA group (56.0 ± 9.0 mL/min *v* 39.6 ± 14 mL/min, $p = 0.001$). Immunostaining intensity in the sections after incubation with each primary antibody increased in the GA + TEA group compared with the GA group.**

Conclusions: **The results of this study indicated that TEA increased ITA free blood flow significantly via increased VEGF, i-NOS, and adenosine-A2B receptor expressions. Therefore, the use of TEA as an adjunct to GA might be considered as an alternative to vasoactive agents for increasing ITA flow in CABG surgery.**

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KEY WORDS: internal thoracic artery, coronary artery bypass graft surgery, thoracic epidural anesthesia, general anesthesia, blood flow, endothelium, inducible nitric oxide synthase, adenosine A2B receptor, vascular endothelial growth factor

THE INTERNAL THORACIC ARTERY (ITA) is the most commonly preferred conduit for coronary artery bypass graft surgery. Clinical and functional superiority of the ITA are associated with enhanced native blood flow by the endothelium-dependent relaxation through the expression of different vasodilatory mediators such as vascular endothelial growth factor (VEGF) and nitric oxide.[1-3] The adequacy of ITA flow in coronary artery bypass graft surgery is crucial in meeting metabolic demands of an ischemic myocardium. Different vasoactive agents including calcium channel blockers, phosphodiesterase inhibitors, papaverine, and nitroglycerin have been used to increase ITA flow and to avoid catastrophic consequences of graft hypoperfusion.[4]

Thoracic epidural anesthesia (TEA) has proved its feasibility and potential benefits in cardiac surgery.[5-10] It provides excellent anesthesia, improved pulmonary function, early extubation, hemodynamic stability in the perioperative period, and myocardial protection. The cardioprotective effect of TEA is associated with the inhibition of sympathetic stimulation between C5 and T5 segments.[8-11] With regard to the effects of TEA on vascular reactivity, it has been noted that TEA increased the diameter of stenotic coronary artery segments in patients with ischemic heart disease.[12] Similar to the coronary arteries, the sympathetic stimulation of ITA is mediated through α-adrenoceptors.[13] There have been no data about the effect of TEA on ITA blood flow in patients undergoing coronary artery bypass graft surgery. Therefore, the authors hypothesized that the addition of TEA that inhibits sympathetic stimulation would increase ITA blood flow, and this might occur through expressions of some endothelial vasoactive mediators that increases nitric oxide. This might be of clinical importance because the use of TEA might be considered as an alternative to vasoactive agents for increasing ITA flow in coronary artery bypass graft surgery. The aim of the present study was to investigate whether the use of TEA as an adjunct to general anesthesia (GA) can increase blood flow of the ITA. An immunohistochemical study on ITA specimens was made to evaluate expressions of VEGF and inducible nitric oxide synthase (i-NOS) and adenosine A2B receptors on the ITA wall.

PATIENTS AND METHODS

The Ethics Committee of the University Hospital approved the study, and informed consent was obtained from all patients. A single surgeon performed all operations. The study was planned for 30 patients with documented 3-vessel coronary artery disease who were scheduled for elective coronary artery bypass graft surgery with harvesting of the left ITA through median sternotomy. The patients were assigned randomly assigned into 2 groups who received GA (the GA group was the control group [15 patients]) or GA plus TEA (GA + TEA group, 15 patients). In the preoperative period, the patency of the left ITA was confirmed by coronary angiography in all patients.

Exclusion criteria from the study included decreased ventricular function (ejection fraction <40%), emergency operations, previous cardiothoracic operation, unstable angina, resting bradycardia (<60

*From the Departments of *Cardiovascular Surgery and †Anesthesiology, Istanbul Bilim University, Florence Nightingale Hospital, Istanbul, Turkey; and ‡Department of Histology and Embryology, Kocaeli University, Kocaeli, Turkey.*

Address reprint requests to Ismihan Selen Onan, MD, Department of Cardiovascular Surgery, Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery, Education & Research Hospital, Istanbul Caddesi, Bezirganbahçe Mevkii, 34303 Istanbul, Turkey. E-mail: selenibis@hotmail.com

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beat/min), and critical left main coronary artery disease (>50% stenosis). Additionally, patients with contraindications to the epidural technique including pre-existing coagulopathy, preoperative anticoagulation (full therapeutic doses of standard or low–molecular-weight heparin, warfarin, thrombolytic drugs, or potent antiplatelet drugs), systemic or local infection, previous cervical or upper thoracic operations or vertebral deformities, and drug hypersensitivity were excluded. An epidural catheter was inserted the night before surgery in the operating room. One anesthesiologist placed all epidural catheters, and the same person gave the epidural and GA in each individual patient.

All patients were monitored during the placement of the catheters. Patients in the GA + TEA group received a thoracic epidural catheter after the achievement of local anesthesia by using a median approach. The epidural space was identified by a loss-of-resistance technique with saline solution in each patient.[8,10] A side-holed epidural catheter (18-G; B-Braun, Melsungen, Germany) was inserted between T1 and T5 (T2-T3 or T3-T4) spinal levels.[7-10] The catheter was advanced 3 cm into the epidural space. A test dose of 3 to 4 mL of 2% lidocaine was given to confirm placement of the catheter, and sensory spread was tested with ice. Radiographic confirmation of the epidural catheters was performed using Iopamiro 300 (nonionic, water-soluble contrast medium; Iopamidol Bracco, Milan, Italy). All patients were informed of the risk of the dye injection to confirm the placement of the catheters before interventions. The catheters were tested with ice before surgery.

All patients were premedicated with an intramuscular administration of midazolam (0.08 mg/kg). In both groups, anesthesia was induced with midazolam (0.1-0.2 mg/kg), fentanyl (7-10 μg/kg), and rocuronium (0.6 mg/kg). After tracheal intubation, ventilation was controlled with 30% oxygen and 70% nitrous oxide. The maintenance of anesthesia was established with an intermittent delivery of rocuronium (0.2 mg/kg), propofol (3-4 mg/kg/h), and fentanyl (3.5-4.5 μg/kg/h).

The patients in the GA + TEA group received a 20-mg bolus of 0.25% bupivacaine through the epidural catheters 1 hour before surgery. During the intraoperative period, 0.25% bupivacaine was infused at a rate of 20 mg/h.[8,10] The patients received a continuous epidural infusion of 0.125% bupivacaine, 4 to 10 mL/h, after surgery to attain sensory blockade. The goal was to maintain sensorial block between T1 and T10 throughout infusion. The epidural catheters were removed at 24 hours postoperatively after the removal of the chest tubes and before the delivery of anticoagulants. The patients were followed up for any complications of TEA and surgery.

The same surgeon operated on all patients. The left ITA was harvested with the aid of electrocautery (Force2 Electrosurgical Generator; Valleylab, Boulder, CO) and hemoclips to control the side branches. The conduit was dissected from the chest wall with a wide pedicle between its bifurcation and origin from the subclavian artery. After systemic heparinization (300 U/kg), ITA was transected proximally to its bifurcation. The distal 2-cm segment of the conduit was resected for immunohistologic analysis. Then, ITA blood flow was determined by measuring the volume of blood expelled from the end of the freely bleeding artery in a 60-second period. The blood was collected and measured by the primary surgeon. The blood was collected in a sterile container, and then its amount was measured using a sterile disposable 10-mL syringe. The time was recorded by a circulating nurse. Hemodynamic parameters including systolic, diastolic, and mean blood pressures and heart rate were recorded during the measurement of blood flow. During flow measurements, the heart rate was kept between 60 and 80 beats/min, and the mean arterial blood pressure was maintained between 70 and 80 mmHg. Additionally, the time between the induction of anesthesia and the measurement of ITA flow was recorded.

Before the measurement of ITA free flow, no patient was taking medications (oral or intravenous) known to influence ITA vasoreactivity, including a calcium channel blocker or a nitrovasodilator. During surgery, the authors did not use topical or intraluminal vasodilator agents such as papaverine for ITA before the measurements of free flow.

Human ITA tissues were obtained from both patient groups after harvesting of the vessel from the chest wall. Small pieces of ITA tissues were fixed for 24 to 48 hours by 4% paraformaldehyde in 0.1 mol/L of phosphate buffer (ph = 7.4), washed in water, and dehydrated in increasing alcohol series (70%, 80%, 90%, and 100%) and xylene before embedding in paraffin wax. Sections (10-μm thick) were obtained using a sliding microtome. Sections were deparafinized and rehydrated. Immunocytochemistry was performed using the avidin-biotin-peroxidase method (Zymed, San Francisco, CA). Antigen retrieval was performed using unmasking solution (0.01 mol/L of citrate buffer, pH = 6) in a microwave oven (5 minutes 3 times). The rehydrated sections were pretreated with 3% hydrogen peroxide for 10 minutes to eliminate endogenous peroxidase activity. Sections were washed in phosphate-buffered saline (PBS) Triton X-100 (Tx; Dow Chemical Company, Midland, MI). To eliminate nonspecific binding, sections were pretreated with normal 1% nonimmune goat serum. Sections were incubated in mouse monoclonal VEGF antibody (Santa Cruz Biotechnology; dilution: 1/50), rabbit polyclonal iNOS antibody (Zymed, San Francisco, CA; dilution: 1/250), and rabbit adenosine anti-A2B receptor antibody (Millipore Laboratories; dilution: 1/10) for 24 hours at 4°C in a humidified chamber. After washing in PBS-Tx, biotinylated anti–immunoglobulin G secondary antibodies (Zymed) were applied for 15 minutes at room temperature. After the sections were washed in PBS-Tx, they were incubated in a chromogen solution (Liquid DAB- Black Substrate Kit; Zymed) for 5 minutes at room temperature. As the control, the primary antibody was omitted and replaced with nonimmune serum.

Immunoreactivity of the specimens was examined by invert light microscopy (BX50F-3; Olympus, Tokyo, Japan), and they were photographed (×40, ×100, and ×400 magnifications). Three independent histopathologists, blinded to the study protocol and to each other, performed microscopic analysis of all specimens. In each group, the intensity of the positive immunostained cells in each section was assessed by visual observation. Immunoreactivity then was graded according to a 4-degree (++++) semiquantitative scale: minimal immune staining (+), mild immune staining (++), moderate immune staining (+++), or severe immune staining (++++).

A power calculation indicated that a sample size of 15 patients in each group would achieve 95% power to detect a 5% difference in test scores between the groups. Statistical analysis was performed with SPSS for Windows version 15.0 (SPSS Inc, Chicago, IL). Data are expressed as the mean (standard deviation) or the number of patients. One-way analysis of variance, the Student *t* test, and the chi-square test were used for comparison of the data. Significance was determined at a p value less than 0.05.

RESULTS

The demographic characteristics of the patients are presented in Table 1. The mean ITA free flow was significantly higher in the GA + TEA group (56.0 ± 9.0 mL/min; 95% confidence interval, 51.0-60.9) when it was compared with the GA group (39.6 ± 14.0 mL/min; 95% confidence interval, 31.9-47.4; p = 0.001) (Table 2). At the time of the measurement of ITA free flow, hemodynamic parameters including systolic/diastolic/mean blood pressure and the heart rate were similar between the groups. In all patients, the body temperature (rectal) and the results of arterial blood gas analysis before measurements were within physiologic ranges.

Immunoreactivity after incubation with primary antibodies (VEGF, iNOS, and adenosine A2B receptor antibodies) was more prominent in the GA + TEA group. The intensity of

Table 1. Demographics of the Patients in the GA and GA + TEA Groups

	GA Group (n = 15)	GA + TEA Group (n = 15)
Age (y)	59.4 ± 9.3	58.5 ± 6.0
Sex (male)	13 (86.7)	14 (93.3)
Height (cm)	169.0 ± 6.4	169.0 ± 7.4
Weight (kg)	81.5 ± 15.9	80.1 ± 10.9
Body surface area (m^2)	1.91 ± 0.19	1.90 ± 0.15
Ejection fraction (%)	55.3 ± 8.5	50.2 ± 5.8
Hypertension	11 (73.3)	14 (93.3)
Diabetes mellitus	3 (20.0)	5 (33.3)
Obstructive lung disease	1 (6.7)	1 (6.7)
Smoking	2 (13.3)	3 (20.0)
Preoperative medication		
β-Blocker	7 (46.7)	10 (66.7)
ACE inhibitor	5 (33.3)	6 (40.0)
Calcium channel blocker	—	—
Nitrate	—	—

NOTE. The data were presented as the number of patients (percentage) or the mean value ± standard deviation.

Abbreviation: ACE, angiotensin-converting enzyme.

VEGF immunostaining in the GA + TEA group (++++) was considerably higher than that in the GA group (++) (Fig 1). Immunoreactivity to VEGF involved tunica media and endothelial cells of the ITA wall in both groups. Immunoreactivity for the iNOS antibody was apparent in all layers of the ITA wall (Fig 2). The intensity of iNOS-positive cells was greater in the GA + TEA group (++++) than in the GA group (+). Expressions of the adenosine A2B receptor antibody was increased in all layers of the ITA wall in the GA + TEA group (+++), whereas the GA group showed minimal immunostaining (+) (Fig 3). There was no immunocytochemical staining in negative control sections. The semiquantitative evaluation of immunoreactivities is given in Table 3.

No neurologic sequelae associated with TEA were observed. There was no surgery-related complication in the postoperative period such as graft failure and related myocardial ischemia/infarction. All patients were discharged uneventfully from hospital.

DISCUSSION

In the current study, the authors observed that ITA free blood flow increased in patients who underwent coronary artery bypass graft surgery under GA and TEA between T1 and T5 levels. Although the mean ITA flow in the TEA + GA group was measured to be 56.0 ± 9.0 mL/min, it was 39.6 ± 14.0 mL/min in the GA group. The preoperative demographics of the patients in both groups were similar, and no patient was taking medications that might influence ITA vasoreactivity such as calcium channel blockers, nitrovasodilators, or papaverine. Hemodynamic parameters including systolic/diastolic/mean blood pressure and heart rate were recorded in all patients at the time of the measurement of ITA blood flow. The mean arterial pressure was stabilized above 70 mmHg to achieve objective results about ITA blood flow. In addition to mean arterial pressure, the lack of a more sensitive hemodynamic parameter such as cardiac output or systemic vascular resistance was a limitation of the study[4]; however, no patient included in the study protocol had an indication for the insertion of a pulmonary artery catheter.

Vascular endothelial growth factor, iNOS, and adenosine A2B receptors are widely accepted to have crucial roles in vasodilation, angiogenesis, and cardioprotection. These mediators have additive effects and induce expression of one another. It has been noted that VEGF regulates endothelial nitric oxide synthase expression and vascular reactivity of ITA.[14-17] Liu et al[14] showed that VEGF induced relaxation in the human ITA through nitric oxide release. Additionally, adenosine agonists can induce VEGF expression by way of A2B receptors.[18] These receptors regulate vascular smooth muscle tone through the production of nitric oxide.[19] In the current study, expressions of these mediators that cause nitric oxide release and associated vasodilatation were investigated on ITA specimens. The results suggested that the addition of thoracic epidural anesthesia increased ITA blood flow consistent with the effects of this modality on vascular tone. An enhanced expression of VEGF, iNOS, and adenosine A2B receptor accompanied these findings.

The expression of VEGF causes endothelium-dependent relaxation in the human ITA through nitric oxide release.[14,15,20,21] The induction of nitric oxide release by VEGF may be of great importance in the maintenance of vascular homeostasis. In the adult, vascular smooth muscle cells of the ITA actively secrete VEGF.[22] The higher nitric oxide production after VEGF stimulation may play a role in the superior long-term patency of the ITA in coronary artery bypass graft surgery. Although nitric oxide release from ITA was not investigated in this study, the intensity of VEGF immunostaining on the ITA specimens group was high in the TEA + GA when it was compared with the GA group. Immunoreactivity in the ITA sections after VEGF immunostaining involved both the tunica media and the

Table 2. ITA Blood Flow and Hemodynamic Parameters at the time of Flow Measurement

	GA Group	GA + TEA Group	*p* Value
ITA blood flow (mL/min)	39.6 ± 14.0	56.0 ± 9.0	0.001
Systolic blood pressure (mmHg)	117.6 ± 5.3	120.9 ± 17.3	0.49
Diastolic blood pressure (mmHg)	71.0 ± 9.8	71.3 ± 8.1	0.92
Mean blood pressure (mmHg)	86.5 ± 7.9	87.8 ± 9.5	0.68
Heart rate (beats/min)	70.2 ± 4.2	70.8 ± 12.7	0.84
Time after the induction of general anesthesia (min)*	65.0 ± 12.4	56.4 ± 11.8	0.06

NOTE. The data were presented as the mean value ± standard deviation. A *p* value of less than 0.05 was considered to be statistically significant.

*The time between the induction of GA and the measurement of ITA blood flow.

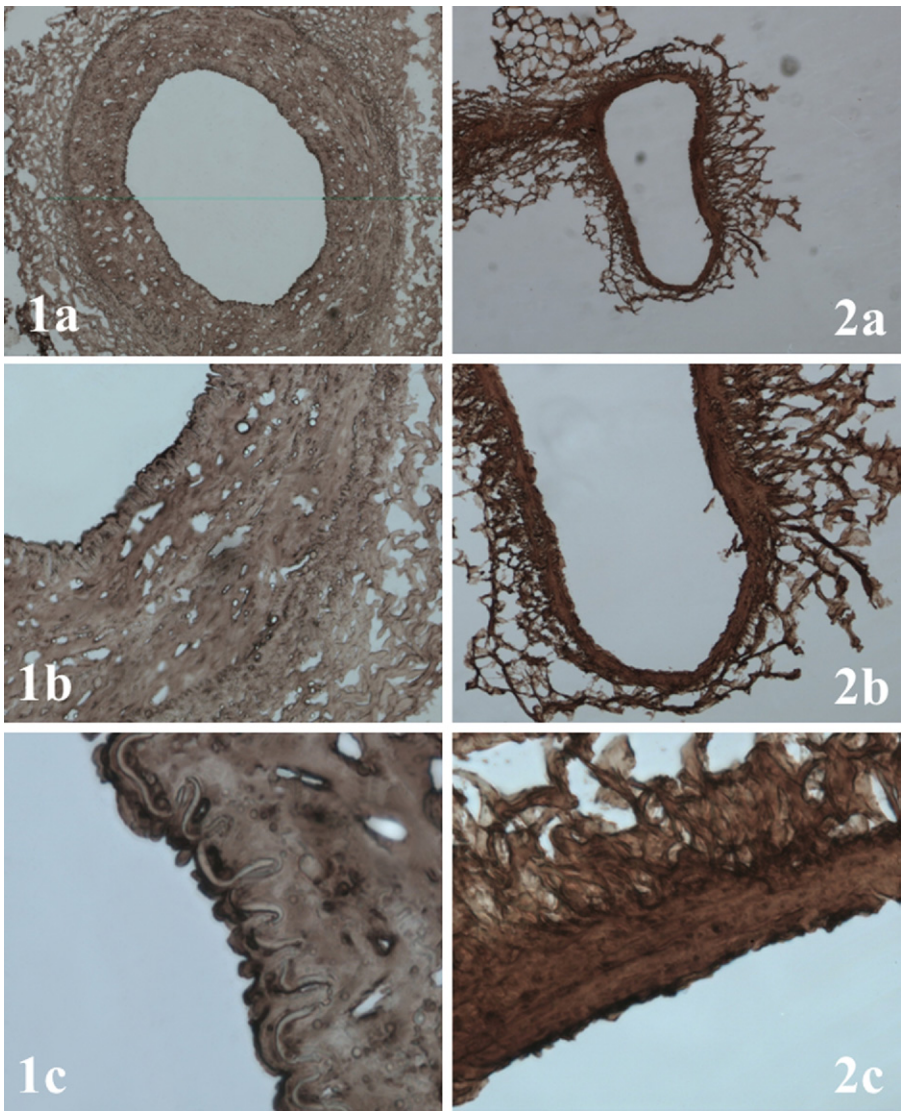


Fig 1. Photomicrographs of VEGF immunostaining in the GA and GA + TEA groups. Note the VEGF immunostaining in the sections from the GA + TEA group (++++) (magnification: 2a: ×40, 2b: ×100, 2c: ×400) was considerably higher than in the GA group (++) (magnification: 1a: ×40, 1b: ×100, 1c: ×400). (Color version of figure is available online.)

intima. The results showed that TEA might lead to vasorelaxation of the ITA and increased blood flow. In coronary artery bypass surgery that uses an ITA conduit, the vasodilatory effect of VEGF might be useful for relieving graft failure.

The inducible form of nitric oxide synthase is produced in macrophages, smooth muscle cells, and endothelial cells by cytokines. This mediator plays a role in the generation of nitric oxide in the vascular wall, regulating blood vessel tone.[22] The inducible form of NOS is not expressed under normal conditions, but it is induced by inflammatory cytokines and reflects a cellular response to inflammation.[23] It has been noted that TEA can influence operative stress and a related response of the immune system by increasing cytokines and cAMP levels.[24,25] Koide et al[24] indicated that the elevation of intracellular cAMP, particularly in combination with inflammatory cytokines, positively regulated nitric oxide production through iNOS expression in vascular smooth muscle cells. In the current study, the expression of iNOS in tissue sections was evaluated by qualitative visual grading techniques that estimate the intensity of the stain. The authors observed that iNOS immunoreactivity was evident in all layers of ITA sections. Meanwhile, immunostaining for iNOS showed an increased intensity in the GA + TEA group (++++) compared with the GA group (+). The use of TEA as an adjunct to GA may increase the synthesis of nitric oxide by inducing the expression of iNOS. This may be an important association between the increased expression of iNOS and ITA blood flow.

Adenosine acts through 4 subtypes (A1, A2A, 2B, and A3) of G protein–coupled cell surface receptors. Although the precise physiologic functions of the A2B receptors remain undefined, roles for A2B receptors have been suggested in the regulation of vascular smooth muscle tone.[18,19] Grant et al[26] noted that adenosine A2B receptor activation promoted endothelial cell proliferation and VEGF release in human retinal endothelial cells. Shin et al[27] suggested that adenosine-induced vasodilation via the activation of A2B adenosine receptors of the rat pial artery was coupled to the production of nitric oxide, which contributed little to cerebral blood flow autoregulation.

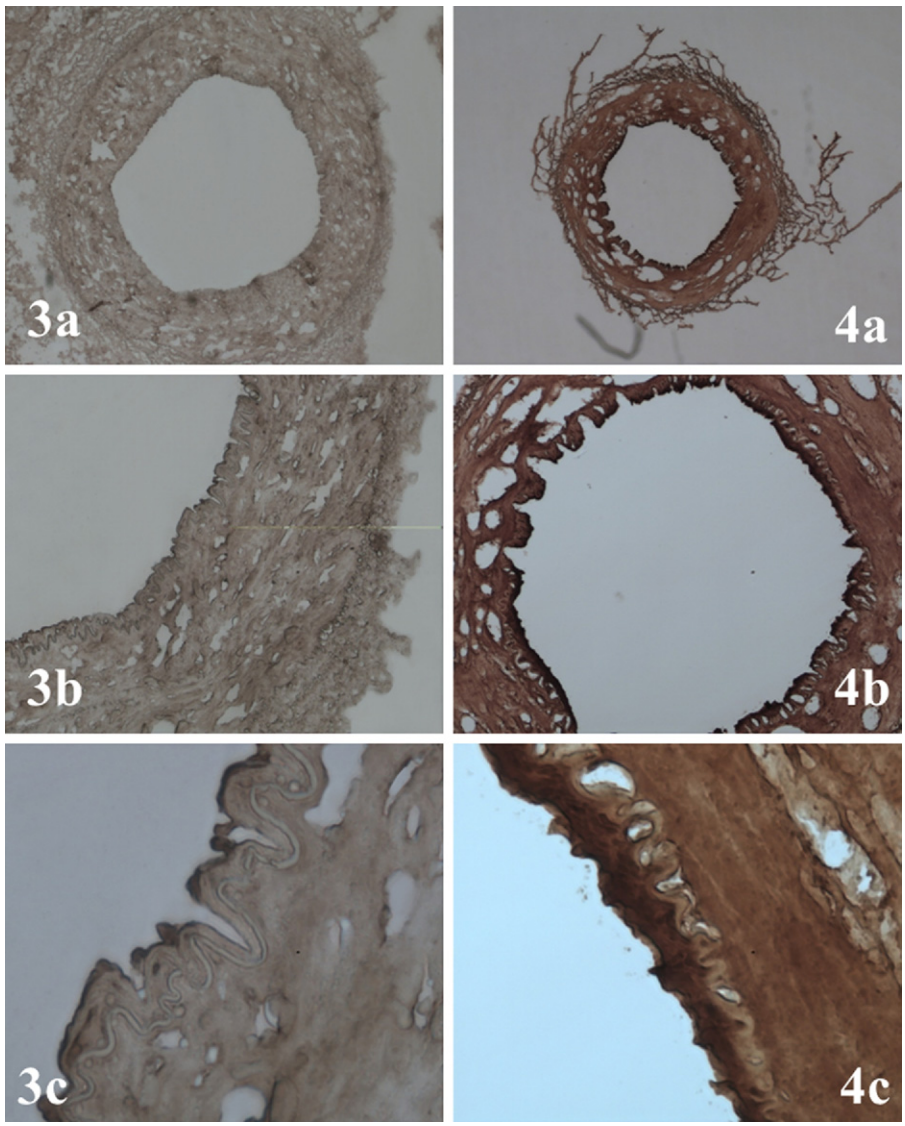


Fig 2. Photomicrographs of iNOS immunostaining in the GA and GA + TEA groups. Note that the immunostaining is increased in all layers of the ITA wall in the GA + TEA group (magnification: 4a: ×40, 4b: ×100, 4c: ×400) compared with the GA group (magnification: 3a: ×40, 3b: ×100, 3c: ×400). (Color version of figure is available online.)

In this study, the authors showed that adenosine A2B receptors were expressed on the endothelium and smooth muscle cells of the ITA wall. Examination of the histologic sections after incubation with adenosine A2B-receptor antibody revealed an increased immunoreactivity in the GA + TEA group when it was compared with the GA group. Therefore, the authors suggested that the use of TEA increased the expressions of adenosine receptors and contributed to increased ITA blood flow. This might be related to either an increased expression of VEGF or nitric oxide by TEA.

In the current era, the strategy to use TEA routinely in coronary artery bypass graft surgery has not been established regarding the indication of the placement of the epidural catheter in each patient. This is because of the complexity of the clinical presentation and the concomitant risk factors of patients undergoing coronary surgery. It may be unlikely that the use of a high thoracic epidural (between T1 and T5) will become common in the practice of cardiac anesthesia in most centers. This is, in part, because of the perceived risks of this technique and the fact that the placement of the TEA should be accomplished on the day before surgery. In particular, epidural hematoma can occur when large doses of heparin are used, especially during cardiopulmonary bypass. The risk of spinal injury from a neuraxial blockade–induced hematoma in conventional cardiac surgery has been estimated with 95% confidence to be from 1:150,000 to 1:1,500 for an epidural blockade.[28] Thus, the catheters were inserted to avoid such complications the night before to proceed to surgery.

In this study, the authors observed that TEA performed as an adjunct to GA in coronary artery bypass surgery increased the ITA blood flow. The additional measurements of VEGF and iNOS suggested an endothelium augmentation of nitric oxide vasodilation as part of the mechanism.[14,15,20,21] Immunohistologic examination of the specimens in the GA + TEA group showed increased expressions of VEGF, iNOS, and adenosine A2B receptors in the ITA wall compared with the GA group.

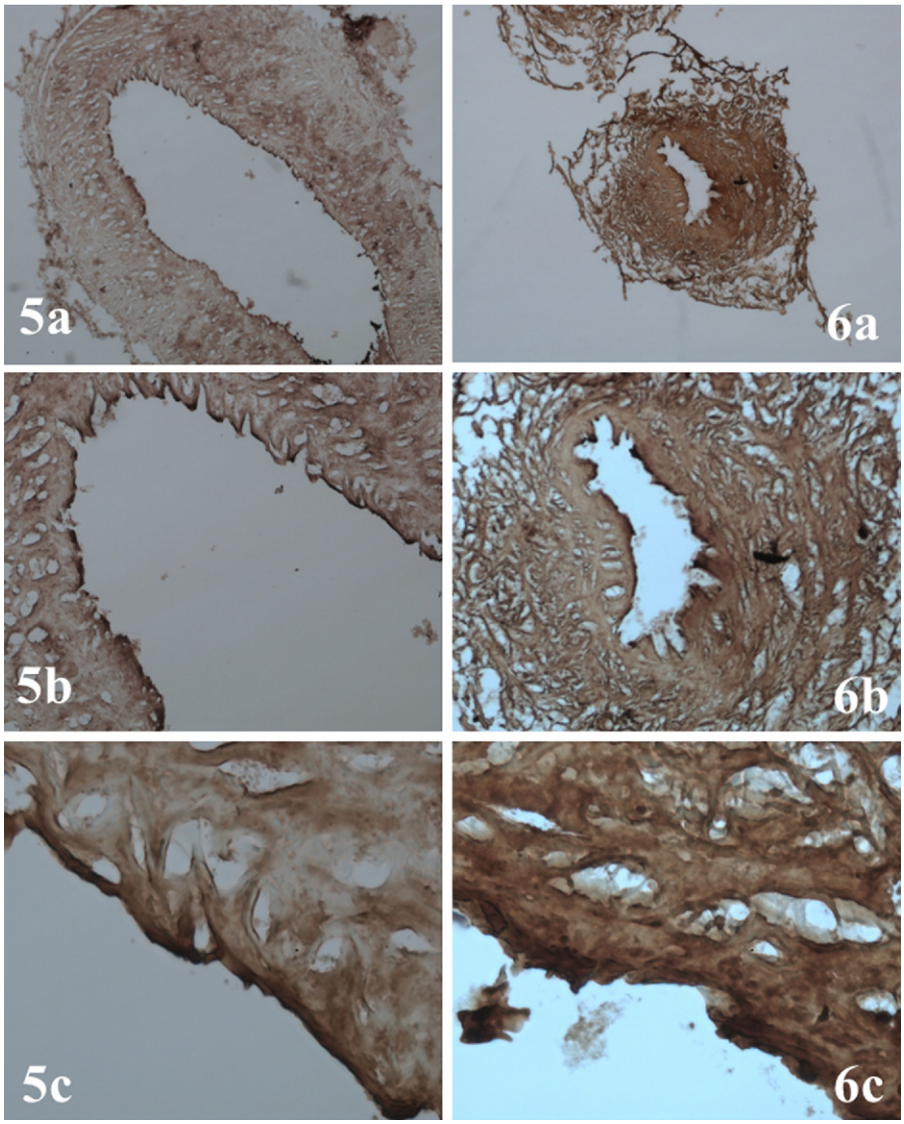


Fig 3. Photomicrographs of adenosine immunostaining in the GA and GA + TEA groups. Note an increased immunoreactivity in the all layers of the ITA wall was apparent in the GA + TEA group (+++) (magnification: 6a: ×40, 6b: ×100, 6c: ×400) compared with the GA group (+) (magnification: 5a: ×40, 5b: ×100, 5c: ×400). (Color version of figure is available online.)

All these secondary mediators are produced by ITA and are known to induce endothelial nitric oxide release, and they lead to vasorelaxation.[1-3] Therefore, the authors suggested that TEA might be useful to prevent perioperative ischemia and associated cardiac events because of graft failure. In particular, this procedure may provide a benefit in full arterial myocardial revascularization when grafts with a relatively high tendency for vasospasm such as the radial or gastroepiploic artery are used. Moreover, the maintenance of TEA after surgery may be beneficial to avoid postoperative ITA spasm. Thus, the present clinical study provides a basis for future establishment of such an indication.

Table 3. Semiquantitative Evaluation of VEGF, i-NOS, and Adenosine Immunoreactivities

	GA Group	GA + TEA Group
VEGF immunoreactivity	++	++++
iNOS immunoreactivity	+	++++
Adenosine anti-A2b receptor immunoreactivity	+	+++

Abbreviation: iNOS, inducible nitric oxide synthase.

Different vasoactive agents including calcium channel blockers, nitroglycerine, phosphodiesterase inhibitors, and papaverine are used in coronary artery bypass graft surgery. These agents are effective in the prevention of ITA vasospasm and associated myocardial ischemia in the perioperative period.[29] In the authors' clinical experience, they use papaverine intraluminally to avoid vasospasm of the ITA in coronary artery bypass graft surgery. Papaverine has a relatively short plasma half-life, up to 2 hours, and therefore its effect on the ITA is limited. Although there are difficulties in the clinical use of TEA because of potential neurologic complications, the epidural block may provide continuous vasorelaxation after operations until the removal of epidural catheters. Actually, the comparison of ITA flows in the TEA group before and after

delivery of papaverine might be of greater clinical relevance. The rationale of the study was actually a hypothesis that the epidural block might increase ITA flow. The authors observed an association between TEA and increased ITA flow that occurred through cellular mediators or signal molecules. More studies are needed to determine whether or not epidural anesthesia has any effect on perioperative vasospasm of ITA.

This study has several potential limitations. The small sample size and homogeneity of the patient population were the major limitations. The assessment of nitric oxide expression on the ITA wall might be a reasonable approach to clarify the mechanism of increased expressions of VEGF, iNOS, and adenosine A2B-receptor antibodies in this study. The lack of hemodynamic parameters such as cardiac output and systemic vascular resistance during the measurement of ITA free flow was another limitation. The lack of examination of α-adrenergic receptors and its subtypes on the ITA wall could be considered to be another limitation. Ejection fractions of the patients were relatively preserved, and the preload at the time of measurement of the ITA flow was managed carefully in each patient. The presence of another TEA group treated with papaverine or another vasoactive agent could make the results clinically more valuable. The authors could not numerically assess the immunohistochemistry results and did not perform Western immunoblotting experiments. This was a limitation because protein concentrations were not quantified or subjected to rigorous statistical analysis.

In conclusion, ITA blood flow was increased in patients with TEA that was used as an adjunct to GA in coronary artery bypass graft surgery. Immunostaining showed that this might be associated with increased expressions of VEGF, iNOS, and adenosine A2B receptors on the ITA wall. These results may have important clinical implications in the prevention of perioperative vasospasm in human ITA; the use of TEA as an adjunct to GA can be an alternative to the other vasoactive agents to prevent ITA spasms.

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