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Diltiazem provides higher internal mammary artery flow than nitroglycerin during coronary artery bypass grafting surgery☆

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Abstract

Objectives: Perioperative internal mammary artery (IMA) vasospasm in patients undergoing coronary artery bypass grafting (CABG) surgery may lead to morbidity and mortality. Surgical stimulus is one of the common causes of IMA vasospasm. Preventive measures, beside treatment should be taken into consideration to obtain vasospasm free IMA. The effect of a pharmacologic agent on IMA flow when it is administered before harvesting the artery has not been documented. We designed a prospective randomized clinical study to compare the IMA free blood flows in patients receiving either diltiazem or nitroglycerin, starting infusion of study drugs before a surgical stimulus was applied to the IMA region and continuing throughout the isolation period. **Methods**: Sixty patients undergoing elective CABG surgery with the left IMA received diltiazem ($n = 30$, 0.05–0.1 mg/kg per hour) or nitroglycerin ($n = 30$, 0.25–2.5 μg/kg per minute) in a randomized manner. Infusions of study drugs were started before applying a surgical stimulus to the IMA region and continued throughout the harvesting period. The first free flow was measured after IMA was cut above its bifurcation and the second after its distal segment was resected. Heart rate, temperature, mean arterial and central venous pressures were recorded. Data were analyzed with Student's *t*-test and Fischer's exact test. **Results**: Preoperative and hemodynamic data were similar between the groups. The means of first and second IMA flows in patients treated with diltiazem (53.8 ± 30.1 and 72.3 ± 35.4 ml/min) were significantly higher than in those treated with nitroglycerin (25.7 ± 16.2 and 48.9 ± 23.8 ml/min; $P = 0.000$, 0.004, respectively). IMA flows significantly increased after distal segment resection both in diltiazem (34%) and nitroglycerin groups (90%; $P = 0.000$, 0.000, respectively). **Conclusions**: Diltiazem infusion which started prior to harvesting provided higher IMA blood flow compared to nitroglycerin infusion. Considering the percentage of increases in flows after resection of distal segment, the most prone part to vasospasm, we assume that a certain amount of spasm occurred in IMA in spite of infusion of study drugs, such that less with diltiazem and more with nitroglycerin. Diltiazem plays more important role than nitroglycerin in the prevention of vasospasm.
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Keywords: Coronary artery bypass grafting; Vasospasm; Diltiazem; Nitroglycerin

1. Introduction

The internal mammary artery (IMA) is the traditional conduit for coronary artery bypass grafting (CABG) because its patency rate is longer than saphenous vein [1]. However, IMA spasm can occur during preparation of the artery for myocardial revascularization and surgical stimulus is known as one of the important factors of vasoconstrictor activity [2]. IMA graft spasm may lead to myocardial ischemia and deterioration of myocardial function. Moreover, insufficient IMA flow can be associated with perioperative morbidity and mortality [3].

Starting from Green [4], the pioneer of IMA graft surgeon who first injected papaverine into the IMA, different pharmacologic agents have been used to overcome IMA spasm, administered either topically [5,6] or intravenously [7,8]. In these studies [5–8], the agents were administered after isolation of the artery was completed

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and distal segment of IMA was cut, that is, after surgical stimulus.

It has been shown that the effects of pharmacologic agents to vasoconstrictor stimuli on isolated vessel segments differ according to applying times. While some pharmacologic agents were effective when applied before a constrictor stimulus, some others were effective after a constrictor stimulus [9–13].

Preventive measures should be taken into consideration to provide sufficient grafted IMA blood flow in patients undergoing CABG surgery, besides the treatment strategies. For this aim, pharmacologic agents should be administered early enough during the surgery [2]. To date, the effect of a pharmacologic agent on IMA flow when it is administered before a vasoconstrictor stimulus is applied to the IMA region has neither been documented nor the clinical effects of systemic use of diltiazem and nitroglycerin in this respect have been compared.

This prospective randomized clinical study was designed to compare the IMA free blood flows in patients receiving either diltiazem or nitroglycerin, starting infusion of study drugs before a surgical stimulus was applied to the region of IMA and continuing throughout the preparation period of the artery for myocardial revascularization.

2. Methods

The study was approved by the ethics committee of the University hospital, and informed consent was obtained from all patients that participated to the study. The study was planned for a total of 60 patients undergoing elective first time CABG with the left IMA.

Poor ventricular function (ejection fraction $<40\%$), unstable angina, resting sinusal bradycardia (<55 beat/min), left bundle branch block, recent Q wave myocardial infarction (within 3 weeks), renal insufficiency (serum creatinine >1.9 mg/dl), obesity (body mass index >30), known nitroglycerin tolerance or medication with glibenclamide, furosemid and/or simvastatin prior to surgery were the preoperative exclusion criteria. Hemodynamically unstable patients who required infusion of study drugs beyond the ranges of our study protocol were also excluded intraoperatively.

In all patients, preoperative cardiac medication was continued until the morning of the surgery. Patients were premedicated with famotidine 20 mg and diazepam 5–10 mg at the evening before the operation and with diazepam 5–10 mg 2 h before surgery at the ward. On arrival to the preholding area, large-bore intravenous catheter was placed and morphine 0.1 mg/kg and diphenhydramine 20 mg were administered 45 min preoperatively. An arterial catheter was placed in the radial artery prior to general anesthesia. The anesthetic management was similar in all patients. After standard monitoring of vital signs was established and preoxygenation was performed, anesthesia was induced with etomidate 0.2–0.3 mg/kg, fentanyl 5–15 μg/kg and maintained with sevoflurane $<1.5\%$ (inspired concentration) and oxygen 50% in air. Fentanyl 2–5 μg/kg was given as needed. Rocuronium 0.6 mg/kg was injected for facilitating tracheal intubation and pancuronium 0.03 mg/kg for maintenance of neuromuscular blockade. Central venous catheterization was performed via right vena jugularis interna with a triple-lumen catheter. Intravenous fluid was administered to maintain normal values of central venous pressure (CVP). Positive pressure ventilation was adjusted to maintain end-tidal CO_2 in the normal range (35–40 mmHg).

Sixty patients that were randomized equally into two groups, using a table of randomized number, received either diltiazem (0.05–0.1 mg/kg per hour, Diltizem-L, Mustafa Nevzat Drug Industry, Istanbul, Turkey) or nitroglycerin (0.25–2.5 μg/kg per minute, Nitroglycerin Injection, Abbott Laboratories, North Chicago, IL) after sternotomy and prior to starting the dissection of the left IMA. Study drugs were infused through a catheter lumen used for no other purposes. During the study period, infusion rates of study drugs were adjusted within the ranges given above to maintain similar values in mean arterial pressure (MAP) during both IMA flow measurements.

The left IMA was prepared by the same surgical team. Both the surgeons making the measurements and the staff in the operating room were blinded to the pharmacologic agent infused during the study period. Anesthesiologists were remained unblinded due to ethical reasons in order to manage the side effects of study drugs properly in the event they occur.

The left IMA was harvested with the aid of diathermy and hemoclips to control side branches and was dissected from the chest wall with a wide pedicle beginning from the level of subclavien vein to just before its bifurcation. Five minutes after systemic heparinization (300 units/kg), IMA was cut just proximal to its bifurcation. Then, IMA flow was determined by measuring the volume of blood expelled from the end of the freely bleeding artery in a 30 s period. IMA flow per minute was then calculated.

After first measurement of IMA flow, the distal end of the artery was occluded with a hemoclip and the artery was laid on a moist swab in its anatomic position without applying any pharmacologic agent to the tissue. After arterial cannulation was performed, the distal end of IMA was resected as necessary for the CABG according to the estimated site of LAD anastomosis. In all cases, occluded area of the distal segment was resected. Subsequently, second IMA flow was measured before venous cannulation for constitution of cardiopulmonary bypass.

Durations between starting of infusion of study drugs and measuring IMA flows, mean infusion rates of study drugs and the length of the resected segment from the IMA were determined. Also, heart rate (HR), MAP, CVP and nasopharyngeal temperature were recorded synchronously during each IMA flow measurement.

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The infusion of study drugs were discontinued after the second IMA flow was obtained and the study was concluded. In case IMA flow was below 25 ml/min during second measurement, vasodilator agent was applied topically.

2.1. Statistical analysis

SPSS for Windows, Version 10.0 was used for statistical analysis. All analysis was done on an intention to treat basis. Between groups, demographic and hemodynamic data, IMA flows, the length of the resected segment and temperature were analyzed with Student's *t*-test, and pre-existing disease, preoperative medication and gender distribution were analyzed with Fischer's exact test. Comparison of IMA flows, hemodynamic parameters and temperature within groups was performed using paired Student's *t*-test. Mann–Whitney *U* test was used for analyzing the effect of treatment with calcium channel blockers (CCBs) preoperatively on IMA flows within groups. The statistical tests were two-tailed. Results are expressed as mean ± SD (range) or number (%) where appropriate. A P value <0.05 was considered significant.

3. Results

Three patients were excluded from the study intraoperatively. Reasons for exclusion were as follows: high dose of nitroglycerin infusion (>2.5 μg/kg per minute) for maintaining hemodynamic stability (one patient in nitroglycerin group), high serum creatinine level (2.4 mg/dl) in the morning of the operation day (one patient in diltiazem group, serum creatinine level was 1.9 mg/dl 2 days before the operation), and IMA was not used as a graft (one patient in diltiazem group, because of assessing unsuitable conduit before completion of the dissection). A further three patients were substituted without breaking the randomization code. So, data of 60 patients who underwent CABG surgery with the left IMA from May 2002 until April 2003 were collected and analyzed.

Preoperative data of patients in both groups are shown in Table 1. No statistically significant differences were found between groups with respect to demographics, cardiac status, pre-existing disease and preoperative medication.

Durations between starting of infusion of study drugs until measuring first IMA blood flow (duration of infusion$_1$, min) and between starting of infusion of study drugs until measuring second IMA blood flow (duration of infusion$_2$, min) were not statistically different between diltiazem group (40.6 ± 7.5 and 61.7 ± 11.6) and nitroglycerin group (39.4 ± 6.8 and 57.4 ± 9.7; $P = 0.520$, 0.126, respectively). The mean infusion rate of diltiazem was 0.09 ± 0.0 mg/kg per hour in diltiazem group and that of nitroglycerin was 2.1 ± 0.3 μg/kg per minute in nitroglycerin group during the study period. The mean length of the resected segment was significantly longer in nitroglycerin group (2.1 ± 0.7 cm) than in diltiazem group (1.7 ± 0.5 cm; $P = 0.041$).

Table 1
Preoperative data of patients

	Diltiazem group ($n = 30$)	Nitroglycerin group ($n = 30$)
Age (years)	63.5 ± 9.7 (44–75)	62.8 ± 11.2 (39–83)
Weight (kg)	71.7 ± 10.8 (56–92)	71.4 ± 10.3 (50–90)
Male/female	21 (70%)/9 (30%)	21 (70%)/9 (30%)
BSA (m^2)	1.8 ± 0.1 (1.5–2.1)	1.8 ± 0.1 (1.4–2.1)
Past MI	13 (43%)	12 (40%)
Pre-existing disease		
Hypertension	23 (76%)	20 (67%)
Diabetes mellitus	13 (43%)	14 (47%)
Preoperative medication		
B-blockers	11 (37%)	9 (30%)
CCBs	11 (37%)	10 (33%)
ACE Inhibitors	9 (30%)	15 (50%)
Nitrates	1 (3%)	2 (7%)
Digoxin	1 (3%)	2 (7%)
Diuretics	2 (7%)	3 (10%)

Mean ± SD (range) or number (%). No significant difference between groups. BSA, body surface area; MI, myocardial infarction; CCBs, calcium channel blockers; ACE, angiotensin converting enzyme.

The mean values of the first and the second IMA free flows were 53.8 ± 30.1 and 72.3 ± 35.4 ml/min in diltiazem group and 25.7 ± 16.2 and 48.9 ± 23.8 ml/min in nitroglycerin group, respectively. Diltiazem infusion provided higher IMA flows than nitroglycerin during first and second IMA flow measurements with significant differences ($P = 0.000$, 0.004, respectively). Mean IMA blood flows after resection of distal segment of IMA were increased by 34% in patients receiving diltiazem and by 90% in patients receiving nitroglycerin. Additionally, the second IMA flows were significantly higher than the first ones within both diltiazem ($P = 0.000$) and nitroglycerin groups ($P = 0.000$; Fig. 1). In the diltiazem group, the means of the first

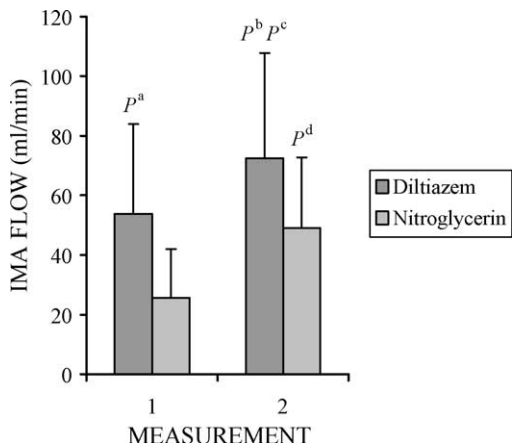


Fig. 1. Means of IMA flows (ml/min) during the first and second measurements in patients treated with diltiazem or nitroglycerin. P^a (0.000) and P^b (0.004) between groups, P^c (0.000) and P^d (0.000) within groups.

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and the second IMA flows were 58.0 ± 36.9 and 75.6 ± 33.5 ml/min in patients who were under treatment with CCBs prior to surgery, and 51.3 ± 26.3 and 70.4 ± 37.3 ml/min in patients who were not. No significant differences were found for the first ($P = 0.763$) and the second IMA flows ($P = 0.451$) in this respect within the diltiazem group. In the nitroglycerin group, these flows were 29.7 ± 21.7 and 47.8 ± 27.6 ml/min in patients who were treated with CCBs preoperatively, and 23.8 ± 12.8 and 49.5 ± 22.3 ml/min in patients who were not. There were not any significant differences in this regard within the nitroglycerin group either ($P = 0.724$, 0.509, respectively).

The mean values of HR, MAP, CVP and temperature did not differ significantly between groups during both IMA flow measurements. The mean value of MAP significantly decreased ($P = 0.042$) in diltiazem group and the mean value of HR significantly increased ($P = 0.036$) in nitroglycerin group during second measurement when compared to first measurement. Also, the mean value of temperature significantly decreased during second measurement of IMA flow when compared to first measurement in diltiazem ($P = 0.007$) and nitroglycerin groups ($P = 0.000$; Table 2).

IMA blood flow was found below 25 ml/min in four patients in nitroglycerin group and in one patient in diltiazem group during the second measurement. Vasodilator agent administered topically in these patients before constitution of cardiopulmonary bypass. Neither systemic vasopressor nor any other vasodilator was administered during the study period. There were no adverse reactions such as hypotension (<60 mmHg, MAP), bradycardia (<55 beat/min) or heart block necessitating pharmacologic treatment, discontinuation of diltiazem and nitroglycerin, or temporary pacing during the study period. Two patients in diltiazem group and one patient in nitroglycerin group underwent off-pump coronary bypass grafting surgery. Sinus rhythm was maintained spontaneously in 12 patients of diltiazem group and in seven patients of nitroglycerin group after aortic cross clamp was removed. After defibrillation, the rest of patients' rhythm returned to sinus rhythm in both groups.

Table 2
Hemodynamic data and temperature

	Diltiazem group ($n = 30$)	Nitroglycerin group ($n = 30$)
MAP (mmHg)		
First	83.1 ± 6.8 (70–100)	80.8 ± 5.5 (71–90)
Second	81.5 ± 7.4 (66–97)	80.5 ± 5.0 (71–89)
P	0.042	0.482
HR (beat/min)		
First	75.7 ± 11.4 (61–98)	73.8 ± 8.4 (57–89)
Second	76.3 ± 10.8 (60–98)	76.7 ± 10.8 (57–98)
P	0.717	0.036
CVP (mmHg)		
First	6.2 ± 2.1 (2–10)	5.4 ± 1.7 (3–9)
Second	6.2 ± 1.9 (2–10)	5.7 ± 1.6 (3–9)
P	0.758	0.199
Temperature (°C)		
First	35.6 ± 0.6 (34.4–36.8)	35.6 ± 0.5 (34.5–37.2)
Second	35.4 ± 0.6 (34.0–36.8)	35.4 ± 0.5 (34.5–37.2)
P	0.007	0.000

Mean ± SD (range). First, during first measurement of IMA blood flow. Second, during second measurement of IMA blood flow. *P* values were within groups, no significant difference between groups.

4. Discussion

This is the first report that has compared the effects of diltiazem and nitroglycerin on IMA free flow, starting infusion of study drugs before a vasoconstrictor stimulus is applied to the IMA region and continuing the infusion of study drugs throughout the harvesting period. Higher IMA free flows were obtained with diltiazem compared to nitroglycerin both after the IMA was cut just before its bifurcation and also after the resection of distal segment, suggesting that diltiazem might play an important role in the prevention of IMA spasm rather than nitroglycerin.

The chosen drugs in the present study, that are, diltiazem, a CCB, and nitroglycerin, a vasodilator, are widely used pharmacologic agents in the treatment of coronary artery disease, because both drugs have vascular selective properties. Moreover, with the proper selection of cases, perioperative use of these drugs has offered some benefits to the patients undergoing cardiac [14] or noncardiac surgery [15]. In a recent published meta-analysis, Wijeysundera and Beattie [15] reported the efficacy of CCBs, especially diltiazem on the incidence of ischemia, supraventricular tachycardia, death/myocardial infarction and major morbid events.

The effects of diltiazem and nitroglycerin in regard to protecting the myocardium to ischemia [16–18], and cost-effectiveness [19] had been compared previously. In spite of these comparisons, the effects of diltiazem and nitroglycerin on IMA blood flow have not been studied precisely. Although, Hannes et al. [16] postulated that perioperative diltiazem was efficious in the prevention of IMA spasm compared to nitroglycerin by observing reductions in arrhythmias and transient ischemic events, they did not assess the IMA blood flow directly.

With the exception of papaverine, the first report about the topical effect of a pharmacologic agent on IMA flow appeared in 1992 [5]. Thereafter, in 1994, Izzat et al. [7] for the first time informed that the clinical duration of action of a pharmacologic agent by topical application could not extend to the postoperative period and might not be useful for early postoperative IMA spasm. They investigated the effects of dobutamine, glycerol trinitrate, sodium nitroprusside and adenoximone, all administered intravenously, to identify the best drug for the treatment of IMA vasospasm [7]. In reports related with IMA spasm [5–8], the study drugs were administered after the IMA was dissected

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and cut distally from its bifurcation. Although surgical trauma can be minimized by careful techniques, routine harvesting of IMA is associated with a moderate degree of contraction of the vessel in spite of all the precautions taken, and surgical trauma is accepted as the most common cause of abnormal constrictor activity [2]. So, the effects of pharmacologic agents were investigated most likely in the presence of vasoconstrictor stimuli and the efficacy of the drugs in reversing vasospasm was determined. The present work differs from these studies in this respect.

The reason for obtaining higher IMA flows with diltiazem rather than nitroglycerin can be based upon the time of drug administration. The present study confirms the results of in vitro studies [9,10] in clinical setting, such that, CCBs have important roles in the prevention of IMA spasm when given before applying any constrictor stimulus rather than nitrates. Liu et al. [9] informed that nisoldipine pretreatment was effective when IMA segment was contracted by thromboxane mimetic U46619 and potassium chloride, but nitroglycerin had little effect in the prevention of contraction when induced by same vasoconstrictor agents. In another study, He et al. [10] tested the reactivity of ring segments of human IMA to various constrictor agents in organ baths and found that pretreatment with nifedipine had a role in the prevention of the contraction when induced by U46619 and potassium chloride, whereas glyceryl trinitrate did not and they concluded that CCBs or specific receptor antagonists should be tested in clinical settings for prophylaxis of IMA spasm.

Nitroglycerin [9], and glyceryl trinitrate [10] were effective in reversing contraction when IMA segments were contracted with U46619 and potassium chloride. Similarly, in a recent study, Wei et al. [11] reported that nitroglycerin might be effective in the treatment when segments of IMA were precontracted with arginine vasopressin. Chanda and Canver [12] investigated the vasodilator effect of nitroglycerin to reverse pre-existing vasospasm induced by endothelin 1, angiotensin II, 5-hydroxytryptamine and norepinephrine in coronary artery segments and found similar results. Contrary to nitroglycerin, Shapira et al. [13] reported that diltiazem was ineffective when segments of radial artery, internal thoracic artery and saphenous vein were precontracted with U46619.

On the other hand, a reduced level of endothelin, a vasoconstrictor peptide which predisposes perioperative vasoconstriction and ischemia, could be a contributing factor for obtaining higher IMA flows in patients treated with diliazem because Haak et al. [20] found lower endothelin levels in patients receiving diltiazem than in those receiving nitroglycerin intraoperatively.

Pharmacologic reactivity of human IMA is different among various sections and distal segment of IMA is the most prone part to vasospasm [21]. IMA flows increased approximately 90% in nitroglycerin group, and 34% in diltiazem group after distal segment of IMA was partially trimmed off. Although the length of the resected segment, which was significantly longer in nitroglycerin group, might have a role in these results, we assumed that distal part of IMA was still in a certain amount of spasm in both groups in different degrees. Vasospasm at the distal segment of IMA in patients pretreated with nitroglycerin was more obvious than in those pretreated with diltiazem, because higher IMA flows were obtained with diltiazem during both IMA flow measurements. As a result, we indicated that diltiazem played a more active role in the prevention of IMA spasm but could not provide full relaxation of the artery.

The nature of vasoconstriction during harvesting of the artery may possibly explain why full relaxation of the artery could not be obtained by diltiazem. It is highly possible that vasospasm in IMA during preparation of the artery as a conduit is the result of multiple vasoconstrictor activities. Multiple factors, such that, circulating hormones, neural factors, locally released vasoconstrictor substances are likely the causes of abnormal constrictor activity [2]. CCBs are effective in either preventing or reducing the contraction if the vasoconstriction is mediated by depolarizing agents, such as potassium chloride [9,10] but they are not effective against a wide range of constrictor stimuli [2], and are less effective in the case of receptor-mediated contraction when induced by alpha adrenoceptors, receptors of locally released substances [9,10] or arginine vasopressin [11]. So, drug combinations acting through separate pathways to vasoconstrictor stimuli might be more effective than any drug alone in the prevention of IMA spasm as shown in the treatment of vasoconstriction [22]. Liu et al. [9] informed that a synergistic effect was produced by combining nisoldipine with nitroglycerin at low concentrations for either the prevention or the treatment of contractions in isolated IMA segments. Similarly, Kawasaki et al. [23] investigated the effects of diltiazem and nitroglycerin on prostoglandin F_2 alpha-induced periodic contractions of isolated human coronary arteries and concluded that the simultaneous use of diltiazem and nitroglycerin would be more effective than when they are used individually in the prevention and treatment of coronary artery spasm. Experimental studies revealing the advantages of a combination therapy in IMA vasospasm made guidance to further clinical trials [24]. The next step of the present study is to investigate the effects of combination therapy on IMA blood flow in the same group of patients with the similar study design.

Patients receiving glibenclamide, furosemide and/or simvastatin preoperatively were excluded from the study because the possible combinations of these drugs with the study drugs would have a potential for producing a drug interaction or a synergism.

On the basis of our study design, such that, by infusing study drugs for a short period of time ($\approx$ 1 h) during the pre-bypass period, it is hard to associate the effects of study drugs with postoperative adverse events like postoperative

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myocardial infarction and death, because in our study the effects of study drugs were less likely to extend to the postoperative period. Beside, outcome measures related with the administration of study drugs were reported previously [16,19]. In those studies, infusion of diltiazem and nitroglycerin lasted for 24 h. Similarly, the reason for not observing adverse reactions like hypotension, bradycardia, or heart block during the study period may depend on both short duration of infusion of study drugs and our exclusion criteria. We preoperatively excluded patients with sinusal bradycardia and/or left bundle branch block.

In conclusion, the beneficial effect of diltiazem on IMA blood flow compared to nitroglycerin is clear when its infusion begins before applying any surgical stimulus to IMA region. We therefore recommend diltiazem infusion as an adjunctive therapy, starting immediately after the induction of anesthesia in patients undergoing CABG surgery where IMA vasospasm is a concern. Additionally, a combination therapy could be more effective than diltiazem alone in the prevention of IMA spasm and the matter, possible synergistic effect of diltiazem with other vasodilators needs further investigation in clinical settings.

4.1. Study limitations

The study has some potential limitations. First limitation is the lack of control measurements of IMA flows before starting the infusion of study drugs. Within the study design, flow measurements could only be obtained by the aid of spectrometer or ultrasound, but such devices were not available during the conduction of the study. On the other hand, although the measurement of blood flow during the postanastomotic period is more accurate than the measurement before the anastomosis, relatively small sample sizes were taken for determining the IMA flows in studies using such devices [24] which might have underpowered the results that were obtained.

Another limitation is the lack of hemodynamic parameters such as cardiac index and systemic vascular resistance during measurements of IMA flow. In our routine practice, pulmonary artery catheter is placed in patients presenting for CABG surgery according to the international guidelines which has changed little in recent years [25]. No patient included in the study had an indication for the insertion of pulmonary artery catheter. Besides, it was previously noted that IMA flow primarily depends on MAP and resistance of the vessel [8].

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