Effective dose of dobutamine in augmenting free flap blood flow during reconstructive surgery of the lower extremity

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Abstract
Success of surgical free flap transfer depends on achieving and maintaining adequate perfusion across the microvascular anastomosis. The purpose of this prospective study was to determine the optimal infusion rate of dobutamine to augment duplex ultrasound measured blood flow to the tissue flap during surgery.

Twenty-one patients undergoing general anesthesia for lower limb reconstructive surgery were recruited. The optimal dobutamine dose was evaluated using the modified Dixon’s up-and-down method, starting at 6 μg·kg⁻¹·min⁻¹, and then titrated in increments of 1 μg·kg⁻¹·min⁻¹.

The optimal dose of dobutamine for improving blood flow to the tissue flap was 3.50±0.57 μg·kg⁻¹·min⁻¹ in 50% of patients. The 95% effective dose of dobutamine calculated by probit analysis was 4.46 μg·kg⁻¹·min⁻¹ (95% confidence interval: 3.99–7.00 μg·kg⁻¹·min⁻¹).

The results of our study suggest that a dobutamine infusion rate less than 5 μg·kg⁻¹·min⁻¹ provides significant improvement of blood flow to the tissue flap, while minimizing cardiovascular side effects.

Abbreviations: ED = effective dose, GA = general anesthesia.

Keywords: blood flow, dobutamine, free flap

1. Introduction
Reconstructive free flap surgery involves the transfer of free pedicle muscle flaps using a microsurgical technique. Success of surgical free flap transfer depends on achieving and maintaining adequate perfusion across the microvascular anastomosis.[1,2] Besides meticulous surgical technique, the mainstays for preventing vascular occlusion include the maintenance of normothermia, mild hypervolemia, and reduced blood viscosity. Maintaining of optimal blood flow through the vascular anastomoses is crucial for the success of such procedure. Thus, perioperative fluid and hemodynamic management by the anesthesiologist is crucial in preventing hypoperfusion of the transferred tissue and graft failure.[2]

The use of perioperative systemically administered vasoactive agent is generally avoided due to the fear that those vasoactive agents might hinder the blood flow and compromise the viability of the flap. However, several authors have been advocated that dobutamine, unlike other inotropic, may increase free flap perfusion.[3–5] In a swine model, Corderio et al proposed that dobutamine increases both cardiac output and blood flow to island musculocutaneous flaps. They further stated that dopamine does not affect and that phenylephrine adversely affects flap blood flow.[3] Similarly, Suominen et al[4] documented that a dobutamine infusion of 8 μg·kg⁻¹·min⁻¹ resulted in increased flap blood flow as the result of higher cardiac output and decreased systemic vascular resistance; whereas a dopamine infusion of 8 μg·kg⁻¹·min⁻¹ had no effect on flap blood flow because of increase in systemic vascular resistance. In addition, Scholz et al[6] also demonstrated that blood flow to the flap significantly increased above baseline values with dobutamine infusion of 4 and 6 μg·kg⁻¹·min⁻¹.

Despite the beneficial effect of dobutamine on flap perfusion, the optimal infusion rate for maximizing blood flow to the flap while minimizing the adverse effects is still unclear. Therefore, we undertook this study to evaluate the appropriate dose of dobutamine to improve free flap blood flow in patients undergoing low extremity reconstruction surgery under general anesthesia (GA).

2. Methods
Twenty-one patients were included in the study after institutional review board approval and written informed consent. The subjects were planned to undergo lower extremity reconstructive...
surgery using an anterolateral thigh free flap under GA. Patients were aged 21–59 years and were of ASA physical status I. Exclusion criteria included diabetes, hypertension, ischemic heart disease, cardiac arrhythmia, prior deep vein thrombosis, and peripheral vascular disease.

All subjects fasted at least 6 h before surgery, and no premedication was given. Upon arrival to the operating room, routine monitoring was initiated, comprising of non-invasive blood pressure, electrocardiography, and pulse oximetry. All patients were anesthetized by the same anesthesiologist and received intravenous fluid 10 mL·kg⁻¹·min⁻¹ Ringer’s lactate solution prior to induction. GA was induced with standard doses of pentothal sodium, vecuronium, and fentanyl. The trachea was intubated, and mechanically controlled ventilation with 2–3 vol % sevoflurane in 50% oxygen-air was used to maintain the end-tidal carbon dioxide at 4.5–5.0 kPa. Throughout the entire study period, the core body temperature was continuously monitored in order to maintain normothermia with forced heating blankets. At the end of surgery, we checked the patients’ hematocrit and tried to maintain between 30% and 35%, and packed red cells were given, if necessary.

Duplex sonography was taken at baseline (prior to the induction of anesthesia), before dobutamine infusion, and 15 min after dobutamine infusion. The investigator who monitored the patients’ hemodynamics and flow blood flow parameters was blinded to the rate of dobutamine infusion. Duplex investigation was performed using an EUB 7500 HV (Hitachi Medical Corporation, Tokyo, Japan) with a high resolution (10 MHz) linear-array transducer. The probe position and 60° of angle were scrupulously maintained using a protractor and marks in every examination. Investigation of anastomosed donor arterial hemodynamics included time velocity integral, cross-sectional area, and volume flow. All data were measured three times during each examination by a single blinded investigator, and averaged values were used. The reproducibility of the duplex measurements had presented in our previous publication.[6]

The infusion of dobutamine was started before the flap anastomosis, and rate of dobutamine was determined by the response of the previously tested patient according to the Dixon’s up-and-down method (using 1.0 μg·kg⁻¹·min⁻¹ as a step size). The first patient received 6.0 μg·kg⁻¹·min⁻¹ of dobutamine. To allow steady state conditions to be achieved, a pre-determined dose of dobutamine was continuously infused for 15 min. In the implementation of Dixon’s up-down dose-finding method, augmentation of blood flow within ±5% of baseline was defined as a positive response. If the patient had a positive response, the dose of dobutamine was reduced for the successive subjects. On the contrary, a negative response was defined when the blood flow after 15 min of dobutamine infusion fell short of ±5% of baseline, which resulted in an increased dose for the next subject. To minimize the influence of surgical stimulation, all study-related measurements and procedures were performed during a natural break in the operation. If clinically significant hypertension (systolic blood pressure >180 mmHg) or tachycardia (heart rate >120 bpm) occurred during the protocol, the patient was managed appropriately and excluded.

Statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL). Data were collected from patients using Dixon’s method to provide seven pairs of data where an increase in dobutamine dose changed a negative response to a positive response in successive patients. The dose of dobutamine with a 50% probability of sufficient improvement of blood flow was defined as the 50% effective dose (ED₅₀), and was determined by calculating the mean of the midpoint dose of the seven pairs of data described above. The ED₅₀ and 95% effective dose (ED₉₅) were also determined using probit analysis. Repeated measures analysis of variance was used for the analysis of hemodynamic data, with post hoc testing by the Tukey method. A P value <.05 is considered a statistically significant difference.

3. Results

Twenty-one patients were enrolled in this study, of whom 12 were male and 9 were female. Patients’ details are presented in Table 1.

Figure 1 plots the improvement of blood flow for each consecutive patient along with the Dixon’s up-and-down sequence. The results of the calculations for the seven crossover pairs indicated that the ED₅₀ of dobutamine for sufficient improvement of free flap blood flow during GA was 3.50 ± 0.57 μg·kg⁻¹·min⁻¹. Probit analysis showed that the ED₅₀ and ED₉₅ of dobutamine were 3.58 μg·kg⁻¹·min⁻¹ (95% CI: 2.94–4.09 μg·kg⁻¹·min⁻¹) and 4.46 μg·kg⁻¹·min⁻¹ (95% CI: 3.99–7.00 μg·kg⁻¹·min⁻¹), respectively (Fig. 2).

![Figure 1](image-url)  
**Figure 1.** The response of 21 consecutive patients and the dose of dobutamine. The arrow indicates the midpoint dose for the cross-over to a positive response. The dose of dobutamine for improvement in free flap blood flow in 50% of patients was 3.50 ± 0.57 μg·kg⁻¹·min⁻¹.

### Table 1

| Parameters | Sex; male/female | Age; year | Weight; kg | Height; cm | Cause of surgery; n | Traumatic injury | Malignant tumor of soft tissue | Operation time; min | Anesthesia time; min | Crystallloid solution; mL | Colloid solution; mL |
|------------|-----------------|-----------|------------|------------|--------------------|-----------------|----------------------|-------------------|-------------------|----------------------|---------------------|
| Sex; male/female | 12/9 | 46 [36.25–51.75] (21–59) | 65.8 [55.825–75.8] (40–87) | 164.2 [159.375–171] (151.1–181) | | 11 | 10 | 319 [253–470] (203–708) | 345 [295–407] (230–765) | 1250 [900–2200] (550–2000) | 500 [437.5–500] (300–1000) |
Figure 2. Dose-response curve from the probit analyses of individual dobutamine doses and the response to the infusion in the subjects. The doses of dobutamine at which there was a 50% and 95% probability of improving blood flow were 3.58 and 4.46 μg·kg⁻¹·min⁻¹, respectively.

Patient hemodynamic data are shown in Table 2. Blood pressure prior to dobutamine infusion was significantly lower than at baseline (P < .05). After dobutamine infusion, SBP returned to baseline levels, whereas the diastolic pressure did not. After the completion of sonographic measurements and study protocol, one patient receiving 6 μg·kg⁻¹·min⁻¹ and one patient receiving 3 μg·kg⁻¹·min⁻¹ experienced clinically significant hypertension. For these patients the infusion of dobutamine was ceased immediately.

4. Discussion

The results of our study demonstrated that the ED50 and ED95 of dobutamine for improvement of blood flow to the anastomosed free flap were 3.58 and 4.46 μg·kg⁻¹·min⁻¹, respectively. To our knowledge, this is the first report to determine the optimal dose of dobutamine for enhancing blood flow to the free flap during GA, and our results suggest that there is a significant augment of blood flow at relatively smaller doses of dobutamine compared with those previously suggested.

Anesthetic management for free flap surgery aims to optimize blood flow to the flap tissue across the anastomosis by increasing circulating blood flow and preventing peripheral vasoconstriction. Although the effects of inhalational anesthetic agents on the regional blood flow in the free flap are not yet well known, most volatile anesthetics decrease blood pressure by decreasing total peripheral resistance and depressing myocardial contractility. Importantly, it has been demonstrated that implementation of epidural anesthesia generated a significant enhancement of the arterial leg inflow contrasting the blood flow attenuation sustained with GA. During prolonged operations under GA, patients may also become hypothermic and hypovolemic, which predisposes them to generalized vasoconstriction and diminished blood flow to the lower limb and the transferred flap tissue. Although overall blood flow in a free microvascular flap is complex, any cause of flow attenuation sustained with GA is believed to be harmful to the flap perfusion, such as profound hypotension, hypovolemia, anesthesia-induced decreases of myocardial contractility, and low cardiac output.

Theoretically, dobutamine has advantages as a potent β1- and β2-agonist, which provides direct inotropic action coupled with systemic vasodilatation and afterload reduction. An adequate arterial blood pressure with vasodilatation ensures good tissue perfusion by providing sufficient regional blood flow, improving patency of the microvasculature, and maintaining the fluidity of the blood in the microcirculation. In this respect, several authors have recently begun to advocate its use for improving flap blood flow, and in a swine model it was shown that flap blood flow is increased with dobutamine rates of 3, 6, and 12 μg·kg⁻¹·min⁻¹. In humans, there have also been a small number of reports that dobutamine may increase free flap perfusion; however, the recommended doses of dobutamine are varied, ranging from 4 to 8 μg·kg⁻¹·min⁻¹. In our study, the ED50 and ED95 of dobutamine for improving blood flow to the anastomosed flap above that of baseline were 3.58 and 4.46 μg·kg⁻¹·min⁻¹, respectively. These results imply that most patients could achieve sufficient enhancement of blood flow to the flap at dobutamine rates of even less than 5 μg·kg⁻¹·min⁻¹. As the use of dobutamine is not fully harmless without side effects, a low-dose infusion of dobutamine would minimize potential adverse effects, while still rendering beneficial effects on flap perfusion.

Blood flow in free vascularized flap tissue is different from normal tissue in several respects. For instance, free vascularized tissue is subjected to complete denervation, and although the arteries in free flaps have no neurogenic response, they still respond to pharmacologic agents. Lorenzen demonstrated that blood flow through the free flap does not depend on

| Table 2 |
| Changes of blood flow to free flap, cardiovascular and systemic variables, median [IQR] (range). |
| Baseline | Pre-infusion | Post-infusion |
| FV, mL·min⁻¹ | 9.36 [2.95–17.01] (1.04–21.28) | 6.24 [3.253–14.78] (0.69–21.28) | 9.0 [4.86–19.71] (1.36–62.64) |
| CSA, cm² | 0.03 [0.02–0.0375] (0.01–0.07) | 0.03 [0.02–0.04] (0.01–0.06) | 0.03 [0.0225–0.0475] (0.01–0.05) |
| SBP, mm Hg | 123 [112.75–145.25] (102–170) | 97 [87.5–107.25] (81–147) | 131 [110–146.75] (96–155) |
| MAP, mm Hg | 73 [68.75–78.5] (43–107) | 70 [63.75–76.5] (62–98) | 78 [75.25–81.5] (66–101) |
| HR, beat·min⁻¹ | 74 [70.25–92.5] (52–110) | 71 [62.25–86.75] (51–112) | 72 [59–96.5] (54–126) |
| Temperature, °C | 37.1 [36.7–37.3] (35.8–37.7) | 36.9 [36.3–37.2] (35.7–37.6) | 37.0 [36.5–37.2] (35.8–37.7) |
| ETCO₂, Kpa | 4.7 [4.3–4.8] (4.1–5.4) | 4.4 [4.2–4.5] (3.7–4.9) | 4.7 [4.1–4.9] (4.0–5.3) |

CSA = cross-sectional area, DBP = diastolic blood pressure, ETCO₂ = end tidal carbon dioxide, FV = flow volume, HR = heart rate, MAP = mean arterial pressure, SBP = systolic blood pressure.

1 P < .05 compared with baseline.

2 P < .05 compared with pre-infusion.
recipient artery flow, and that the flow in the free flap rises to the level of donor artery flow after the completion of the anastomosis. Furthermore, Suominen et al.\cite{1} showed that 8 \( \mu \) g.kg\(^{-1}\).min\(^{-1}\) of dobutamine infusion increases blood flow in both donor and recipient arteries simultaneously, and it is known that modulators cause systemic vasodilation, which includes the vessels of the transplanted tissue.\cite{2} These results support that measuring the blood flow to the flap tissue at the donor artery, as a surrogate measure of recipient artery flow, may be valid in evaluating the flap blood flow. In addition, air in the graft may cause erratic flow pattern and vessel spasm in the graft or native artery. Thus, low or zero mean flow value could be shown without pulsation. In our study the surgeons did not have any problems in applying the Doppler probe, and it was not difficult to interpret the achieved data.

There are several limitations to our study. First, we did not evaluate whether intraoperative infusion of dobutamine decrease postoperative flap failure rate. Most flap failures is known to occur during the first 3 days after surgery.\cite{3} Virtual no experimental or clinical study has been carried out on the effects of intraoperative inotropic agents on outcomes of free flap procedures. Further studies are warranted, particularly as non-invasive monitoring techniques are now available that allow continuous monitoring of blood flow in transferred tissue after surgery. Second, although the Doppler ultrasound method is non-invasive, it has not gained much popularity with clinicians because flow measurements by this technique are dependent on vessel diameter, vessel shape, probe angle, and motion artifacts. Despite this limitation, Doppler ultrasound has been suggested as useful in monitoring arterial blood flow in skin flaps, and reliability of the technique might be improved when the probe is placed around the supplying vessels.\cite{4} Lastly, we did not checked actual changes in cardiac output or systemic vascular resistance during dobutamine infusion. We hope to see that in the next study, which may give us more insights in what is happening.

In conclusion, the optimal infusion rate of dobutamine for improving blood flow to the free tissue flap in 95% of patients undergoing lower limb reconstructive surgery is 4.46 \( \mu \) g.kg\(^{-1}\).min\(^{-1}\). The results obtained here suggest that if Doppler ultrasound or surrogate parameters for titration are unavailable during free flap surgery, <5 \( \mu \) g.kg\(^{-1}\).min\(^{-1}\) of dobutamine would provide a significant improvement of blood flow to the free transferred flap, while minimizing cardiovascular side effects.

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