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The effect of dobutamine on blood flow of free tissue transfer flaps during head and neck reconstructive surgery*

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Summary

In view of the controversy over the use of inotropes in free tissue transfer surgery, we assessed the effect of different intra-operative dobutamine infusion rates on blood flow in the anastomosed recipient artery. Twenty patients undergoing head and neck tumour resection and immediate reconstructive surgery with free tissue transfer were recruited. After completion of the microvascular anastomoses, patients received dobutamine infusions of 2, 4 and 6 $\mu g.kg^{-1}.min^{-1}$ in a randomised order. After steady state dobutamine concentration was achieved, mean and maximum blood flow in the arterial anastomosis was measured at each concentration, using the Medi-Stim Butterfly Flowmeter system. Systemic haemodynamic parameters were simultaneously recorded using a pulse contour cardiac output system. Both mean and maximum blood flow increased significantly in the anastomosed artery at dobutamine infusions of 4 and 6 $\mu g.kg^{-1}.min^{-1}$ and this was accompanied by increased cardiac output. This may improve free flap perfusion.

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The use of free tissue transfer including microvascular anastomoses of recipient and donor vessels is a complex method of wound closure for large non-linear defects whether caused surgically or traumatically. Historically tumour ablation surgery was accompanied by attempts at reconstruction using skin grafts, pedicle flaps or surgical obturators. Whilst success rates with these techniques were consistently high, the cosmetic and functional outcome was less acceptable. Free tissue transfer utilising microvascular anastomoses has provided a superior alternative to the reconstruction of surgical defects in the head and neck region.

The success rate of such transfers is around 92% in the UK and the majority of failures usually occur with venous occlusion within 24 h of the initial surgery. It is alleged that the majority of anastomotic occlusions are as a result of poor surgical technique but every head and neck surgeon has performed technically proficient anastomotic procedures only to be confounded by an occlusion in the post operative period.

There is little doubt that other pathophysiological factors are involved though identifying these is proving difficult and surgeons are seeking methods to optimise the chances of anastomotic success. The mainstays to prevent occlusion, aside from meticulous surgical technique, are the maintenance of normothermia, mild hypervolaemia and reduced blood viscosity.

Many workers are wary of using inotropic agents as a method of improving perfusion of the transplanted tissue as they believe them to cause a steal phenomenon and direct blood away from the flap. There have, however, been a small number of reports that dobutamine, unlike inotropic agents that have vasoconstrictor properties, may increase free flap perfusion [1, 2].

If optimal blood flow can be maintained through the anastomoses then the success rate for such procedures will be optimised. This study was designed to assess the effect of varying dose regimes of dobutamine on the blood flow in anastomosed arteries of free tissue flaps.

Method

Following Bro Taf Local Research Ethics Committee approval and written informed consent, 20 patients were

recruited for the study. They were ASA grade 1–3, presenting for oro-facial tumour resection and immediate reconstructive surgery utilising a radial forearm and/or a fibula free flap. Exclusion criteria were severe asthma, cor-pulmonale, cardiac failure, cardiac arrhythmias, severe hypertension and ischaemic heart disease.

A standardised anaesthetic was administered involving premedication with temazepam, induction with propofol, muscle relaxation with vecuronium and a fentanyl infusion. The patients' lungs were mechanically ventilated, to maintain the end tidal carbon dioxide concentration between 4.5 and 5.0 kPa, via a naso-tracheal tube and anaesthesia maintained with isoflurane 1–2% in oxygen enriched air. All patients were anaesthetised by the same anaesthetist.

For the measurement of cardiovascular and haemodynamic parameters we used a pulse contour cardiac output analysis system, PiCCO Pulsion system (PULSION Medical systems, Munich, Germany). The thermistor tipped catheter was placed in the femoral artery and connected to the pulse contour analysis computer. The output was also connected to the main monitor and used to display arterial pressure. A central venous catheter was sited via the subclavian vein opposite to the site of the tumour resection for measurement of central venous pressure, administration of dobutamine and to enable calibration of the PiCCO. Calibration was by the recommended thermodilution technique using a cold bolus of 20 ml saline to achieve the curve. This was repeated three times and an average measurement taken. Cardiac output (CO), cardiac index (CI), mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), systemic vascular resistance (SVR), systemic vascular resistance index (SVRI), intrathoracic blood volume index (ITBVI) and stroke volume variation (SVV) were continuously displayed during the operation. The system was re-calibrated immediately prior to the study measurement period.

Intra-operatively a combination of crystalloids and gelatine based colloids were given to maintain a central venous pressure (CVP) between 5 and 15 mmH_2O, an intrathoracic blood volume index (ITBVI) between 800 and 1100 ml, a stroke volume variation less than 10% and an urine output of 0.5–1 $ml.kg^{-1}.h^{-1}$. Packed red cells were given to maintain a haemoglobin of 80–100 $g.l^{-1}$. Core temperature was continuously monitored and maintained above 36.0 °C.

The anastomoses performed during the reconstructive procedure were arterial to common facial artery as an end to end anastomosis and venous to the internal jugular vein as an end to side anastomosis. Once the vascular anastomoses were secured the flow in the anastomosed donor artery, distal to the anastomosis, was measured with the Medi-Stim Butterfly Flowmeter (Medi-Stim AS, Oslo, Norway) a third generation ultrasonic transit time flowmeter. Recordings were made of mean and maximum flow (see Fig. 1).

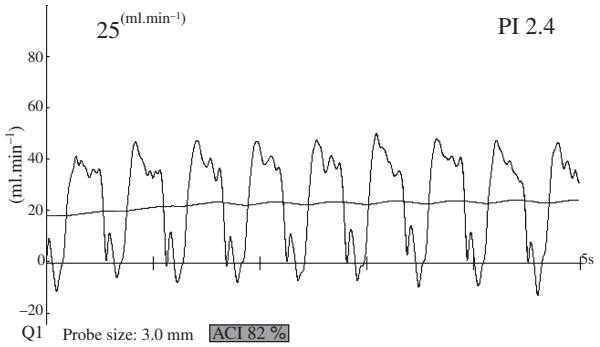

Figure 1 Typical transit time flow meter recording. PI, Pulsatility Index (resistance to flow); ACI Acoustic Coupling Index; Real time (pulsatile) and average flow rate.

Simultaneous baseline haemodynamic measurements of systolic blood pressure, mean arterial blood pressure, central venous pressure, cardiac index, intrathoracic blood volume index, stroke volume variation, and temperature and end tidal carbon dioxide were taken. After the baseline readings the dobutamine infusion was commenced.

Dobutamine, at rates of 2, 4, and 6 $\mu g.kg^{-1}.min^{-1}$, was infused according to a predefined, computer generated (LABVIEW; National Instruments, Austin, TX, USA, Version 2.0) random sequence for a 10-min period. This time period was to allow steady state conditions to be achieved. All flow measurements and haemodynamic measurements were repeated at the end of this 10 min period and once completed the rate of infusion was altered according to the randomisation sequence. This was repeated for all three dobutamine regimes.

The investigator monitoring the haemodynamic and free flap flow parameters was blinded to the rate of infusion. The whole of the study procedure was undertaken during a natural, though artificially prolonged, break in the operation. This minimised the influence of surgical stimulation. Following completion of the study protocol, surgery was completed and the patient transferred to the intensive care unit for recovery. Current departmental guidelines for the post-operative management of these patients were followed which included a dobutamine infusion at a rate of 2 $\mu g.kg^{-1}.min^{-1}$.

Statistical methods

Each patient received each of the three different rates of infusion of dobutamine (2, 4 and 6 $\mu g.kg^{-1}.min^{-1}$) in a

random order. The Friedman test was used to test whether the rate of infusion of dobutamine had an effect on blood flow. The significance level was set at 0.05. With a power of 80%, 14 patients needed to be recruited to demonstrate a standardised difference of 0.75 (clinically important difference/standard deviation). We recruited 18 patients as the blood flow data was unlikely to be normally distributed and to allow for patients not completing the study.

In a post hoc analysis, the method described by Siegel [3] was used to detect differences between the various infusion rates. This method involves the calculation of the mean ranks for each infusion rate and determining whether the magnitude of the difference between the mean ranks is greater than a critical difference. For 18 patients and four groups (0, 2, 4 and 6 $\mu g.kg^{-1}.min^{-1}$) the critical difference between mean ranks is 1.14.

The Friedman test was also used to test whether the rate of infusion of dobutamine had an effect on the other outcomes, such as heart rate, systolic blood pressure and cardiac index.

Results

Twenty patients participated in this study. Twelve were male and eight female. The mean age was 57.9 years, (range 31–75 years), the mean weight was 66.8 kg (47–130 kg) and the mean height was 170.2 cm (152–185 cm). Nine patients were smokers and four had a history of severe alcohol abuse. Five patients were ASA 1, fourteen were ASA 2 and one was ASA 3. In fifteen patients a radial forearm free flap was used to cover the facial defect, four patients had a fibula free flap and one patient received both.

Two patients were excluded from the analysis. One patient did not complete the study. This patient was a 51 year-old gentleman who had a coronary artery stent inserted 2 years before his maxillo-facial surgery. He had no symptoms of ischaemic heart disease and his blood pressure was well controlled on atenolol. When the dobutamine infusion was commenced the ECG trace showed marked ST depression indicating cardiac ischaemia. The infusion was discontinued, the patient withdrawn from the study and surgery continued uneventfully. A second patient had unusually high value of average free flap flow at baseline levels. This was only recognised when starting the statistical analysis and was 10–30 times higher than the rest of the values measured during the study. It was most likely a measurement error and the patient was excluded. Reliable values were obtained from 18 patients.

There was a significant effect of dose on both mean flow and maximum free flap flow (see Table 1).

Table 1 Free flap blood flow, haemodynamic and systemic variables at the different dobutamine infusion regimes, median [IQR] (range).

	Base-line	2 $\mu g.kg^{-1}.min^{-1}$	4 $\mu g.kg^{-1}.min^{-1}$	6 $\mu g.kg^{-1}.min^{-1}$	Overall p value
Mean flow; $ml.min^{-1}$	4 [2–5] (1–19)	5 [3–9] (1–30)	7 [4–11] (1–91)	9 [4–12] (0–20)	0.0002
Max. flow; $ml.min^{-1}$	30 [15–54] (7–83)	44 [29–59] (15–161)	50 [31–82] (13–175)	57 [38–99] (15–217)	< 0.0001
HR; $beat.min^{-1}$	83 [73–87] (64–113)	92 [85–108] (69–117)	102 [87–114] (73–129)	106 [97–126] (69–136)	< 0.0001
SBP; mmHg	102 [98–112] (86–141)	119 [102–135] (91–159)	127 [119–134] (90–144)	127 [118–149] (93–177)	0.0001
MAP; mmHg	73.5 [64.0–80.3] (56.0–97.0)	75.0 [70.8–89.0] (57.0–100.0)	78.0 [72.5–88.3] (58.0–95.0)	81.0 [70.8–90.3] (59.0–118.0)	0.062
CI; $l.min^{-1}.m^{-2}$	3.8 [3.4–5.8] (2.2–7.1)	5.7 [4.5–6.8] (2.5–8.9)	5.5 [4.7–7.2] (2.5–9.9)	6.3 [4.8–8.0] (3.5–9.5)	< 0.0001
CVP; mmHg	13.5 [9.8–17.3] (7.0–22.0)	12.5 [9.0–14.8] (7.0–22.0)	13.0 [10.0–15.8] (6.0–21.0)	13.0 [8.8–15.0] (6.0–21.0)	0.091
SVRI; $dyne.s.m^2.cm^{-5}$	1075 [931–1306] (673–2206)	1042 [759–1141] (673–1891)	941 [752–1158] (571–1974)	900 [648–1097] (529–1837)	0.002
ITBV; ml	1062 [952–1161] (550–1659)	1011 [898–1138] (605–1712)	952 [898–1138] (655–1712)	1011 [898–1138] (655–1712)	0.45
Temperature; °C	37.0 [36.5–37.3] (35.5–37.7)	37.2 [36.7–37.4] (35.6–37.9)	37.2 [36.6–37.3] (35.7–37.9)	37.2 [36.8–37.4] (35.6–37.8)	
$EtCO_2$; kPa	4.4 [4.2–4.6] (3.8–5.0)	4.6 [4.3–4.8] (3.9–5.4)	4.7 [4.2–4.9] (4.0–5.5)	4.7 [4.2–4.9] (4.0–5.5)	

Max. flow, maximum flow; MAP, mean arterial pressure; SBP, systolic blood pressure; HR, heart rate; CI, cardiac index; CVP, central venous pressure; SVRI, systemic vascular resistance index; ITBV, Intrathoracic blood volume; $EtCO_2$, end tidal carbon dioxide.

	Baseline	2 μg.kg^{-1}.min^{-1}	4 μg.kg^{-1}.min^{-1}	6 μg.kg^{-1}.min^{-1}	
Baseline		1.06	1.53*	2.19*	Max ↓
2 μg.kg^{-1}.min^{-1}	0.50		0.47	1.14	
4 μg.kg^{-1}.min^{-1}	1.39*	0.89		0.67	
6 μg.kg^{-1}.min^{-1}	1.56*	1.06	0.17		
	Mean →				

Table 2 Difference in mean ranks for pairwise comparisons of the different doses of dobutamine for both mean and maximum flows. For 18 patients and four groups the critical difference is 1.14. Critical differences are indicated by an asterisk (*).

For both mean and peak flow, there was a significant difference between the flow at baseline and with either 4 or 6 μg.kg^{-1}.min^{-1}. There was no significant difference at baseline and 2 μg.kg^{-1}.min^{-1} of dobutamine (see Table 2).

With increasing doses of dobutamine there was a significant increase in heart rate (HR) systolic blood pressure (SBP) and cardiac index (CI) ($p = 0.0001$). A significant decrease in systemic vascular resistance index (SVRI) with increasing dobutamine infusion rate was observed ($p = 0.002$). The mean arterial pressure (MAP), central venous pressure (CVP) and intrathoracic blood volume (ITBV) did not change significantly (Table 1). There were no clinically important changes in temperature and end tidal carbon dioxide concentration throughout the study period.

Discussion

Hypoperfusion, secondary ischaemia and necrosis in musculocutaneous flaps used for reconstructive surgery is a significant clinical problem. During surgery, blood vessels of with a diameter of between 1 and 4 mm are anastomosed and it is important to maintain optimum haemodynamic parameters to maximise flap perfusion. The arteries can be categorised as resistance vessels and are subject to reflexes that control blood flow. Changes in viscosity, internal diameter and perfusion pressure will all influence blood flow. Systemic arterial pressure is the major determinant of pressure gradient across the transplanted tissue and flow in microcirculation can decrease due to a decrease in arterial pressure, an increase in venous pressure or an increase in the resistance to flow upstream as a result of vasoconstriction or increased blood viscosity [4]. There are also other intrinsic and extrinsic factors that influence flap blood flow. It has been shown that the blood flow in the recipient artery is regulated by the flap itself, according to the flap requirement for oxygen [5]. It has also been shown that flow increases in denervated muscle when it is transferred from one part of the body to another [6]. Although transplanted tissue is sympathetically denervated, blood vessels can still be put into spasm by physical and humoral influences including cold, manipulation, circulating catecholamines and metabolites generated by ischaemia. Metabolic autoregulation can only function in the presence of an adequate perfusion pressure [7].

In practice the basis of intra and post-operative management is the maintenance of normothermia, normo- or mild hypervolaemia, low blood viscosity and reduction of systemic sympathetic stimulation. It is only in recent literature that authors have begun to advocate the use of inotropic agents [2, 8]. This may be because of a greater acceptance and understanding of the mode of action of 'newer' inotropic agents or that despite the preceding criteria being met there is still room for improvement. In our study we have demonstrated that dobutamine at 4 and 6 μg.kg^{-1}.min^{-1} significantly increases the blood flow to the anastomosed flap above baseline values. Whilst the cardiac index increased there was no change in the indicators of vascular filling, CVP and ITBVI. This indicates that the increased flap flow was due to the increase in cardiac output, a combination of increased HR and SBP and a decrease in systemic vascular resistance, rather than an increase in intravascular volume.

Cordeiro et al. [1] showed in a swine model that blood flow is predominantly determined by CO and SVR and these parameters can be manipulated by inotropic agents. It was shown in this model that CO is increased with dobutamine 3, 6 and 12 μg.kg^{-1}.min^{-1}and with dopamine at 2.5–5 μg.kg^{-1}.min^{-1}. They also showed that flap blood flow increased with dobutamine and remained unchanged with dopamine. Suominen et al. [2] compared the effect of intravenous dopamine and dobutamine on blood flow during microvascular transversus rectus abdominus muscle flap operations. They showed that dobutamine at 8 μg.kg^{-1}.min^{-1} increased CO, decreased SVR and increased flap flow, whilst dopamine at 8 μg.kg^{-1}.min^{-1} increased CO but SVR and flap blood flow remained unchanged. In this study the donor and recipient vessels had been dissected but not divided at the time of inotrope infusions. We have shown that there is a significant increase of flap flow when using smaller doses of dobutamine (4 and 6 μg.kg^{-1}.min^{-1}) after completion of the anastomoses.

Other pharmacological agents have been investigated with variable effect on flap blood flow. Ichioka et al. [8] showed that intravenous amrinone, a selective phosphodiesterase III inhibitor, at a rate of 10 μg.kg.min^{-1} has no significant effect on flap blood flow but topical

application of amrinone (5 $mg.ml^{-1}$) may be useful to resolve vasospasm.

It is stated that phenylephrine at doses of 1.5 and 3 $\mu g.kg.min^{-1}$ decreases the flap flow [1] while Banic et al. [9] showed in a porcine model that phenylephrine at 1 $\mu g.kg.min^{-1}$ has no adverse effect on blood flow in free musculocutaneous flaps. This group also studied the effects of sodium nitroprusside on blood flow in free flaps in the same porcine model showing this drug to cause no significant change in CO, a 30% decrease in mean arterial pressure and a 40% decrease in free flap flow.

In our study we used the Medi-Stim transit time flow meter (TTFM) to assess blood flow in the free flap after completing the anastomosis. This equipment has been designed for use in cardiac and vascular surgery to assess the patency of and the flow in arterial and venous grafts. The transit time method of measurement uses two piezo crystals transmitting ultrasound through the blood vessel towards a reflector on the other side of the vessel. Volume flow is calculated by measuring the difference between transit times of the ultrasound beam upstream and downstream in the blood vessel [10, 11]. TTFM has several advantages with respect to the Doppler technique in that measurements are independent of vessel diameter, motion artefacts, vessel shape and probe position (angle) [12]. It is quick and simple to use and calibration is not necessary [13].

The ease of use and quick flow measurements during the operation made the TTFM particularly suitable to conduct the study, since there was no significant prolongation of the surgery due to measurements. However, it has its limitations: air in the graft may give erratic flow pattern and vessel spasm in the graft or native artery may give low or zero mean flow value without pulsation. In our study the surgeons had no problems applying the probe to the vessel and it was not difficult to interpret the measurement data.

Combining microvascular reconstruction techniques with standard primary local and regional ablative surgery has inevitably extended surgical time significantly. Currently, the majority of head and neck oncological cases requiring microvascular surgical techniques are operations that last between 8–12 h. The patient population may also present with other significant clinical conditions with the majority of patients being heavy smokers and drinkers. There is a high incidence of coincidental cardiovascular disease and age is no contraindication to surgery. In our patient population one patient was withdrawn from the study as the ECG demonstrated a significant elevation of the ST segments on commencement of the dobutamine infusion. This was despite no history of relevant cardiovascular symptoms. There is an inevitable increase in the intra-operative and post operative monitoring required in these cases, although agreement has yet to be reached as to the best clinical area in which patients should be placed immediately following surgery. If dobutamine or other inodilators are used, due consideration should be given to the relevant cardiovascular monitoring to be employed to detect early signs of myocardial ischaemia.

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