EFFECT OF DOBUTAMINE ON OXYGEN SUPPLY AND UPTAKE IN HEALTHY VOLUNTEERS

S. B. BHATT, R. C. HUTCHINSON, B. TOMLINSON, T. E. OH AND M. MAK

SUMMARY

We have measured the changes in \( V_O_2 \) and the \( V_O_2 - D_O_2 \) relationship during infusion of dobutamine in healthy volunteers. Nine healthy, adult, non-obese, male physicians were infused with an incremental infusion of dobutamine starting at 2.5 \( \mu g \) kg\(^{-1}\) min\(^{-1}\) increasing to 5.0 and then 7.5 \( \mu g \) kg\(^{-1}\) min\(^{-1}\) for 15 min each. \( V_O_2 \) and cardiac index were measured every five minutes. \( V_O_2 \) (\( L/\text{min} \)) increased from a baseline of 128 (SEM 6.1) \( L/\text{min} \cdot m^{-2} \) to 159 (8.0) \( L/\text{min} \cdot m^{-2} \) (\( P < 0.05 \)) at the end of infusion with 7.5 \( \mu g \) kg\(^{-1}\) min\(^{-1}\). The corresponding changes for \( D_O_2 \) (\( L/\text{min} \cdot m^{-2} \)) were from 643 (35) \( L/\text{min} \cdot m^{-2} \) to 1240 (142) \( L/\text{min} \cdot m^{-2} \) (\( P < 0.05 \)). The coefficient of correlation for pairs of \( V_O_2 \) and \( D_O_2 \) values, at baseline and each dobutamine infusion in individual subjects, ranged from 0.89 to 0.99 (mean 0.95, SD 0.03). Dobutamine has potent calorigenic effects: demonstration of a positive correlation between \( V_O_2 \) and \( D_O_2 \) after infusion of dobutamine does not necessarily imply an underlying tissue oxygen debt.

KEY WORDS

Oxygen consumption, delivery. Sympathetic nervous system, pharmacology, dobutamine.

A major advance in the care of critically ill patients in recent years, has been optimization of the oxygen transport variables, oxygen supply (\( D_O_2 \)) and oxygen uptake (\( V_O_2 \)) [1]. This approach appears to have reduced mortality in critically ill surgical patients and in patients with septic shock [2, 3]. Behind this approach lies the concept of "pathological" dependency of \( V_O_2 \) on \( D_O_2 \). This pathological dependency has been demonstrated in patients with ARDS [4], septic shock [5], congestive heart failure [6] and acute liver failure [7]. The increase in \( V_O_2 \) that occurs when \( D_O_2 \) is increased is seen to imply an underlying tissue oxygen debt [8, 9].

In order to demonstrate this \( V_O_2 \) dependence on \( D_O_2 \), the latter has been changed by fluid loading, red cell transfusion, vasodilators or inotropic agents, with variable results. Fluid loading appears to increase \( V_O_2 \) consistently only in patients with increased serum concentrations of lactate [10]. In contrast, inotropic agents (especially dobutamine) appear to increase \( V_O_2 \) in patients with both increased and normal blood lactate concentrations [11].

Catecholamines have a potent calorigenic effect [12]. This effect is understated in studies using these drugs to demonstrate supply dependence of oxygen uptake [13]. Consequently, in studies demonstrating \( D_O_2 \)-dependent increases in \( V_O_2 \) which use adrenergic drugs (particularly in patients with normal blood lactate), the \( V_O_2 \) increase may also reflect the calorigenic effects of these drugs, rather than an underlying tissue oxygen debt. Therefore, we have studied the effects of dobutamine infusion on \( V_O_2 \), \( D_O_2 \) and their inter-relationship, in healthy volunteers at rest, in whom there should be no underlying tissue oxygen debt.

SUBJECTS AND METHODS

The study was approved by the Research Ethics Committee of the Chinese University of Hong Kong. We studied nine healthy, non-obese, male physicians (aged 28–36 yr, mean weight 73 kg (range 52–86 kg)) who consented to participate. The study was conducted in the morning, after the subjects had fasted overnight. The subjects rested supine with minimal movement throughout the study in a room maintained at 24 °C.

I.v. cannulae were placed in antecubital veins of both forearms—for blood sampling from the left arm and for infusions in the right arm. After a 20-min period of stabilization, baseline measurements were taken and then incremental infusions of dobutamine were commenced at 2.5, 5.0 and 7.5 \( \mu g \) kg\(^{-1}\) min\(^{-1}\), with each dose lasting 15 min. After cessation of the dobutamine infusion, measurements were continued for a further 15 min.

\( V_O_2 \) was measured using the Deltatrac metabolic monitor (Datex Instrumentarium Corp., Helsinki, Finland) in its canopy mode. This is a microprocessor-controlled, indirect calorimeter which calculates oxygen consumption every 1 min. A
5-min running average was used for the purposes of computation. The Deltatrac metabolic monitor has been validated to be accurate within 4% for $\dot{V}O_2$ and 2.9% for $\dot{V}CO_2$ [14, 15] and its use has been reported under conditions similar to those of the present study [16].

Cardiac index (CI) (cardiac output per square metre body surface area) was measured using bioimpedance cardiography (BoMed NCCOM3-R7, BoMed Medical Manufacturing Ltd, Irvine, CA, U.S.A.). CI reported by the monitor is updated every 16 accepted beats. The values averaged over 1 min were used for computation. This bioimpedance cardiograph shows good agreement with other methods of measuring cardiac output in healthy subjects [17], in experimental models during infusion of inotropic drugs [18] and in critically ill patients [19].

Arterial pressure was measured every 5 min using an automated oscillometer (Dinamap, Critikon Inc., Tampa, FL, U.S.A.) and oxygen saturation was measured continuously using a pulse oximeter (Satlite, Datex Instrumentarium Corp., Helsinki, Finland).

Blood was obtained for measurement of concentrations of lactate, free fatty acids (FFA), adrenaline, noradrenaline, glucose and haemoglobin (Hb). Samples were obtained from the indwelling cannula at the end of the initial period of stabilization, at the end of each dose of infusion and 15 min after stopping the infusion of dobutamine. FFA were measured using an enzymatic method (Acyl-CoA synthetase and Acyl-CoA oxidase, Wako Pure Chemical Industries, Osaka, Japan) and plasma lactate concentration was measured also using an enzymatic method (lactate dehydrogenase, Sigma Chemical Co., St Louis, MO, U.S.A.). Plasma concentrations of adrenaline and noradrenaline were measured using high pressure liquid chromatography with electrochemical detection using a method modified from Causon, Carruthers and Rodnight [20]. The lower limit of detection was 25 pg ml$^{-1}$ and coefficient of variation was 5.70% for noradrenaline and 9.07% for adrenaline [16]. $\dot{D}O_2$ I ($\dot{D}O_2$/m$^2$ body surface area (b.s.a.)) was calculated according to the relationship:

$$\dot{D}O_2\,I = CI \times Hb \times S_pO_2 \times 13.9$$

where $S_pO_2$ = oxygen saturation (%); Hb = haemoglobin concentration (g dl$^{-1}$).

The changes in $\dot{V}O_2$ I ($\dot{V}O_2$/m$^2$ b.s.a.), $\dot{D}O_2$ I, CI, FFA, lactate and glucose from baseline and with each rate of infusion were analysed using repeated measures analysis of variance and Fisher's protected least significant difference test. $P < 0.05$ was considered significant. The apparent relationship between $\dot{D}O_2$ and $\dot{V}O_2$ was assessed according to a method outlined by Goldstein [21]. The coefficient of correlation was determined for each individual subject (using the pairs of values at baseline and each dobutamine infusion); the distribution of the coefficient of correlation obtained was used to draw inferences about the relationship between $\dot{D}O_2$ and $\dot{V}O_2$ for the population. Results are expressed as mean (SEM).

RESULTS

$\dot{V}O_2$ I increased progressively with each infusion step from a baseline of 128 (6.1) ml min$^{-1}$ m$^{-2}$ to 159.6 (8.0) ml min$^{-1}$ m$^{-2}$ at the end of 15 min of infusion with dobutamine 7.5 μg kg$^{-1}$ min$^{-1}$ (fig. 1). $\dot{V}O_2$ I at the end of each infusion period was significantly greater than baseline and the previous rate of infusion ($P < 0.05$).

$\dot{D}O_2$ I also increased progressively with each infusion step, from a baseline of 643 (35) ml min$^{-1}$ m$^{-2}$ to 1240 (142) ml min$^{-1}$ m$^{-2}$ at the end of the 15-min period of infusion with dobutamine 7.5 μg kg$^{-1}$ min$^{-1}$, $\dot{D}O_2$ I, at the end of each period of infusion was significantly greater ($P < 0.05$) than baseline and the previous rate of infusion ($P < 0.05$).

The increase in $\dot{D}O_2$ I was a result of an increase in CI, from a baseline of 3.42 (0.17) litre min$^{-1}$ m$^{-2}$ to 6.59 (0.92) litre min$^{-1}$ m$^{-2}$ at the end of the 15-min period of infusion with dobutamine 7.5 μg kg$^{-1}$ min$^{-1}$ (table I).

The increase in $\dot{D}O_2$ I following infusion of dobutamine was proportionately greater than the increase in $\dot{V}O_2$ I. The oxygen extraction ratio ($\dot{V}O_2$ I:$\dot{D}O_2$ I) decreased progressively from a baseline of 0.21 (0.19) to 0.13 (0.01) ($P < 0.05$).

The coefficient of correlation for the four pairs...
In the present study, a progressively increasing dose of dobutamine was used in preference to a randomized isolated dosing schedule, because it appeared to simulate the clinical situation more closely. It was evident from the increases in $V_{O_2}$ that, even at the modest doses used in this study, dobutamine had a significant calorigenic effect.

Fellows, Bennett and MacDonald [22] investigated the calorigenic effect of adrenaline and found that an infusion of 50 ng kg$^{-1}$ min$^{-1}$ resulted in a 23.5% increase in $V_{O_2}$. Increases in $V_{O_2}$ of a similar magnitude have been demonstrated by other investigators using adrenaline infusions [23, 24].

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Similarly, large increases in metabolic rate have been demonstrated during isoprorenaline infusions [25] and during high-dose dobutamine infusion in dogs [26]. The increase in oxygen consumption after infusion of noradrenaline appears more modest [27]. These differences are probably caused by the differential potency of catecholamines at the alpha and beta adrenoceptors, or may reflect the limited effect of circulating noradrenaline compared with its activity at nerve terminals [23]. The calorigenic response appears to be mediated predominantly via beta adrenergic receptors [28], and it follows that dobutamine, a beta agonist would have a calorigenic effect. This was confirmed in the present study. A modest dose of dobutamine 7.5 μg kg$^{-1}$ min$^{-1}$ resulted in an increase in $V_{O_2}$ from 128 (6) ml min$^{-1}$ m$^{-2}$ to 159 (8) ml min$^{-1}$ m$^{-2}$.

Svedmyr [24], in a study of the calorigenic effect of adrenaline, found that increased FFA turnover (breakdown of triglycerides to FFA and the resynthesis of triglycerides) contributed to about 30% of the calorigenesis. In the present study with dobutamine infusion, a similar large increase in FFA occurred (from 457.6 (58.9) μmol litre$^{-1}$ to 1284 (132.2) μmol litre$^{-1}$). It would be reasonable to assume that this increased FFA turnover contributed, at least in part, to the increase in $V_{O_2}$. Moreover, investigation into the calorigenic effect of adrenaline suggested that a significant proportion of this calorigenesis may have been caused by increased lactate mobilization [24]. However, in the present

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**Table I. Changes in various variables from baseline during and after infusion of dobutamine (mean (SEM)).** $P < 0.05$: *compared with baseline; †compared with preceding rate of infusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>2.5</th>
<th>5.0</th>
<th>7.5</th>
<th>After infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beat min$^{-1}$)</td>
<td>62 (2.6)</td>
<td>60.7 (2.3)</td>
<td>68.3 (3.9)</td>
<td>84.9 (6.4)†</td>
<td>68.38 (3.8)†</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>118 (2)</td>
<td>142 (4)*</td>
<td>157 (5)†</td>
<td>171 (4)*†</td>
<td>122 (3)†</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>71 (1)</td>
<td>76 (2)*</td>
<td>74 (3)†</td>
<td>75 (1)†</td>
<td>69 (2)†</td>
</tr>
<tr>
<td>Cardiac index (litre min$^{-1}$ m$^{-2}$)</td>
<td>3.42 (0.17)</td>
<td>4.66 (0.4)</td>
<td>5.87 (0.66)†</td>
<td>6.59 (0.92)†</td>
<td>3.57 (0.25)†</td>
</tr>
<tr>
<td>Oxygen extraction ratio</td>
<td>0.21 (0.02)</td>
<td>0.17 (0.02)*</td>
<td>0.15 (0.02)*</td>
<td>0.13 (0.01)*</td>
<td>0.20 (0.02)†</td>
</tr>
<tr>
<td>Blood glucose (mmol litre$^{-1}$)</td>
<td>4.6 (0.1)</td>
<td>4.6 (0.1)</td>
<td>4.4 (0.2)†</td>
<td>4.3 (0.13)*</td>
<td>4.5 (0.1)†</td>
</tr>
<tr>
<td>Plasma adrenaline (μg ml$^{-1}$)</td>
<td>32 (3)</td>
<td>30 (3)</td>
<td>41 (10)†</td>
<td>44 (5)</td>
<td>54 (6)</td>
</tr>
<tr>
<td>Plasma noradrenaline (μg ml$^{-1}$)</td>
<td>141 (29)</td>
<td>76 (13)*</td>
<td>98 (10)*</td>
<td>96 (9)*</td>
<td>128 (0.4)</td>
</tr>
<tr>
<td>Plasma lactate (mmol litre$^{-1}$)</td>
<td>1.4 (0.1)</td>
<td>1.3 (0.1)*</td>
<td>1.2 (0.1)*</td>
<td>1.2 (0.1)*</td>
<td>1.3 (0.1)†</td>
</tr>
</tbody>
</table>

**Fig. 2. Changes in plasma free fatty acid (FFA) during dobutamine infusion.** Before = Before infusion; After = after infusion. $P < 0.05$: *compared with baseline; †compared with preceding dose of dobutamine.
study, plasma lactate concentration decreased significantly after commencement of dobutamine infusion and remained less than the baseline value for the duration of the infusion. Thus the contribution of lactate metabolism to the calorigenic effect of dobutamine was unclear. Other possible causes for the calorigenic effect are stimulation of the Na⁺-K⁺-ATPase pump, the increased cardiac work and increased respiratory work.

Recent advances in the care of the critically ill have suggested that optimization of $D_O$ and $V_O$ may be an important therapeutic aim. Such management appears to have reduced mortality in post-surgical patients [2] and in patients with septic shock [3], and is based on the concept of “pathological” dependency of $V_O$ on $D_O$. This dependency has been demonstrated in a wide variety of clinical states and is seen to imply an underlying tissue oxygen debt [9]. Bihari and colleagues [8] even suggest that demonstration of such a relationship could be used to identify a “covert” oxygen debt. However, in their study, none of the survivors demonstrated an oxygen supply-dependent increase in oxygen uptake when oxygen supply was manipulated by infusion of prostacyclin.

Fluid loading and blood transfusions increase $V_O$ only in patients with increased plasma concentrations of lactate [10]. Manipulating ventilatory variables to change $D_O$ does not consistently change $V_O$ in the same direction [29, 30]. However, infusion of catecholamines appears to increase $V_O$ consistently, whether or not the plasma concentration of lactate is increased [11]. The suspicion that this increase in $V_O$ may be the inherent pharmacological effect of the catecholamine has been raised, although usually underplayed [31]. It has been stated, in studies using catecholamines to demonstrate the $V_O$: $D_O$ relationship, that the inherent calorigenic effect of these drugs is small [13]. In the present study, despite the modest dose of dobutamine used, significant increases in $V_O$ were observed.

The magnitude of increase in $V_O$ recorded in healthy volunteers in the present study is similar to that demonstrated in critically ill patients. Shoemaker, Appel and Kram [9] administered dobutamine in a graded infusion to a group of post-operative, septic and terminally ill patients. $V_O$ increased from 131 (33) ml min⁻¹ m⁻² to 157 (44) ml min⁻¹ m⁻². Similarly, Schwenzer and Kopel [32] infused dobutamine at 10 μg kg⁻¹ min⁻¹ and found that $V_O$ increased from 110 (6) ml min⁻¹ m⁻² to 148 (12) ml min⁻¹ m⁻². In the present study, $V_O$ increased from 128 (6) ml min⁻¹ m⁻² to 159 (8) ml min⁻¹ m⁻² at the end of 15 min infusion with dobutamine 7.5 μg kg⁻¹ min⁻¹.

The proportionately greater increase in $D_O$ compared with $V_O$, leading to a decrease in oxygen extraction ratio from 0.21 (0.02) to 0.13 (0.13) is consistent with the decrease shown during infusion of adrenaline in septic shock [33] and during infusion of dobutamine in patients with sepsis and heart failure [34].

In the present study, we found a positive correlation ($r$: mean 0.95, SD 0.03, range 0.89–0.99) (fig. 3) between $V_O$ and $D_O$ in subjects who were healthy, at rest and presumably without an underlying tissue oxygen debt. The demonstration of such a positive correlation in healthy volunteers at rest, therefore, points merely to an association between $D_O$ and $V_O$, rather than a “pathological” supply dependence of $V_O$.

The increase in CI (from 3.42 litre min⁻¹ m⁻² to 6.59 litre min⁻¹ m⁻²) in the present study was greater than that reported in critically ill patients during a similar dobutamine infusion (from 3.41 litre min⁻¹ m⁻² to 4.81 litre min⁻¹ m⁻²) [34]. Thus it is possible that a larger proportion of the increase in $V_O$ in the present study was a result of the increase in myocardial oxygen consumption ($V_{m_o}$). However, the fractional contribution of $V_{m_o}$ to $V_O$ at rest is small (9.0 ml/100 g left ventricular mass min⁻¹) [35]. The stroke work component of $V_{m_o}$ that would be most affected by the larger increase in CI, contributes to only a small fraction (10–15%) of resting $V_{m_o}$ [35]. Furthermore, persuasive evidence has been advanced regarding the catecholamine-induced calorigenesis being a metabolic effect of substrate cycling [24, 36].

It is possible also that the metabolic effects of dobutamine (or other adrenergic inotropic agents) are fundamentally different in critically ill patients compared with normal healthy volunteers. This has not been established, however. Vincent and coworkers [31], using an infusion of dobutamine 5 μg kg⁻¹ min⁻¹, found significant increases in $V_O$ only in patients with lactic acidosis. They concluded that an increase in $V_O$ distinguished patients with and without underlying tissue hypoxia. These authors recognized the inherent calorigenic effect of adrenergic agents, but hypothesized that the lack of increase in $V_O$ in critically ill patients, without lactacidosis, was probably because the endogenous catecholamine response was turned down when adrenergic agents were infused. In support of this contention, they cited evidence from Colucci and colleagues [37], who infused dobutamine into the coronary circulation of patients with heart failure and found a dose-dependent decrease in the plasma concentration of noradrenaline. However, the maximum decrease in plasma noradrenaline was only 160 (31) ng litre⁻¹. The calorigenic consequences of a
change in plasma noradrenaline of this magnitude are known to be small [23].

We have found concomitant increases in both $\dot{V}O_2$ and $DO_2$, with a strong positive correlation between the two variables, after infusing dobutamine into healthy volunteers at rest. While we do not dispute that optimization of $\dot{V}O_2$ and $DO_2$ is beneficial and may reduce mortality in critically ill patients, we do emphasize that demonstration of a positive correlation between $DO_2$ and $\dot{V}O_2$ arising from dobutamine (or other adrenergic inotropic agents) does not necessarily imply either an underlying tissue oxygen debt or a pathological supply-dependence of oxygen uptake.

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