The effects of dobutamine and dopamine on intrapulmonary shunt and gas exchange in healthy humans

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ABSTRACT
The development of intrapulmonary shunts with increased cardiac output during exercise in healthy humans has been reported in several recent studies, but mechanisms governing their recruitment remain unclear. Dobutamine and dopamine are inotropes commonly used to augment cardiac output; however, both can increase venous admixture/shunt fraction (Qs/Qt). It is possible that, as with exercise, intrapulmonary shunts are recruited with increased cardiac output during dobutamine and/or dopamine infusion that may contribute to the observed increase in Qs/Qt. The purpose of this study was to examine how dobutamine and dopamine affect intrapulmonary shunt and gas exchange. Nine resting healthy subjects received serial infusions of dobutamine and dopamine at incremental doses under normoxic and hyperoxic (FIO2=1.0) conditions. At each step alveolar-to-arterial PO2 difference (A-aDO2) and Qs/Qt were calculated from arterial blood gas samples, intrapulmonary shunt was evaluated using contrast echocardiography, and cardiac output was calculated by Doppler echocardiography. Both dobutamine and dopamine increased cardiac output and Qs/Qt. Intrapulmonary shunt developed in most subjects with both drugs and paralleled the increase in Qs/Qt. A-aDO2 was unchanged due to a concurrent rise in mixed venous oxygen content. Hyperoxia consistently eliminated intrapulmonary shunt. These findings contribute to our current understanding of the mechanisms governing recruitment of these intrapulmonary shunts, as well as of their impact on gas exchange. In addition, given the deleterious effect on Qs/Qt and the risk of neurologic complications with intrapulmonary shunts, these findings could have important implications for use of dobutamine and dopamine in the clinical setting.

Word count: 245

Keywords: inotropes, shunt, gas exchange
Introduction

The recruitment of intrapulmonary (I-P) shunts during exercise has been a topic recent interest(4, 19-21, 41, 42). Studies using both contrast echocardiography(4, 20, 41, 42) and $^{99m}$Tc macroaggregated albumin(19) suggest that exercise opens previously closed large diameter vessels (i.e. I-P shunt vessels) within the pulmonary vasculature which would allow particles, that would otherwise be trapped in the normal pulmonary capillaries, to bypass the capillary network.

Morphologic studies documenting I-P shunts in previously healthy human cadavers(43, 44), the passage of microspheres through healthy human lungs(22), and the demonstration of similar inducible shunts in healthy exercising dogs(40) support the human exercise data. The anatomic basis and physiologic significance of these I-P shunts, especially with regards to their impact on gas exchange, remains unclear(9, 10, 17, 18), as do the mechanisms governing their recruitment.

Both Stickland et al., and La Gerche et al., demonstrated an association between I-P shunt recruitment and cardiac output during exercise(15, 42), but it is unclear whether the increase in cardiac output per se results in I-P shunt recruitment, or if the I-P shunts are an adaptive mechanism to decrease right ventricular afterload, thus allowing for greater augmentation of cardiac output(42).

Dobutamine and dopamine are inotropes commonly used to increase cardiac output, but both agents can have a detrimental effect on pulmonary gas exchange. In critically ill human subjects both inotropes have been shown to increase venous admixture/shunt fraction (Qs/Qt)(28, 31) and impair ventilation-perfusion ($V_a/Q$) matching, while an increase in true right-to-left shunt (i.e. $V_a/Q = 0$), as demonstrated by the retention of inert gas, has been observed with dopamine(31).

Of note, these studies were typically conducted on patients in intensive care, and therefore the effect of these inotropes on humans with healthy cardiopulmonary function is unclear. Given the association between I-P shunt recruitment and cardiac output during incremental exercise, it is possible that I-P shunts are similarly recruited with increases in cardiac output due to dobutamine and/or dopamine infusion, negatively affecting gas exchange.
The purpose of this study was to investigate the effects of dobutamine and dopamine on intrapulmonary shunts, as assessed by contrast echocardiography, in healthy humans. It was hypothesized that both drugs would result in the recruitment of I-P shunt with a corresponding impairment in gas exchange, measured by the alveolar to arterial P\(_{O_2}\) difference (A-aD\(_{O_2}\)) and shunt fraction (Qs/Qt).

**METHODS**

The study received approval from the University of Alberta Health Research Ethics Board and all participants provided written informed consent to participate.

*Subjects*

Eleven healthy subjects without evidence of active cardiopulmonary disease on history, physical exam, pulmonary function tests, and screening cardiopulmonary exercise tests were enrolled. Two subjects with a significant intra-pulmonary shunt (shunt score > 1, see below) on screening contrast echocardiogram were excluded. The final sample included 9 subjects (6 male; 25-36 years) with mean (+/-SD) baseline characteristics: Forced expiratory volume in first second (FEV\(_1\)): 4.2(0.8)L [104(13)% predicted], FEV\(_1\)/FVC: 78(12), lung diffusion capacity for carbon monoxide (DL\(_{CO}\)) (seated): 35(6)mL/mmHg/min [112(12)% predicted], and maximum oxygen consumption: 52(11)mL/kg/min.

*Experimental trial*

**Subject preparation.** A standard intravenous (IV) catheter (Smiths Medical Canada Ltd, Markham, ON) was inserted into an antecubital vein and attached via 6-inch extension tubing to two three-way stopcocks. The proximal stopcock was used for inotrope infusion, the distal stopcock for agitation/injection of saline contrast for contrast echocardiography. An 18-gauge angiocatheter (Becton-Dickinson, Mississauga, ON) was then inserted into the ipsilateral radial
artery using local anesthesia (1% lidocaine HCl, AstraZeneca, Mississauga, ON). Patency of the arterial catheters was maintained with a pressurized flush system of normal saline.

**Experimental protocol.** The entire protocol was performed with the subjects at rest in the supine position. Baseline control data were obtained after the subject had been resting for 5 or more minutes. 100% O₂ was then administered for 2 minutes using a non-rebreathing valve (Hans-Rudolph, 2700, Shawnee, KS), with data collection repeated 1 minute into hyperoxia. Following a return to room air the first inotrope infusion (dobutamine or dopamine) was initiated. The order of drug administration was randomly determined. Incremental inotrope doses were administered using an automatic IV infusion pump (Alaris, San Diego): dopamine HCl (Hospira, Lake Forest, IL) at 2, 6, and 10μg/kg/min, and dobutamine (Sandoz Canada, Quebec) at 2.5, 5, and 10μg/kg/min. After a 4-minute wash-in period on the lowest dose to account for IV dead space, inotropes were infused for 5 minutes at each stage prior to data collection to ensure a steady-state. Following data collection at each stage on room air, subjects breathed 100% O₂ for 2 minutes with measurements repeated 1 minute into the hyperoxia. Hyperoxia was then discontinued and the dose of the drug was increased. After completing the first inotrope infusion a 20-minute wash-out period was given before initiating the second infusion, as both drugs have a reported half-life less than 10 minutes.

**Cardiorespiratory and body temperature measures**
Respiratory gas-exchange data was collected using a metabolic measurement system (Encore229 Vmax, SensorMedics, Yorba Linda, CA). DL_{CO} was determined at baseline and on the highest dose of each inotrope using the single-breath breath-holding method (Encore V62J Autobox, SensorMedics, Yorba Linda, CA). Arterial blood samples were drawn from the arterial catheter and analyzed immediately (ABL800 FLEX Radiometer, Loveland, CO) with correction for temperature, measured by a core temperature pill (VitalSense, Bend, OR) ingested at the start of the trial. Alveolar P_{O2} (PA_{O2}) was calculated using the alveolar gas equation [PA_{O2}=F_{O2}×(P_{B-}}
\[ \text{P}_{\text{H2O}} - (\text{PaCO}_2/RQ) + F_{\text{I}2} \times \text{PaCO}_2 \times (1-R)/R \] with water vapor pressure corrected for temperature.

Standard formulas were used to calculate alveolar to arterial \( P_{O2} \) difference (A-a\( P_{O2} \)) and shunt fraction (Qs/Qt). Of note, to account for any change in alveolar ventilation affecting Qs/Qt, end-capillary oxygen content (Cc\( O2 \)) for each condition was calculated assuming end-capillary \( P_{O2} \) was equivalent to alveolar \( P_{O2} \) at that condition. Central venous oxygen content (Cv\( O2 \)) was calculated using the Fick equation (\( V_{O2} = Q \times [C_{aO2} - C_{vO2}] \)) with measured values for oxygen consumption (\( V_{O2} \)) and arterial oxygen content (C\( aO2 \)), and calculated values for cardiac output (Q).

Echocardiograms were performed by one experienced sonographer (Vivid 7, GE) and recorded onto DVDs that were later analyzed in triplicate by a cardiologist who was blinded to experimental conditions. Stroke volume (SV) was calculated using the average of five consecutive measured velocity time integrals (VTI) in the left ventricular outflow tract (LVOT): SV = LVOT x VTI. Cardiac output (Q) was then calculated as the product of SV and heart rate. To estimate LV systolic function, fractional shortening (FS) was calculated using LV end diastolic (LVED) and end systolic (LVES) dimensions obtained from the parasternal long axis view (FS = [LVED-LVES]/LVED x 100). Pulmonary artery systolic pressure (PASP) was estimated by adding the trans-tricuspid pressure gradient (TR gradient) and the right atrial pressure (RAP). Trans-tricuspid pressure gradient (TR gradient) was estimated from the tricuspid regurgitation velocity (TR gradient = 4 x Tricuspid regurgitation velocity\(^2\)), and right atrial pressure (RAP) using the inspiratory collapse of the inferior vena cava (IVC)(29). In cases where the tricuspid regurgitation jet was suboptimal agitated saline contrast was injected through the antecubital IV catheter to enhance the signal.

**Contrast echocardiography**

The agitated saline contrast echocardiography technique was used to detect intra-cardiac and intra-pulmonary shunt. Standard procedures were employed for the injection of solution(48).
Briefly, 10mL of saline was combined with 0.5mL of air and the solution forcefully agitated through a three-way stopcock between two syringes to form fine suspended bubbles which are generally much larger than the pulmonary capillaries. The solution was injected through the antecubital intravenous catheter while the sonographer imaged all four chambers of the heart. Intra-cardiac shunt was determined by contrast appearance in the LV in less than five cardiac cycles; LV contrast after ≥ 5 cardiac cycles suggests I-P shunt.

Representative saline contrast echocardiograms performed on a subject during incremental dobutamine infusion are shown in Figure 1. I-P shunt was qualitatively scored based on a modification of a previously described scoring system. No contrast bubbles in the left ventricle in any frame received a score of 0, ≤ 3 bubbles a score of 1, 4-12 bubbles a score of 2, and > 12 bubbles a score of 3. For the purpose of our study we considered a shunt score > 1 “significant” shunt, consistent with studies showing small I-P shunt (1-4 bubbles) in up to 25% of healthy subjects, compared to only 3% with moderate or larger shunt (≥ 5 bubbles). High intra-observer reliability of contrast echocardiography during high cardiac output conditions has been previously demonstrated, and periodic reviews of the images by the cardiologist in the current study confirmed consistent scoring.

Statistical analysis

For all inferential analyses, the probability of type I error was set at 0.05. Group data for each variable are expressed as means ± SE. Data were analyzed with a two-way repeated measures ANOVA. Where main effects were found, Fisher least significant difference post hoc tests were used.

RESULTS

Dobutamine

Cardiac response:
Grouped hemodynamic responses are presented in Table 1 and Figures 2&3. Dobutamine increased Q and PASP above baseline at doses ≥5μg/kg/min. SV increased at all stages of dobutamine infusion, whereas a significant increase in heart rate and fractional shortening was seen only at the highest dose.

Pulmonary gas exchange and physiologic shunt:
Group gas exchange and mixed venous data are shown in Table 2. Gas exchange, as assessed by A-aDO2, did not change with dobutamine infusion. There was a small, but significant increase in VO2 from baseline at 5 and 10μg/kg/min. As there was a greater proportional increase in Q relative to VO2 at 10μg/kg/min, calculated CVo2 was increased from baseline. Qs/Qt was increased from baseline at all stages of dobutamine infusion (Figure 2).

I-P shunt
The effect of incremental dobutamine on individual I-P shunt, and peak individual shunt score during dobutamine infusion are shown in Figures 4&5, respectively. An increase in shunt score was seen in all subjects, with 8 of 9 subjects demonstrating significant shunt (Figure 5). Mean shunt score was increased from baseline at all stages of dobutamine infusion (Figures 2&3); grouped data indicate that the increase in shunt score parallels the increase in Q, PASP, and Qs/Qt (Figures 2&3).

Hyperoxia:
Hyperoxia consistently eliminated significant I-P shunt at all stages of dobutamine infusion (mean shunt score <1). Q was decreased across all doses by an average of 901mL/min (p<0.01) with hyperoxia. No consistent change was seen in PASP with hyperoxia.

Dopamine
Cardiac response:
Grouped hemodynamic responses are presented in Table 1 and Figures 2&3. A significant increase in Q and SV from baseline was observed only at the highest dose of dopamine (10μg/kg/min), whereas no change was seen in heart rate or fractional shortening. PASP did not change significantly with dopamine infusion (Figure 3).

**Pulmonary gas exchange and physiologic shunt:**

Gas exchange, as assessed by A-aD O₂, did not change with dopamine infusion (Table 2). Low dose dopamine (2μg/kg/min) resulted in hypoventilation (increased PaCO₂, decreased PaO₂), an effect that was not seen at the highest dose. CvO₂ increased from baseline at the highest dose of dopamine. An increase in Qs/Qt from baseline was seen at all stages of dopamine infusion (Figure 2).

**I-P shunt:**

The effects of dopamine infusion on individual I-P shunt and peak individual shunt score are shown in Figures 4&5, respectively. An increase in I-P shunt score occurred in all subjects during dopamine infusion, with 5 of 9 subjects developing significant I-P shunt (Figure 5). Mean shunt score was increased from baseline at all stages of dopamine infusion and paralleled the increase in Qs/Qt (Figure 2). Of note, two subjects developed significant shunt with low dose (2-6μg/kg/min) dopamine that was not seen at higher doses (10μg/kg/min). In addition, low dose dopamine (2-6μg/kg/min) caused a significant increase in mean shunt score without a corresponding increase in Q or PASP (Figure 3).

**Hyperoxia:**

Hyperoxia consistently eliminated significant I-P shunt in all subjects (mean shunt score=0). Q was decreased by an average of 426mL/min (p=0.03) across all doses with hyperoxia. No change in PASP was observed with hyperoxia.
DISCUSSION

This study examined the effects of dobutamine and dopamine on gas exchange, Qs/Qt and I-P shunt. The majority of subjects developed significant I-P shunt, as assessed by agitated saline contrast echocardiography, during inotrope infusion with a corresponding increase in Qs/Qt. These results suggest that the recruitment of I-P shunts with increasing cardiac output may be contributing to the increase in Qs/Qt commonly observed with inotropic agents.

The increase in Qs/Qt during drug infusion in this study is in keeping with previous studies in patients demonstrating an increase in shunt fraction with increased Q during both dopamine(12, 14, 31) and dobutamine(28, 31) infusions. The correlation between Qs/Qt and Q has also been observed in pigs(34) and in dogs when Q was altered by both pharmacological and non-pharmacological means(23, 38). While it is generally accepted that Qs/Qt may worsen with increased Q during inotrope infusion, the effects of dopamine and dobutamine on Qs/Qt and I-P shunt in healthy humans with normal cardiopulmonary function have not been previously examined.

The development of I-P shunt with increased Q in this study is consistent with previous studies demonstrating I-P shunt recruitment during conditions associated with increased Q, such as exercise(4, 40-42) or hypoxia(20). In this study the hemodynamic responses and pattern of I-P shunt recruitment (and correspondingly the Qs/Qt response) differed between the two inotropes. Dobutamine had a more pronounced effect on both Q and PASP, and the increase in mean shunt score and Qs/Qt appeared to parallel the increase in Q and PASP (Figures 2&3). In contrast, mean shunt score and Qs/Qt increased during dopamine infusion without a significant change in PASP, and low dose dopamine (2-6μg/kg/min) caused an increase in mean shunt score and Qs/Qt with little change in Q. The divergent response observed with dobutamine versus dopamine suggests that I-P shunt recruitment may be occurring via different mechanisms with these two inotropes.
Mechanism of I-P shunt recruitment:

The ability of the pulmonary vasculature to limit right ventricular afterload despite large
increases in Q has been attributed to a drop in pulmonary vascular resistance (PVR) through the
classic flow-dependent mechanisms of capillary distension(6) and recruitment(46). The
association between I-P shunt, Qs/Qt and increased Q in the current and previous studies suggests
a similar flow dependent mechanism in I-P shunt recruitment. Several investigators, however,
have suggested that dobutamine and/or dopamine may have direct vasodilatory effects on the
pulmonary vasculature that could also contribute to the development of I-P shunt. Dobutamine
has a variable effect on PVR in humans(28, 36, 50), but when pulmonary blood flow is kept
constant during dobutamine infusion, PVR does not appear to change(16). The effect of
dopamine on PVR has also been variable in human(12, 14, 28, 31, 36, 50) and animal(5, 16, 27)
studies. However, unlike dobutamine, which stimulates mainly beta1-adrenergic receptors(2), the
physiologic effect of dopamine is dose-dependent: low dose dopamine acts mainly on
dopaminergic (vasodilatory) receptors while moderate to high doses affect beta1- and alpha-
adrenergic receptors(2). Dopamine receptors have been identified within the pulmonary
vasculature(32), and dopaminergic stimulation causes pulmonary arterial relaxation that is
attenuated by dopamine antagonists(11, 30). In the current study the linear relationship between
mean I-P shunt score, Qs/Qt and Q during dobutamine infusion supports a flow-dependent
mechanism of shunt recruitment, similar to normal pulmonary capillary recruitment. In contrast,
low dose dopamine increased mean shunt score and Qs/Qt without changing Q, and two subjects
developed significant I-P shunt with low dose dopamine that was not seen at higher doses. This
suggests that dopamine may be affecting I-P shunt through flow-independent means, possibly via
dopaminergic receptors within the pulmonary circulation that would be activated by low dose
dopamine. Of note, increased levels of circulating dopamine have been observed during exercise
in humans(8); it is possible, therefore, that dopamine-mediated pulmonary vasodilation is
contributing to the recruitment of previously closed I-P shunt vessels during exercise, supporting
the theory that these vessels are anatomically distinct from the normal pulmonary capillary network. Further studies are needed to determine the role of dopaminergic receptors in I-P shunt recruitment.

Consistent with the findings of Lovering et al (21), hyperoxia consistently eliminated significant I-P shunt. As in previous studies (7), Q decreased with hyperoxia due to the increase in CaO₂ allowing for a lower Q to maintain the same oxygen delivery. While the reduction in Q could in part explain the decrease in I-P shunt, significant shunt was seen at a similar cardiac output under normoxic conditions, suggesting that hyperoxia is affecting I-P shunt through additional flow-independent mechanisms. The means by which oxygen tension alters I-P shunt recruitment remains unclear and warrants further investigation.

**Implications:**
The physiologic significance of these inducible I-P shunts and their impact on gas exchange remains highly controversial (9, 10, 17, 18). In the present study a detrimental effect on gas exchange was suggested by the parallel increase in Qs/Qt and mean I-P shunt score; however, ventilation and perfusion were not measured and thus, the extent to which V̇ₐ/Q̇ mismatch affected Qs/Qt cannot be determined. Increased cardiac output during inotrope infusion can result in increased flow to poorly ventilated regions (low V̇ₐ/Q̇) (25, 31), which alone could explain the increase in Qs/Qt observed during dobutamine and dopamine infusion. However, in contrast to earlier work, this study examined the effects of dobutamine and dopamine on Qs/Qt in healthy subjects in whom low V̇ₐ/Q̇ regions would be expected to be minimal, and demonstrated a parallel increase in Qs/Qt and I-P shunt. Further, previous exercise studies in healthy subjects have suggested a relationship between I-P shunt recruitment and worsening A-aDO₂ (20, 42), lending support to the theory that the I-P shunts are contributing to impaired gas exchange. Of note, although in the current study a parallel increase in Qs/Qt and mean shunt score was observed, A-aDₐO₂ did not increase. The lack of effect on A-aD₂O can be explained by the
increase in \(CvO_2\) secondary to increased cardiac output with dobutamine and dopamine infusion and thus a reduction in the ‘entrance difference’ (i.e. \(PA_{O2} - PvO2\)), which by itself would decrease A-aDO\(_2\)(35). Alternately, or in addition, rather than functioning as true right-to-left shunts (\(V_A/Q=0\)) these vessels may participate in limited gas exchange(39).

Whether pure venous admixture (true right-to-left shunt) occurs with these drugs remains unclear. Russell et al.(34) showed an increase in \(Qs/Qt\) with both dobutamine and dopamine in pigs ventilated with 100% \(O_2\). Importantly, 100% \(O_2\) would abolish the effect of diffusion limitation and low \(V_A/Q\) lung units on \(Qs/Qt\), indicating that the increase in \(Qs/Qt\) is instead the result of right-to-left shunt. Further, an increase in true shunt (\(V_A/Q=0\)), as measured by inert gas techniques, has been seen with dopamine infusion in critically ill patients(31). Combined, these observations would suggest that pure right to left shunt may develop with these drugs; however, further studies in healthy subjects using concurrent inert gas techniques are needed.

In addition to gas exchange, the pulmonary vasculature plays an important role as a biological sieve to prevent various venous emboli from entering the systemic circulation. As an example, patients with known pulmonary arteriovenous malformations are at increased risk of paradoxical thrombotic and septic emboli(37). ICU patients, who often receive inotropes as part of clinical care, are also at increased risk of neurologic complications including ischemic stroke(1) and intracerebral infection(13). Although a specific relationship to inotrope use has not been studied in these patients, the recruitment of I-P shunt with dobutamine and/or dopamine could have important repercussions on the efficacy of the lung as a biological filter.

**Methodological considerations:**

Agitated saline contrast echocardiography is a standard technique used to assess intra-cardiac and intra-pulmonary shunt with high intra- and inter-observer reliability both at rest and during exercise(15, 42). However, it has several major limitations that have been addressed at length in
previous studies (4, 20, 42). While contrast grading scales have been proposed for research
purposes (15, 21), the technique is not fully quantitative. Because the exact size of the contrast
bubbles is unknown, small bubbles passing through normal pulmonary capillaries could appear in
the LV; however this is unlikely given that bubbles < 10μm in diameter survive less than
200msec in static blood (26), and in nonstatic conditions would dissolve faster due to increased
fluid pressure (45) and flow velocity (51). Even during intense exercise mean pulmonary capillary
transit time does not fall below 450msec (47), making it highly unlikely that bubbles small
enough to pass through normal pulmonary capillaries would survive long enough to be visualized
in the LV during inotrope infusion. Physiologic capillary distension due to increased perfusion
pressure could allow larger bubbles to traverse the pulmonary circulation. However, Glazier et
al. (6) demonstrated that even with perfusion pressures up to 100cmH2O maximum capillary
diameter did not exceed 13μm, making this an unlikely explanation for the appearance of LV
contrast. Increased perfusion pressures could also cause deformation of larger contrast bubbles
that would allow for their passage through normal pulmonary capillaries, but Roelandt
demonstrated that even with injection through a firmly wedged Swan-Ganz catheter, an injection
pressure of 300mmHg, much higher than any physiologic PASP, was needed to observe contrast
in the LV (33). As noted above, we saw I-P shunt with low-dose dopamine without a
corresponding increase in PASP or Q, thus arguing against the appearance of LV contrast as a
result of increased perfusion pressure causing either capillary distension or bubble deformation.

Finally, another limitation of this study lies in the inherent difficulty of estimating PASP from
noninvasive measures (3); ideally, a Swan-Ganz catheter would be inserted to provide the most
accurate measurement of pulmonary vascular pressures.

**Conclusion**

Both dobutamine and dopamine resulted in the development of significant I-P shunt in the
majority of normal subjects with a parallel increase in shunt fraction. The pattern of I-P shunt
recruitment during dobutamine versus dopamine infusion, as well as the effect of hyperoxia, suggests that both hemodynamic and non-hemodynamic mechanisms may be contributing to shunt recruitment. These findings add to our understanding of the various mechanisms controlling the recruitment of these inducible I-P shunts, and the impact of these shunt vessels on gas exchange. As well, they further illuminate the effects of dobutamine and dopamine in humans, and offer a possible explanation for the increase in Qs/Qt commonly observed during inotrope infusion. Given the effect on Qs/Qt as well as the increased risk of neurologic complications with I-P shunt, these findings could also have important implications for use of these inotropes in critically ill patients.
Author contributions:

All authors contributed to the conception and design of the experiments, as well as the drafting and revision of the manuscript. T. Bryan, M.K. Stickland, S. Van Diepen, and M. Bhutani lead on the data collection, analysis and interpretation of the data.

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REFERENCES:


34. Russell WJ, and James MF. The effects on arterial haemoglobin oxygen saturation and on shunt of increasing cardiac output with dopamine or dobutamine during one-lung ventilation. *Anaesthesia and intensive care* 32: 644-648, 2004.


37. Shovlin CL, Jackson JE, Bamford KB, Jenkins IH, Benjamin AR, Ramadan H, and Kulinskaya E. Primary determinants of ischaemic stroke/brain abscess risks are independent of...
severity of pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia.


FIGURE CAPTIONS:

Figure 1: Representative saline contrast echocardiograms on a 35-year-old subject at baseline and during incremental drug (dobutamine) infusion.
Top panel: echocardiograms at baseline. A) pre-contrast; B) < 5 cardiac cycles; C) > 5 cardiac cycles. No intra-cardiac/pulmonary shunt visualized.
Bottom panel: echocardiograms during drug infusion. D) 2.5μg/kg/min (shunt score =1); E) 5μg/kg/min (shunt score = 2), F) 10μg/kg/min (shunt score = 3).

Figure 2: Mean (+/- SEM) physiologic shunt fraction (Qs/Qt) and intra-pulmonary shunt as assessed by contrast echocardiography (shunt score) in relation to cardiac output at baseline and during incremental dobutamine (left) or dopamine (right) infusion.
NOTE: * p<0.05 vs. baseline for shunt fraction / shunt score, # p<0.05 for cardiac output.

Figure 3: Mean (+/- SEM) intra-pulmonary shunt score in relation to pulmonary artery systolic pressure (left) and cardiac output (right) at baseline and during inotrope infusion.
NOTE: * p<0.05 vs. baseline for shunt score, # p<0.05 for PASP/cardiac output.

Figure 4: The effect of incremental drug infusion on intra-pulmonary shunt score. Dobutamine left, dopamine right.

Figure 5: The effect of incremental drug infusion on peak individual shunt score. Dobutamine left, dopamine right. Dotted lines represent mean shunt score.
NOTE: * p<0.05 vs. baseline
Table 1: Mean hemodynamic responses at baseline and during drug infusion (n=9)

<table>
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<th>Baseline</th>
<th>Dobutamine (μg/kg/min)</th>
<th>Baseline</th>
<th>Dopamine (μg/kg/min)</th>
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NOTE: standard error values are in parentheses. * p < 0.05 versus baseline (no drug).
Table 2: Mean gas exchange and mixed venous data at baseline and during drug infusion (n=9)

<table>
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<tr>
<th></th>
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<th>Dobutamine (μg/kg/min)</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2.5</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>PaO2 (mmHg)</td>
<td>85 (2)</td>
<td>87 (1)</td>
<td>90 (2)</td>
<td>92* (2)</td>
</tr>
<tr>
<td>SaO2 (%)</td>
<td>97 (0.3)</td>
<td>97 (0.3)</td>
<td>97* (0.2)</td>
<td>98* (0.3)</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>37 (0.7)</td>
<td>37 (1)</td>
<td>36 (1)</td>
<td>34* (1)</td>
</tr>
<tr>
<td>A-aDO2 (mmHg)</td>
<td>4.6 (0.9)</td>
<td>6.0 (0.7)</td>
<td>4.7 (0.3)</td>
<td>5.2 (1.3)</td>
</tr>
<tr>
<td>DLCO (mL/min/mmHg)</td>
<td>40 (2)</td>
<td>N/A</td>
<td>N/A</td>
<td>38 (2)</td>
</tr>
<tr>
<td>VO2 (L/min)</td>
<td>0.32 (0.01)</td>
<td>0.34 (0.01)</td>
<td>0.38* (0.02)</td>
<td>0.37* (0.01)</td>
</tr>
<tr>
<td>CV02 (mL O2/dL)</td>
<td>12.1 (0.8)</td>
<td>12.4 (0.6)</td>
<td>12.6 (0.6)</td>
<td>13.7* (0.6)</td>
</tr>
</tbody>
</table>

NOTE: Standard error values are in parentheses. *p < 0.05 versus baseline. CV02 was calculated rather than measured, as outlined above. PaO2, PaCO2: partial pressure of oxygen and carbon dioxide, respectively, in arterial blood; SaO2: arterial blood oxygen saturation; A-aDO2: alveolar to arterial P O2 difference; DLCO: diffusion capacity for carbon monoxide; CV02: central venous oxygen content.