The Immediate Hemodynamic and Metabolic Effects of Bolus Injections of Pharmacologic Agents During Cardiopulmonary Bypass

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Abstract

The cardiovascular and arterial reservoir level responses to injections of phenylephrine (1.2 micrograms/kilogram [ugm/kg]), chlorpromazine (.01 milligram/kilogram [mg/kg]), phentolamine (.01 mg/kg), pancuronium (.045 mg/kg), diazepam (.11 mg/kg), fentanyl citrate (5.2 ugm/kg) and morphine sulfate (.12 mg/kg) into the defoamer of a bubble oxygenator were observed.

The arteriolar geometric component (GC) was isolated by dividing the systemic vascular resistance (SVR) by the blood viscosity estimated with hematocrit and temperature. The patient’s venous capacitance change was measured by observing the change in the oxygenator arterial reservoir volume (RV). Direct measurement of arterial and venous oxygen saturation, blood flow, and hemoglobin concentration were employed to calculate the patient’s actual oxygen transfer (VO₂). The percent of ideal VO₂ (%VO₂,i) then was calculated by dividing the actual VO₂ by the VO₂ expected for the patient’s age, body surface area and temperature.

Percent change from baseline value in the three indices was reported for three consecutive forty second intervals. Average baseline SVR index, cardiac index, temperature, drug amount and number of circulations are reported in a two-minute graphic profile.

Phenylephrine decreased %VO₂,i and increased RV, while chlorpromazine, diazepam, and fentanyl citrate increased %VO₂,i and decreased RV to varying degrees. Pancuronium and morphine sulfate did not affect GC. However, they caused transient increases in %VO₂,i. Phentolamine concurrently decreased %VO₂,i and GC.

The hemodynamic-oxygen consumption profile is a useful clinical tool in determining adequacy of the total body O₂ delivery in patients of extreme weight and body surface area or in patients receiving vasoactive drugs during cardiopulmonary bypass (CPB).

Background

The use of pharmacologic agents during CPB to control arterial blood pressure and to assure adequate perfusion is commonplace. However, the ar-
tial blood pressure is often the only parameter employed to monitor perfusion changes with drug use.

One measurement that can estimate change in tissue perfusion during CPB is the patient’s total body oxygen consumption (VO₂). VO₂ measurement is especially useful in CPB patient management when the actual VO₂ is idealized to patient age, body surface area and temperature (%VO₂,i)\(^2\).

In the face of an adequate blood flow, arterial oxygen content and viscosity, VO₂ may remain constant throughout a wide range of change in systemic vascular resistance (SVR). Inadequate perfusion pressure, elevated systemic vascular resistance, peripheral vascular disease and possible arteriovenous shunting may limit VO₂ by mal-distributing CPB blood flow.

The use of calculated SVR to monitor vascular geometric change during CPB is biased by extreme change in patient hematocrit and temperature. The SVR can be corrected for viscosity, by dividing the SVR by the viscosity estimated from the known hematocrit and temperature.

This calculation yields a parameter, the geometric component (GC), that reflects change in the vascular geometry.\(^3\) Arteriolar vasoconstriction and the closing of parallel vascular tissue beds increases the GC. Conversely, vasodilation decreases the GC. Change in VO₂ will be a function of alterations in GC during bypass if perfusion to oxygen consuming tissue is limited or increased with pharmacologic therapy.

This study was performed to evaluate the relationship between %VO₂,i and the geometric component of SVR and to present data on the pharmacologic manipulation of the hemodynamic-VO₂ profile.

**Method**

Parameters used to calculate the average % change from baseline in GC, % ideal VO₂ and oxygenator arterial RV were collected during all phases of hypothermic CPB in twenty procedures. Baseline values were collected just before the drug was introduced into the oxygenator defoaming area. Blood flow rate was not altered during the two minute sampling period, nor was the RV supplemented. Temperature and hematocrit were stable during the observation period. These bolus injection observations were in patients that were not randomized and were receiving standard drug therapy during CPB. Table 1 lists the drugs that were studied and the number of times each was evaluated.

**Systemic Vascular Resistance**

The mean radial artery (mABP) and Swan-Ganz catheter central venous pressure (CVP) were collected from calibrated strain gauge transducers and the CPB blood flow (BF) was recorded from a calibrated twin roller pump, SVR was calculated by Equation 1:\(^2\)

\[
SVR = \frac{(mABP - CVP) \times k}{k_1} \quad \text{Eq.} \ 1
\]

where; \(SVR\) = dyne · sec · cm\(^{-5}\)
\(mABP\) = mmHg
\(CVP\) = mmHg
\(k\) = 1333 dyne · cm\(^{-2}\) · mmHg\(^{-1}\)
\(BF\) = three centimeter · minute\(^{-1}\) (ml/mn)
\(k_1\) = 60 seconds · minute

Viscosity was estimated with hematocrit (HCT) and temperature (T) from the following BASIC computer statement:\(^3\);

**TABLE 1**

<table>
<thead>
<tr>
<th>PHARMACOLOGIC AGENT</th>
<th>VASCULAR RESISTANCE</th>
<th>OXYGEN CONSUMPTION</th>
<th>VENOUS CAPACITANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine n = 36</td>
<td>Increase p &lt; .05</td>
<td>Decrease p &lt; .05</td>
<td>Increase p &lt; .05</td>
</tr>
<tr>
<td>Chlorpromazine n = 9</td>
<td>Decrease p &lt; .05</td>
<td>Increase p &lt; .05</td>
<td>Decrease N.S.</td>
</tr>
<tr>
<td>Phenolamine n = 7</td>
<td>Decrease p &lt; .05</td>
<td>Increase p &lt; .05</td>
<td>Decrease p &lt; .05</td>
</tr>
<tr>
<td>Pancuronium n = 18</td>
<td>N.C.</td>
<td>Increase N.S.</td>
<td>Increase p &lt; .05</td>
</tr>
<tr>
<td>Diazepam n = 11</td>
<td>Decrease N.S.</td>
<td>Increase N.S.</td>
<td>N.C.</td>
</tr>
<tr>
<td>Fentanyl Citrate n = 4</td>
<td>Decrease p &lt; .05</td>
<td>Increase N.S.</td>
<td>Decrease N.S.</td>
</tr>
<tr>
<td>Morphine Sulfate n = 4</td>
<td>N.C.</td>
<td>Increase N.S.</td>
<td>Decrease N.S.</td>
</tr>
</tbody>
</table>

N.C. = no change, p = probability, N.S. = not significant at p < .05.
\[
B = e^{(-0.4827 \times T + .9213)}
\]

Eq. 2

\[
\text{Viscosity} = e^{(0.02345 \times \text{HCT} + B)}
\]

where:

\[
\text{Viscosity} = \text{centipose}
\]

\[
e = \text{Exponential } e (2.718)
\]

The geometric component was calculated with Equation 3:

\[
\text{GC} = \text{SVR/Viscosity}
\]

Eq. 3.

Oxygen Consumption

The tissue oxygen consumption from hemoglobin was calculated employing extracorporeal circuit arterial (SaO₂), venous (SvO₂) line oxygen saturation measured by the Oxy-Sat Meter and the most recent hemoglobin concentration (HB) measurement. Actual VO₂ was calculated:

\[
\text{VO}_2 = \frac{(\text{SaO}_2 - \text{SvO}_2) \times (\text{HB})(1.34)}{100} \times \text{BF}
\]

Eq. 4

where; \( \text{VO}_2 \) = milliliters \( \text{O}_2 \) · minute\(^{-1}\)

\( \text{HB} \) = gram %

1.34 = milliliter \( \text{O}_2 \) · gram HB\(^{-1}\)

\( \text{BF} \) = milliliter blood · minute\(^{-1}\)

The expected oxygen consumption (VO₂,i) based on body surface area (BSA), temperature and age (A) was predicted by Equation 5:

\[
\text{VO}_2,i = \frac{2000}{\sqrt{A} + 9} \times \frac{\text{BSA}}{37^2} \times \frac{1}{T^2}
\]

Eq. 5

where; \( \text{A} \) = patient age in years

\( \text{BSA} \) = body surface area in \( \text{m}^2 \)

\( T \) = temperature in °C

The actual VO₂ was divided by the ideal VO₂ to estimate % ideal VO₂:

\[
\% \text{VO}_2,i = \left( \frac{\text{VO}_2}{\text{VO}_2,i} \right) \times 100
\]

Eq. 6

\(^{a} \text{Bentley Laboratories Inc., Irvine, CA 92704}\)

\(^{b} \text{Cobe Laboratories Inc., Lakewood, CO 80215}\)
at any sample time is reported as a significant change in Table 1.

The control cardiac index (liter/minute/M²), SVR index (SVR/M²), drug dosage schedule, and nasopharyngeal temperature are reported with each profile. The average number of circulations (CN) the bolus made at the end of the sample period is reported. CN was predicted by Equation 7 using the patient’s circulating blood volume (CBV), (calculated as 8% of the patient’s body weight in kilograms), extracorporeal circuit volume (ECCV), and blood flow (BF);

\[
CN = \frac{2 \text{ minutes}}{\left( \frac{\text{CBV} + \text{ECCV}}{\text{BF}} \right)} \quad \text{Eq. 7}
\]

where; CBV = milliliters
ECCV = milliliters
BF = milliliter/minute

Results and Discussion

Figures 1 through 7 provide graphic profiles of each agent’s specific effect on the vascular geometric component, oxygenator reservoir volume and the combined hemodynamic and pharmacologic alteration of VO₂ immediately following injection.

In retrospect, the vasodilators were administered to patients with a vascular resistance index (SVRI) greater than 700 dyne·sec·cm⁻⁵·M²⁻¹ during hypothermia. The vasoconstrictor was studied in patients with a SVRI less than 350 dyne·sec·cm⁻⁵·M²⁻¹.

Phenylephrine (Neosynephrine)

This alpha adrenergic stimulating drug increased the geometric component and decreased venous capacitance (Figure 1). If blood tem-
temperature and hematocrit remain constant, a 30% average increase in mABP is realized at 80 seconds after injection in this model. The increasing vascular resistance accompanied by increasing reservoir volume is typical of the patient's response to naturally released catecholamines during nonpulsatile CPB flow. There was a trend for %VO₂,i to decrease accompanying the vasoconstriction. The decreased VO₂ associated with the vasoconstriction would present as a rising venous blood O₂ content or an increased SvO₂ and decreased demand on the artificial oxygenator.

**Chlorpromazine (Thorazine)**

This sedative is a potent alpha adrenergic blocking agent that is capable of reversing the vasoconstriction which accompanies hypothermic CPB flow. There is an immediate substantial drop in vascular resistance that appears to be predominantly arteriolar in the absence of increasing venous capacitance (determined by fluid uptake without a change in GC). The vasodilation secondary to chlorpromazine increased %VO₂,i. The increased VO₂ possibly reflected an increased blood flow to tissue either with higher oxygen consumption or with an oxygen debt and therefore would be beneficial. Increased oxygen extraction by the patient will decrease SvO₂ and reduce arterial blood pO₂ if the oxygenator ventilation rate is not changed.

**Diazepam (Valium)**

This hypnotic agent is capable of transiently lowering arterial blood pressure in anesthetized patients (Figure 3). Accompanying the vasodilation was a transiently increased %VO₂,i. Oxygenator reservoir volume is not affected by this dosage.
Morphine Sulfate

The vasodilation and increased patient capacitance observed by Hsu and Hickey were not as apparent at an average dose of .12 mg/kg compared to their .5 mg/kg (Figure 4). An immediate increase in oxygen consumption was noted. However, the increase in %VO$_2$,i occurred before vasodilation. The beginning of an increase in patient capacitance recorded by Hsu was apparent at two minutes in this model.

Fentanyl Citrate

This potent narcotic analgesic is capable of causing moderate vasodilation following a bolus injection (Figure Five). The transient vasodilation was accompanied by an increase in VO$_2$ and a less predictable increase in patient capacitance. The increased %VO$_2$,i was short lived and began to decrease two minutes after injection.

Pancuronium (Pavulon)

This non-depolarizing muscle relaxant decreased patient capacitance and increased %VO$_2$,i on the average (although not significantly) while not affecting the vascular geometric component (Figure 6).

Phentolamine (Regitine)

This potent alpha adrenergic receptor blocking agent caused vasodilation and ultimately, an average decrease (N.S.) in patient capacitance (Figure 7). There was a decrease in %VO$_2$,i that was not consistent with vasodilation and Arikawa's
previous findings, perhaps due to the immediate, decreased sympathetic activity at the tissue level.

Summary

Except for phentolamine, arteriolar vasodilation increased patient oxygen extraction and vasoconstriction decreased patient oxygen uptake.

Bolus injection studies and the graphic profiles presented here support the thesis that for a given population of CPB patients, VO₂ is largely determined by systemic vascular resistance when blood flow, arterial oxygen content, blood viscosity and anesthetic level are similar. The VO₂-hemodynamic profile is a useful parameter to determine the overall O₂ delivery-utilization status of the patient.

References