Effects of Cardiovascular Drugs on Oxygen Consumption/Oxygen Delivery Relationship in Patients with Congestive Heart Failure*

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The oxygen consumption (\(V_O_2\))/oxygen delivery (\(D_O_2\)) relationship was analyzed in ten patients with severe congestive heart failure (CHF) and normal blood lactate levels. First dobutamine and then enoximone, after a washout period, were administered to each patient to increase cardiac output by at least 15 percent. Similar increases in \(D_O_2\) were obtained with both drugs: from 285 ± 46 to 383 ± 87 ml/min/m² for dobutamine, and from 285 ± 54 to 382 ± 99 ml/min/m² for enoximone. However, while \(V_O_2\) did not change (132 ± 24 vs 132 ± 21 ml/min/m²) (\(V_O_2/D_O_2\) independency) with a dobutamine infusion (mean dose of 10 ± 2 µg/kg/min), a significant increase in \(V_O_2\) from 134 ± 22 to 157 ± 21 ml/min/m² was observed with a bolus infusion of enoximone (mean dose of 1.7 ± 0.5 mg/kg). These results, observed in patients with CHF without patent oxygen debt, suggest that an artefactual \(V_O_2/D_O_2\) dependency might be induced by the cardiovascular drug used to elevate \(D_O_2\), probably because of a drug-induced oxygen demand increase.

(Chest 1992; 101:1582-87)

In physiologic conditions, if \(D_O_2\) decreases, tissue \(O_2\) needs can be still satisfied because of an appropriate increase in \(O_2\) tissue extraction. The \(V_O_2\) still equals \(O_2\) demand and remains relatively constant (\(V_O_2/D_O_2\) independency). However, if \(D_O_2\) falls below a critical value, \(V_O_2\) cannot be maintained in agreement with \(O_2\) demand because \(O_2\) tissue extraction cannot increase in proportion to the reduced \(D_O_2\). Subsequently, \(V_O_2\) becomes directly related to \(D_O_2\) (\(V_O_2/\ D_O_2\) dependency)

and lactatemia, a marker of anaerobic metabolism, increases. In healthy animals, a critical \(D_O_2\) level of 8 to 10 ml/min/kg has been demonstrated. In anesthetized patients, a critical value of 330 ml/min/m² has been reported.

A physiologic \(V_O_2/D_O_2\) dependency should denote that \(V_O_2\) is related to \(D_O_2\) below this normal critical \(D_O_2\). However, in various critical illnesses (ARDS, sepsis, and liver failure), a \(V_O_2/D_O_2\) dependency was observed even if \(D_O_2\) was within the normal range. This so-called pathologic \(V_O_2/D_O_2\) dependency was ascribed to an impairment of \(O_2\) tissue extraction, because of abnormal blood flow distribution and/or microthrombi formation and/or \(O_2\) diffusion impairment due to an interstitial edema.

Over the last years, the recognition of a \(V_O_2/D_O_2\) dependency has been recommended because such a phenomenon has been associated with increased mortality. Moreover, a so-detected \(O_2\) debt could be then reversed by therapy increasing \(D_O_2\). Several investigators proposed to perform at bedside an \(O_2\) flux test to detect a \(V_O_2/D_O_2\) dependency; prostacyclin, converting enzyme inhibitor, and dobutamine were previously used for this purpose. Nevertheless, rigorous conditions are required for a meaningful interpretation of the test: first a short interval between the two sets of measurements (before and after the drug administration) is required to minimize potential spontaneous fluctuations in metabolic needs; second, the drug used for the test does not induce per se an increase in \(O_2\) demand.

We focused this study on this latter concern, by performing, in a series of patients with chronic CHF in stable condition, two consecutive \(O_2\) flux tests with two different drugs as follow: (1) dobutamine, a synthetic catecholamine with predominant \(β_1\)-adrenergic activity having an inotropic effect; and (2) enoximone, a phosphodiesterase III inhibitor having both inotropic and vasodilatory properties.

Patients

Ten patients were enrolled in the study: three women and seven men. Their mean age was 66 ± 18 years. Table 1 lists the main characteristics of these patients. All patients were admitted in our medical intensive care unit for acute cardiogenic pulmonary edema.
and underwent pulmonary artery catheterization for hemodynamic monitoring. Six patients were receiving mechanical ventilation, while four patients were spontaneously breathing with intranasal O₂ administration. All patients suffered from severe chronic CHF (NYHA class 4). Congestive heart failure was secondary to coronary artery disease in seven patients and idiopathic dilated cardiomyopathy in three patients. All patients were receiving long-term diuretic therapy in association with nitrites (in six patients), and converting-enzyme-inhibitor (in four patients). Therapy was withheld the day before the study. At the time of the study, the acute pulmonary edema was resolved and no clinical signs of shock persisted. All patients met the following criteria: CI ≥ 2.5 L/min/m², PAOP ≥ 18 mm Hg, and blood lactate levels within the normal range (i.e., <2 mmol/L). Exclusion criteria included uncontrolled tachyarrhythmias and CHF from restrictive or hypertrophic cardiomyopathy or valvular stenosis. Nine of the ten patients were discharged from the intensive care unit, and one died.

**METHODS**

Pulmonary artery catheterization was performed with a 7F Swan-Ganz catheter inserted percutaneously via an internal jugular vein to measure PAP and PAOP. All values were measured at end expiration. Patients were studied while supine and zero pressure was taken as atmospheric pressure at the midaxillary line. The CO was calculated with an Edwards model 9250 A computer, as the mean of four measurements obtained by injecting 10 ml of dextrose solution. Systemic BP was recorded with a radial artery catheter. All pressures were measured via quartz transducer (Hewlett Packard 1290). Arterial and mixed venous blood samples were simultaneously withdrawn for determination of blood gases immediately after CO measurement. Thus, PaO₂ and PpO₂ (Corning 178), and SaO₂ and SvO₂ (COximeter, Corning 2500) were measured. Hemoglobin concentration Hb (g/dl) was also measured. Heart rate was taken from the ECG.

\[ CaO₂ = (SaO₂ × Hb × 1.34) + (PaO₂ × 0.003) \]
\[ CvO₂ = (SvO₂ × Hb × 1.34) + (PvO₂ × 0.003) \]

DO₂ (ml/min/m²) and VO₂ (ml/min/m²) were calculated as follows:

\[ DO₂ = CI × CaO₂ × 10 \]
\[ VO₂ = CI × (CaO₂ − CvO₂) × 10 \]

The O₂ER was calculated as the ratio of VO₂ and DO₂:

\[ O₂ER = VO₂/DO₂ \]

Blood lactate concentration was determined using an enzymatic method.

**Study Protocol**

A control period of 2 h was required before starting the study. One set of hemodynamic measurements was obtained at the beginning and a second set at the end of this period. The BE, CI, and PAOP should not fluctuate by more than 10 percent over this period. Then, the final set of measurements was considered as the baseline (B1) before starting. Blood lactate level was measured at this time. Because of the short elimination half-life of dobutamine and the long elimination half-life of enoximone, we infused dobutamine first, followed by a reequilibration period, then an infusion of enoximone. Dobutamine was intravenously infused at incremental doses (5, 10, and 15 µg/kg/min) until baseline CO was increased by at least 15 percent, to avoid a false increase due to errors of measurement. The CO was measured after 15 minutes of infusion of each dose level. When the dose achieving the endpoint was reached, all the hemodynamic parameters were measured.

Then, dobutamine infusion was discontinued and a reequilibration period of 1 h was required to allow hemodynamic condition to return to baseline. The BE CI, and PAOP should not differ from B1 values by more than 10 percent. When this goal was achieved, a complete set of hemodynamic measurements was obtained and considered as baseline 2 (B2) set.

Thereafter, enoximone was given as a bolus (1 mg/kg) infused over 15 min, with CO measurement obtained 30 min after the end of the infusion. If CO did not increase by more than 15 percent, a supplemental bolus of 0.5 mg/kg of enoximone was given over 15 min, and CO measurement was obtained again 30 min after the end of that infusion. If necessary, a third bolus (0.5 mg/kg) was infused to obtain an increase in CO by more than 15 percent. When this endpoint was achieved, a complete set of hemodynamic measurements was performed.

No change in drug therapy was allowed during the study. Informed consent was obtained from each patient; the protocol was approved by the ethics committee of our institution.

**Statistics**

Statistical analysis of the data was performed using a two way variance analysis complemented by a comparison between time using Scheffe test (Statwiew II-Anova). Bilateral hypothesis was used with an alpha risk chosen of p<0.05. Results are expressed as mean ± SD.

**RESULTS**

The mean basal value of blood lactate concentration was 1.05 ± 0.5 mmol/L. Increase in CO by more than 15 percent was achieved by a mean dose of 10 ± 2 µg/kg/min of dobutamine (5 µg/kg/min in one patient, 10 µg/kg/min in eight patients, 15 µg/kg/min in one patient) and a mean cumulative dose of 1.7 ± 0.5 mg/kg of enoximone (1 mg/kg in three patients, 1.5 mg/kg in one patient, 2 mg/kg in six patients). Table 2 summarizes the main hemodynamic findings. A significant and similar increase in CI was achieved by both

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**Table 1 — Characteristics of the Patients at Time of Study**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Sex</th>
<th>Etiology of Cardiomyopathy</th>
<th>Ventilation Mode</th>
<th>Basal CI, L/min/m²</th>
<th>Basal PAOP, mm Hg</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>M</td>
<td>Idiopathic</td>
<td>MV</td>
<td>1.4</td>
<td>24</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>M</td>
<td>Ischemic</td>
<td>SV</td>
<td>1.7</td>
<td>23</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>M</td>
<td>Ischemic</td>
<td>SV</td>
<td>2.3</td>
<td>25</td>
<td>S</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>M</td>
<td>Idiopathic</td>
<td>SV</td>
<td>2.0</td>
<td>25</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>M</td>
<td>Ischemic</td>
<td>MV</td>
<td>1.5</td>
<td>35</td>
<td>S</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
<td>F</td>
<td>Ischemic</td>
<td>SV</td>
<td>2.5</td>
<td>35</td>
<td>S</td>
</tr>
<tr>
<td>7</td>
<td>78</td>
<td>F</td>
<td>Ischemic</td>
<td>MV</td>
<td>2.0</td>
<td>25</td>
<td>S</td>
</tr>
<tr>
<td>8</td>
<td>78</td>
<td>F</td>
<td>Ischemic</td>
<td>MV</td>
<td>2.4</td>
<td>19</td>
<td>D</td>
</tr>
<tr>
<td>9</td>
<td>77</td>
<td>M</td>
<td>Idiopathic</td>
<td>MV</td>
<td>2.5</td>
<td>34</td>
<td>S</td>
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<tr>
<td>10</td>
<td>78</td>
<td>F</td>
<td>Ischemic</td>
<td>MV</td>
<td>1.7</td>
<td>18</td>
<td>S</td>
</tr>
</tbody>
</table>

*MV indicates mechanical ventilation; SV, spontaneous ventilation; S, survivor; and D, deceased.*

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every patient, VO₂ was unchanged with dobutamine (Fig 1, left), while in seven from them, VO₂ increased by more than 15 percent with enoximone (Fig 1, right). Thus, VO₂ with enoximone was significantly higher than VO₂ with dobutamine (157 ± 31 vs 132 ± 24; p<0.01). Consequently, O₂ER was significantly decreased with dobutamine (from 47 ± 7 to 34 ± 5 percent) but not with enoximone (48 ± 7 to 42 ± 7 percent).

drugs (42 ± 24 percent for dobutamine, 37 ± 24 percent for enoximone). Neither of the two drugs altered BP significantly, whereas they decreased PAP and PAOP significantly (p<0.05 for dobutamine, p<0.01 for enoximone). Dobutamine increased HR significantly (p<0.01) while enoximone did not. No change in SaO₂ was observed with drug therapy so that DO₂ increased markedly and by a similar amount with both drugs (p<0.001). The most interesting finding concerns the evolution of VO₂ under drug therapy: in

### Table 2—Main Hemodynamic and Gasometric Parameters during Study*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline 1</th>
<th>Dobutamine</th>
<th>Baseline 2</th>
<th>Enoximone</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP, mm Hg</td>
<td>78 ± 14</td>
<td>77 ± 15</td>
<td>77 ± 15</td>
<td>74 ± 7</td>
</tr>
<tr>
<td>PAP, mm Hg</td>
<td>35 ± 8</td>
<td>30 ± 8‡</td>
<td>35 ± 6</td>
<td>28 ± 8§</td>
</tr>
<tr>
<td>PAOP, mm Hg</td>
<td>25 ± 5</td>
<td>20 ± 7‡</td>
<td>26 ± 5</td>
<td>18 ± 7‡</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>83 ± 15</td>
<td>94 ± 17†</td>
<td>84 ± 16</td>
<td>66 ± 13</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>2.0 ± 0.4</td>
<td>2.6 ± 0.6§</td>
<td>2.0 ± 0.4</td>
<td>2.7 ± 0.5§</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>94 ± 2</td>
<td>92 ± 4</td>
<td>93 ± 5</td>
<td>94 ± 3</td>
</tr>
<tr>
<td>SvO₂, %</td>
<td>50 ± 7</td>
<td>61 ± 4†</td>
<td>50 ± 7</td>
<td>56 ± 7‡</td>
</tr>
<tr>
<td>C(a-v)O₂</td>
<td>6.9 ± 1.8</td>
<td>4.8 ± 1.1†</td>
<td>6.9 ± 1.9</td>
<td>5.9 ± 1.2</td>
</tr>
<tr>
<td>Do₂, ml/min/m²</td>
<td>285 ± 46</td>
<td>303 ± 87†</td>
<td>285 ± 54</td>
<td>392 ± 96‖</td>
</tr>
<tr>
<td>Vo₂, ml/min/m²</td>
<td>132 ± 21</td>
<td>132 ± 24</td>
<td>134 ± 22</td>
<td>157 ± 31*</td>
</tr>
<tr>
<td>O₂ER, %</td>
<td>47 ± 7</td>
<td>34 ± 5†</td>
<td>48 ± 7</td>
<td>42 ± 7</td>
</tr>
</tbody>
</table>

*p<0.01 from B₁, dobutamine and B₂ values.
†p<0.01 from B₁, B₂, and enoximone values.
‡p<0.05 (from B₁ and B₂ values).
§p<0.01 (from B₁ and B₂ values).
||p<0.001 from B₁ and B₂ values.

*Effects of Cardiovascular Drugs on Oxygen Consumption (Tibou et al)
DISCUSSION

The purpose of our study was to analyze the concomitant evolution of DO2 and VO2 following cardiovascular drug administration. This study demonstrates that an O2 flux test may give contradictory results when performed in the same patient with two different cardiovascular drugs. While one would predict an O2 debt in seven out of our ten patients because of an apparent VO2/DO2 dependency revealed by enoximone administration, the same patients demonstrated a VO2/DO2 independency with dobutamine infusion, thus denoting the absence of tissue hypoxia. Similar levels of CO were reached with both drugs so that the increase in VO2 with enoximone was due to the failure of C(a-v)O2 to decrease with enoximone. We do not strongly believe that the unchanged C(a-v)O2 was explained by the inability of CO to increase with enoximone and that the observed increase in CO was secondary to error measurements with thermodilution technique: first because there is no reason that errors occur only with enoximone, and second, because the mean dose of enoximone used in this study (1.7 ± 0.5 mg/kg) is considered as efficient to increase CO significantly in patients with CHF.10,30 Indeed, in our patients, enoximone at this dose demonstrated its cardiovascular efficiency as it decreased PAOP and PAP by the same amount that dobutamine did. After that, these methodologic limitations were excluded, the failure of C(a-v)O2 to decrease with enoximone could be explained by one of the two following hypothesis: (1) enoximone by its action on the peripheral vasomotor tone might open previously constricted vessels; the increase in VO2 of these reopened areas would then witness the recovery of a previous O2 debt; however, this hypothesis is unlikely because of the lack of clinical signs of shock and of lactic acidosis at baseline; and (2) enoximone might increase tissue O2 demand and then VO2 independent of its effect on DO2. This potential effect of enoximone on peripheral tissue O2 needs has not been previously addressed. Enoximone, as other vasodilators, might increase tissue O2 demand by a sympathetically mediated effect resulting from an induced baroreceptor reflex.32 Indeed, endogenous catecholamine secretion may have thermogenic effects and then induce an increase in tissue O2 requirements;32,33 in healthy volunteers, an increase in O2 demand has been previously observed with epinephrine, norepinephrine,34 or dopamine.35 On the other hand, enoximone might also increase O2 demand by itself. This hypothesis is not irrelevant with the mechanism of action of phosphodiesterase inhibitors. Indeed these substances, like catecholaminergic agents, produce their cellular effects via an increase in cytosolic cyclic AMP (cAMP) concentration. Thereby, the induction by enoximone of an increase in metabolic and O2 requirements is quite possible. Now, it is not easy to explain why enoximone might increase an O2 demand increase in most of our patients while dobutamine did not, since both drugs increased cytosolic cAMP. Perhaps, enoximone acting within the cells by inhibiting cAMP degradation has more ubiquitous effects than dobutamine which acts only on target cells with specific surface receptors. Additionally, enoximone, by its vasodilatory properties, might open previously constricted vessels leading to an amplification of the effect of O2 demand increase related to cAMP production. Increased VO2 associated with increased DO2 has also been previously reported with enoximone in hyperlactatemic patients with cardiogenic shock.16 However, the finding of a VO2/DO2 dependency in that setting could be presumably explained by the presence of an O2 debt before treatment. Although the above-mentioned speculative considerations could account for the increase in global VO2 observed in most of our patients with enoximone at this dose, it must be noted that in three out of our ten patients, VO2 did not increase. Unchanged VO2 was also observed by Installe et al30 in a series of patients with CHF receiving a mean dose of 2 mg/kg of enoximone.30 Our data also indicate that a mean dose of 10 μg/kg/min of dobutamine did not induce an increase in global O2 needs in CHF patients. This seems to be in agreement with other studies on patients with CHF, which failed to demonstrate an increase in VO2 with dose of 5 to 15 μg/kg/min of dobutamine.36-38 All these findings support the use of low doses of dobutamine when an O2 flux test is required, at least in patients with CHF. This is quite in agreement with the findings reported by Vincent et al.18 In their study, VO2 increased when DO2 was increased with dobutamine (5 μg/kg/min) in critically ill patients with hyperlactatemia, while the dobutamine-induced DO2 increase was not associated with VO2 increase in those with normal blood lactate levels.18 Obviously, it is not excluded that high doses of dobutamine may produce global O2 needs elevation39 as previously reported by Gilbert et al11 with catecholamines. In their study, fluid loading and blood transfusion, while increasing DO2, increased VO2 also, only in septic patients with hyperlactatemia. By contrast, the use of catecholamines in another group of septic patients resulted in an increase in both DO2 and VO2 in hyperlactatemic as well as in nonhyperlactatemic patients. The role of a thermogenic effect of the catecholaminergic agents was thus underlined by the authors.11

Our results suggest that the interpretation of an O2 flux test must be particularly cautious when CO is increased by a cardiovascular drug. This concern is particularly crucial in critically ill patients, since an O2 debt detected by a dependent VO2/DO2 relationship has been associated with an increased mortality.10
Such a detection could justify an augmentation of DO2 to reduce O2 debt and to prevent the development of multiple organ failure.29 The routine practice of lactemia measurement should improve the interpretation of VO2/DO2 relationship in terms of drug-induced increase in O2 demand, when an O2 flux test is performed.

Some investigators could have some concern about the possibility of a mathematical coupling between VO2 and DO2 when both were calculated by the same thermodilution cardiac output measurement. However, even if a mathematical coupling might influence results, this should not represent a problem in our comparative study since this potential bias should be present whatever the treatment used, and an independent VO2/DO2 relationship was observed with dobutamine.

Beside the concern of misinterpretation of the VO2/DO2 relationship, another finding of our study must be pointed out. Indeed, the observation of relatively low basal values of DO2 (mean value of 285 ml/min/m2) in association with normal blood lactate levels must be briefly discussed: nine of our ten patients exhibited basal DO2 lower than 330 ml/min/m2 (Fig 1, left), a value generally considered as the critical value of DO2 in normal subjects.5 Although this latter value was determined in nonphysiologic conditions (anesthesia) and probably cannot be considered as a fixed value, since depending at least on O2 demand, our findings would indicate that in resting conditions, O2 tissue extraction is not impaired but even presumably enhanced in CHF patients. This hypothesis is consistent with previous reports of blood flow redistribution33 or increased P50 in the setting of chronically reduced CO. Indeed, blood flow redistribution toward organs with high O2 extraction ratios would maintain VO2 despite reduced CO. The increased P50 would also denote an adaptive mechanism allowing a better O2 release from hemoglobin to the peripheral cells. These enhanced O2 extraction capabilities were also suggested by the observation in CHF patients,18 as in our series, of higher O2ER values in normolactacemic conditions, than in normal subjects whose O2ER was estimated at around 33 percent.8

In conclusion and within the limits of our study in patients suffering from CHF, enoximone infusion was associated with an increase in VO2, but dobutamine was not. These results might be taken into account in VO2/DO2 relationships in critically ill patients.

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