ABSTRACT  The physiology of oxygen delivery was studied in 118 stable patients from 3 months to 20 years old with congenital heart disease. During cardiac catheterization, oxygen consumption (VO₂), arterial and venous blood gases and oxygen saturations (range 41% to 98%), hemoglobin concentration, diphosphoglycerate (2,3-DPG), and P₅₀ levels were measured, and then cardiac output, systemic oxygen transport (SOT), arterial and venous oxygen contents, and the VO₂/SOT ratio (fractional O₂ extraction) were calculated. P₅₀ averaged 31 mm Hg, compared with 27 mm Hg in 10 control children (p < .01). The composite O₂-hemoglobin dissociation curve in vivo was broad: Po₂ varied from 37 to 65 mm Hg at 80% saturation. P₅₀, 2,3-DPG, hemoglobin concentrations, and O₂ saturation varied widely and inconsistently with Po₂ and arterial and venous O₂ content, but resulted in clustering of the arterial oxygen content near 165 ± 23 (SD) ml/liter over a wide range of Po₂ and hemoglobin concentrations. SOT varied in direct relation with flow (r = .82, p < .001), but not with oxygen content, Po₂, or P₅₀. VO₂ varied widely at normal or high levels of SOT, but decreased linearly at SOT levels below 400 ml/min/m². Oxygen extraction varied inversely with venous O₂ content, rising to about 50% and plateauing below venous contents of 100 ml/liter. O₂ extraction did not correlate with Po₂, arterial O₂ content, or P₅₀. These data suggest that: (1) O₂ saturation cannot be predicted or calculated accurately from measured Po₂, but must be measured directly, (2) 2,3-DPG, hemoglobin concentration, and P₅₀ fluctuate to stabilize arterial oxygen content, (3) SOT is determined primarily by cardiac output in subjects who are adapted chronically, (4) O₂ extraction rises, due to a fall in venous O₂ content, to maintain VO₂ as transport falls, (5) below a critical level of SOT, O₂ extraction ceases to rise and VO₂ falls with further reduction in transport.  


We have determined a number of variables of oxygen physiology in infants and children undergoing cardiac catheterization. This study addresses the chronic, adaptive mechanisms that contribute to the balance of oxygen supply and demand in infants and children with congenital cardiac abnormalities.

**Materials and methods**

**Patient population.** One hundred eighteen subjects from 3 months to 20 years of age (mean 3.4 years) were studied during cardiac catheterization over the period from October 1983 to June 1985. Infants under 3 months of age were excluded from study to eliminate confusion related to the presence of fetal hemoglobin. Subjects who were acutely ill or hemodynamically unstable were not included, since this study was designed to focus on chronic adaptive mechanisms. The 118 subjects, then, comprise a consecutive sample of patients warranting cardiac catheterization for clinical indications and meeting the other study criteria. Ten subjects referred for evaluation of heart murmurs, but who had no heart disease, served as a control group for P₅₀ determinations. Informed consent for blood sampling was obtained for each subject.
Methods. All subjects under 3 years of age received nothing by mouth for a minimum of 5 hr before the study; children over 3 years of age received nothing by mouth for at least 8 hr before the study. In those more than 6 months of age, meperidine (1.5 mg/kg) and droperidol (0.04 mg/kg) were administered as premedication 1 hr before the study.

After catheter insertion and during measurement of VO₂ by the flow-through, open-system technique, but before angiography or any hemodynamic manipulation, the following measurements were made in 2 ml samples of arterial and venous blood: hemoglobin concentration, arterial Po₂, pH, Pco₂ (Corning), aortic and mixed venous oxygen saturation (Radiometer OM2), diphosphoglycerate (2,3-DPG) concentration corrected for hemoglobin concentration, and P₅₀ (Hemoscan). From the measured data, the following variables were calculated: aortic and mixed venous oxygen content (O₂ content = hemoglobin g/L x 13.4 ml O₂/g hemoglobin/L x O₂ saturation), cardiac index [CI = VO₂/(arteriovenous O₂ content difference)], SOT (CI × arterial O₂ content), and fractional oxygen extraction from arterial blood (VO₂/SOT). Arterial and venous pressures measured at catheterization were recorded in a standard fashion.

Data were entered on a spread-sheet computer program for graphic display of correlations and generation of descriptive statistics. Tests for correlation coefficients and statistical significance were conducted separately (MDC Stat).

Results

Mean (range) values recorded in this series included: age 3.4 years (0.2 to 20.0), arterial Po₂ 64 mm Hg (33 to 114), hemoglobin concentration 14.1 g/dl (10.3 to 24.2), cardiac index 3.1 liters/min/m² (1.5 to 5.0), VO₂ index 137 ml/min/m² (69 to 206), SOT index 426 ml/min/m² (171 to 830), and fractional oxygen extraction 34% (16% to 67%). A population oxyhemoglobin dissociation curve was created by plotting measured arterial and venous oxygen saturations vs Po₂ measured at pH and body temperature in vivo (figure 1). The mean P₅₀ for the study population of 30.8 mm Hg was higher than the level of 27 mm Hg found in 10 control subjects without hemodynamic abnormalities. The level of P₅₀ in the series of subjects appeared to be related both to age and arterial oxygen tension (table 1). Subjects under 6 months of age had P₅₀'s lower than the remainder of subjects, due possibly to higher levels of fetal hemoglobin in individuals 3 to 6 months of age. In addition, subjects with arterial oxygen tensions of less than 50 mm Hg had lower P₅₀'s than those with higher arterial Po₂; however, 14 of the 27 subjects in the Po₂ less than 50 mm Hg group were under 6 months of age (the mean Po₂ for infants < 6 months = 49 mm Hg, as compared with 64 mm Hg for the series as a whole). Therefore, variation in P₅₀ may be related both to age and arterial hypoxemia. Because the arterial-venous pH difference of 7.39 to 7.37 in this series was not higher than the physiologic value of 0.02 to 0.05, the hemoglobin-O₂ dissociation curve descent was not steeper than normal, resulting in a physiologic arterial-venous oxygen content difference for a given arterial-venous change in Po₂.

Po₂ varied widely between 33 and 114 mm Hg.

![Oxyhemoglobin Dissociation Curve](image)

**FIGURE 1.** Arterial and venous Po₂-O₂ saturation measurements superimposed on a “normally positioned” oxyhemoglobin dissociation curve for adult hemoglobin (P₅₀ = 28 mm Hg). The rightward shift of the series points and the broad Po₂ range for a given measured saturation are evident.
TABLE 1
O₂ physiology in congenital heart disease — P₅₀ data from all study patients

<table>
<thead>
<tr>
<th>Age</th>
<th>P₅₀ (mm Hg, mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–6 mo</td>
<td>25.0</td>
</tr>
<tr>
<td>6 mo–1 yr</td>
<td>31.6</td>
</tr>
<tr>
<td>1–5 yr</td>
<td>30.4</td>
</tr>
<tr>
<td>&gt;5 yr</td>
<td>31.0</td>
</tr>
<tr>
<td>Arterial P₂ (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>26.4</td>
</tr>
<tr>
<td>50–70</td>
<td>31.4</td>
</tr>
<tr>
<td>&gt;70</td>
<td>31.5</td>
</tr>
</tbody>
</table>

(oxygen content appeared not to vary consistently with flow, oxygen transport, or VO₂; a direct, linear relationship did exist between cardiac index and SOT (figure 4). The relationship of VO₂ to SOT varied in this between-subject study, but there was a trend toward reduction of VO₂ at transport levels under 400 ml/min/m² (figure 5). Fractional oxygen extraction from arterial blood (VO₂/SOT) rose as SOT fell (figure 6) as a function of reduced mixed venous VO₂ at low levels of SOT (figure 7).

Discussion
The assessment of circulatory integrity by traditional hemodynamic measurements (flow, pressure, resistance) has been supplemented in recent literature by consideration of variables of oxygen physiology.² In these analyses, relationships between VO₂, SOT, and arterial oxygen extraction have emerged. Theoretic considerations and experimental data have supported the concept that VO₂ and SOT are related loosely over the physiologic range, but that at low levels of transport, VO₂ falls proportionately; i.e., it is transport limited.²³,²⁴ Clinical series in adults⁸ and children²⁵ suggest that survival statistics improve in critically ill subjects when VO₂ or SOT are maintained near the normal range. However, physiologic relationships be-

![PO2/Content Relationship](image)

FIGURE 2. Oxygen tension (P₂, mm Hg) and oxygen content (CaO₂, ml/liter) values for the series, with P₂ and CaO₂ displayed on the vertical scale against ascending levels of CaO₂ on the horizontal scale. P₂ variability is contrasted with the narrow range of CaO₂ values for most subjects.
HEMOGLOBIN VS ARTERIAL OXYGEN SAT

FIGURE 3. Arterial hemoglobin concentration plotted against arterial oxygen saturation at rest. The inverse relationship between the variables is seen.

tween SOT and VO₂ variables are just beginning to emerge.

From the equations in the Methods section, it is evident that SOT is both flow and content dependent. Arterial oxygen content, in turn, depends both on carrying capacity (hemoglobin concentration × a constant) and arterial oxygen saturation. Reduced SOT secondary to anemia (reduction in oxygen-carrying capacity) has been studied over the short term in dogs and lambs. In both studies, cardiac output and VO₂ rose initially as transport fell. However, at SOT levels under 10 to 13 ml/kg/min (250 to 325 ml/min/m² assuming a weight of 25 kg corresponds to 1 m² body surface area), VO₂ fell with further reduction in SOT. Reduction in SOT secondary to alveolar hypoxemia has also been studied in sheep. Moss et al. reported "critical" levels of transport — levels below which VO₂ fell — in both lambs and adult animals. The critical value in lambs (15 ml/kg/min) was higher than that in adults (10 ml/kg/min). Below the critical value, VO₂ fell to 70% of control and serum lactate levels rose, suggesting a metabolic impact of the perturbed oxygen physiology. Delevoria-Papadopoulos et al. demonstrated the physiologic impact of alveolar hypoxia on the cerebral circulation; as cerebral arterial oxygen content fell, cerebral blood flow rose in a compensatory fashion. When SOT fell to 70% of control values, cerebral bioenergetic profiles obtained by nuclear magnetic resonance showed a physiologic impact of the reduction in oxygen delivery.

Flow reduction has also been used as an experimental means for reducing SOT. Vallone used cardiac tamponade to reduce blood flow and SOT abruptly in young lambs. VO₂ fell as SOT fell below 13 ml/kg/min. In a related but separate study, Fahey et al. used tricuspid valve occlusion induced by an inflatable balloon to reduce flow in the lamb preparation. When flow fell to 60% of control levels, VO₂ fell and serum lactate levels rose; the "critical" SOT level appeared lower in 8-week-old lambs than in 2-week-old animals.

The current study was constructed to define the profile of variables of oxygen physiology in a group of subjects after adaptation (chronic) to alterations in systemic blood flow and arterial oxygen saturation due to congenital heart disease. Variables of SOT and VO₂ were measured, rather than assumed, because both the supply and demand portions of the oxygen balance relationship must be known to draw conclusions about physiology. Arterial oxygen content also was measured rather than calculated from Po₂ values, because the oxyhemoglobin dissociation curve is a variable relationship that is affected substantially by physiologic compensatory mechanisms in patients with disor-
ders of oxygen delivery. In high-altitude (alveolar) hypoxemia, there is generally a close correlation between arterial oxygen saturation and red cell mass, and between arterial oxygen saturation and 2,3-DPG levels. In primary and secondary polycythemic disorders, as well as in many pulmonary disease states, however, this is not the case, and there is a poor relationship between arterial oxygen saturation and both red cell mass and 2,3-DPG levels. In the present study, the subjects included individuals with normal

\[ \text{OXYGEN TRANSPORT VS FLOW}\]

![Graph A](image1)

\[ \text{OXYGEN TRANSPORT VS CONTENT}\]

![Graph B](image2)

**FIGURE 4.** Oxygen transport plotted against cardiac index (A) and arterial oxygen content (B). A close linear relationship between flow and transport is seen.
hemodynamics and arterial oxygen saturation, reduced
systemic blood flow (systemic outflow tract obstruction,
atroventricular valve incompetence, or large
left-to-right shunts), and reduced arterial oxygen satu-
ration (cyanotic lesions). The study sample as a whole
provided a broad range of oxygen saturation, SOT, and
cardiac output values over which to study relation-
ships.

In this protocol, oxygen saturation, \( \text{PO}_2 \), \( \text{VO}_2 \), and
blood flow measurements were made directly. \( P_{50} \) val-
ues varied significantly and directly with age and arte-
rial \( \text{PO}_2 \), but because the mean \( \text{PO}_2 \) of young (< 6

FIGURE 5. Oxygen transport vs oxygen consumption for all subjects.

FIGURE 6. Fractional oxygen extraction (\( \text{VO}_2/\text{SOT} \)) vs oxygen transport for all subjects.
months) subjects was lower than that for the series as a whole, the relationship between \( P_{50} \) and age or arterial \( P_O_2 \) may have depended entirely on the presence of fetal hemoglobin in the 19 subjects from 3 to 6 months old. Liabilities and resulting inaccuracy from use of \( P_O_2 \) to calculate SOT from a standard curve are illustrated in figure 1; across this chronically compensated study sample, an SOT of 80% corresponded to \( P_O_2 \) values varying between 37 and 50 mm Hg.

Oxygen saturations must be measured directly, rather than calculated from \( P_O_2 \) values, to ensure accuracy of calculated oxygen content. In this population, the oxyhemoglobin dissociation curve was not steep, but was shifted to the right. The rightward position of the curve is compatible with adaptive physiologic mechanisms for central shunts or hypoperfusion. In those settings, \( O_2 \) loading in the lungs is not perturbed, but \( O_2 \) delivery to the tissues is disordered by reduced arterial \( O_2 \) content, reduced arterial blood flow, or both. The rightward shift is adaptive; it increases both arterial and venous (reflecting tissue) \( P_O_2 \) levels.31

Chronic hematologic compensatory mechanisms worked to maintain a narrow range of arterial oxygen content levels for the study population as a whole (figure 2); the combined effects of adjustments in hemoglobin concentration and 2,3-DPG levels (and the resultant impact on \( P_{50} \)) compensated well for alterations in arterial oxygen saturation. The corollary of this finding is that in this sample of adapted subjects, SOT was a direct function of systemic blood flow (figure 4), and arterial oxygen content correlated poorly with flow. Relationships between \( V_O_2 \), SOT, and fractional extraction were complicated in this study by intersubject variability.

In spite of this systematic constraint, \( V_O_2 \) appears to be “transport limited” when oxygen transport falls below 400 ml/min/m\(^2\) (16 ml/kg/min, assuming 1 m\(^2\) corresponds to a body weight of 25 kg). Initially, as oxygen transport falls, oxygen extraction rises secondary to a reduction of mixed venous \( O_2 \) content. After extraction has reached maximum levels, \( V_O_2 \) begins to fall. Presumably, \( V_O_2 \) is limited by reduced flow to nonessential vascular beds. This mechanism would explain the close correlation between \( V_O_2 \) and cardiac index at low levels of \( O_2 \) transport. The mechanism that orchestrates the proposed changes in vascular resistance is beyond speculation. Lactate levels were not measured in any of the subjects reported here.

The issue of arterial hematocrit and blood viscosity must be addressed, since this relationship affects oxygen transport physiology by virtue of its potential effect on vascular resistance and blood flow. In fact, three subjects in this series required repeated phlebotomy and Plasmanate replacement for uncontrolled polycythemia.32 These subjects were studied when asymptomatic, 2 to 3 weeks after a previous phlebotomy. In 1967, Crowell and Smith3 demonstrated a relationship between hematocrit and SOT in a capillary
tube system. In that setting, “optimal hematocrit” — that is, hematocrit at which SOT is highest — is calculable. In settings in vivo, however, this analysis is complicated by variably mediated changes in flow and vascular resistance that preclude easy prediction of optimal hematocrit levels.

Effects of blood viscosity on SOT have now been examined in neonates, subjects with cyanotic congenital heart disease, polycythemic adults with chronic obstructive pulmonary disease, children with left-to-right intracardiac shunts, and in a number of animal preparations. In each case, blood viscosity was observed to rise sharply when hematocrit levels exceeded 65%. However, changes in hematocrit over the range of 30% to 60% have substantial effects on vascular resistance that are not the same in all vascular beds. These findings are complicated further by the effects of reduced oxygen delivery on systemic blood flow itself. Rosenkrantz et al. have suggested that in the cerebral circulation of sheep arterial oxygen content is a more powerful determinant of flow than viscosity in the hematocrit range of 30% to 55%. Other studies by Massik et al. have confirmed that arterial oxygen content is at least as important as viscosity in modulating the level of cerebral blood flow in a lamb preparation. Lastly, Reinhart et al. have established that plasma as well as red cell factors must be addressed in considerations of blood viscosity, especially in the neonate. Therefore, whole blood viscosity must be measured at a variety of shear rates, because predictions from hematocrit alone are bound to be inaccurate. Moreover, the effect of hematocrit on vascular resistance, rather than viscosity, may be a more physiologically relevant relationship.

Confusion still remains about the judicious and appropriate use of blood transfusion in the subject with a precarious oxygen supply/demand balance. In this series of adapted subjects, SOT has been shown to be flow dependent, whereas arterial oxygen content is maintained within a narrow range by regulatory mechanisms. In subjects in acute distress, time may not be sufficient to permit hematologic compensation. In this setting, when SOT reductions are due to low flow or low arterial oxygen content, blood transfusion may be the most direct and effective way of improving oxygen delivery. The effects on viscosity of this approach are not large in the hematocrit range of 25% to 50%, but changes in vascular resistance may be significant. The physiologic need for improving oxygen delivery in various categories of patients with acute and chronic disorders of circulatory and respiratory function must await careful definition of the SOT-VO_2 relationship in these individuals, as well as clinical trials on the physiologic impact of therapy.

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