Insulin-like growth factor 1 improves the relationship between systemic oxygen consumption and delivery in piglets after cardiopulmonary bypass

Jia Li, MD, PhD^a

Elisabeth Stenbøg, MD, PhD^{b,c}

Andrew Bush, MD, FRCP^d

Thorbjørn Grøfte, MD, PhD^c

Andrew N. Redington, MD, FRCP^a

Daniel J. Penny, MD, FRCPI^e

Objective: We sought to assess the effects of insulin-like growth factor 1 on the balance between systemic oxygen consumption and oxygen delivery after cardiopulmonary bypass in piglets.

Methods: Twelve piglets weighing 4.5 to 8.3 kg undergoing hypothermic (28°C) cardiopulmonary bypass for 70 to 120 minutes with 40 minutes of aortic cross-clamping were studied before and during the first 6 hours after cardiopulmonary bypass. Oxygen consumption was continuously measured by an indirect calorimeter, Deltatrac II MBM-200 Metabolic Monitor (Datex Division Instrumentarium, Helsinki, Finland). Oxygen delivery and cardiac output were calculated from oxygen consumption and the arterial and mixed venous oxygen contents sampled before and every 30 minutes after cardiopulmonary bypass. Oxygen extraction ratio was derived by the ratio of oxygen consumption to oxygen delivery. Arterial blood lactate was measured before and every 30 minutes after cardiopulmonary bypass. Six animals were randomly assigned to receive an intravenous infusion of insulin-like growth factor 1 at 1.2 mg/h from 1 to 6 hours after cardiopulmonary bypass; the remaining 6 served as a control group.

Results: Relative to the control group, intravenous infusion of insulin-like growth factor 1 significantly reduced oxygen consumption ($P = .02$) and increased cardiac output ($P = .016$) and oxygen delivery ($P = .049$) during the first 6 hours after surgery with hypothermic cardiopulmonary bypass. As a result, oxygen extraction was significantly decreased ($P = .012$).

Conclusions: Intravenous infusion of insulin-like growth factor 1 improved oxygen transport by reducing oxygen consumption as well as increasing cardiac output and oxygen delivery during the first 6 hours after cardiopulmonary bypass in piglets. This may have important clinical implications for the care of critically ill children after surgery with cardiopulmonary bypass.

The balance between systemic oxygen delivery (DO_2) and oxygen consumption ($\dot{V}\text{O}_2$) is impaired after surgery with cardiopulmonary bypass (CPB). DO_2 is typically decreased as a result of diminished cardiac output (CO), whereas $\dot{V}\text{O}_2$ may be increased, reflecting a hypercatabolic response. The hypercatabolism has been shown to be in part a consequence of a disordered growth hormone and insulin-like growth factor (IGF-1) axis, with depressed IGF-1 levels having been reported

From the Division of Cardiology, Hospital for Sick Children, Toronto, Ontario, Canada,^a the Department of Paediatrics^b and The Institute of Experimental Clinical Research,^c Aarhus University Hospital, Aarhus, Denmark, the Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, London, United Kingdom,^d and the Department of Cardiology, Royal Children's Hospital, Melbourne, Australia.^e

Supported by the British Heart Foundation.

Received for publication May 23, 2003; revisions requested July 26, 2003; revisions received Aug 11, 2003; accepted for publication Sept 18, 2003.

Address for reprints: Daniel J. Penny, MD, FRCPI, Department of Cardiology, Royal Children's Hospital, Parkville, Melbourne, Australia 3052 (E-mail: dan.penny@rch.org.au).

J Thorac Cardiovasc Surg 2004;127:1436-41
0022-5223/\$30.00

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doi:10.1016/j.jtcvs.2003.08.044

in patients after CPB¹ and other critical illness.²⁻⁵ Recently, there has been considerable interest in the role of IGF-1 in illness-related hypercatabolism. First, circulating IGF-1 has been confirmed to have a tonic role in sustaining a general anabolic state and therefore potentially could reduce $\dot{V}O_2$ by countering the catabolic response.⁶⁻⁹ Second, IGF-1 has been shown to have positive inotropic properties by sensitizing the myofilaments to calcium ion,¹⁰ which may increase CO and DO_2 .

Nonetheless, there have been no data reported on the effect of IGF-1 on the overall balance of oxygen transport. The aim of our study was therefore to assess the effects of IGF-1 on the balance between $\dot{V}O_2$ and DO_2 after CPB in young animals.

Methods

Anesthesia

The institutional animal research committee approved the use of Danish Landrace pigs. Twelve animals, aged 2 to 3 weeks and weighing 4.5 to 8.3 kg (mean 6.7 kg), were medicated intramuscularly with ketamine (100 mg) and midazolam (5 mg). All were intubated with cuffed endotracheal tubes and mechanically ventilated with volume-cycled, intermittent, positive-pressure ventilation (Servo 900C; Siemens Medical Systems, Solna, Sweden). Anesthesia was subsequently maintained with a continuous intravenous infusion of fentanyl (300 μ g/h), midazolam (20 mg/h), and pancuronium bromide (2 mg/h). The right carotid artery and internal jugular vein were cannulated for arterial pressure monitoring, blood sampling, and infusions. Bladder catheterization was performed.

CPB

After median sternotomy and heparinization (unfractionated heparin at 300 IU/kg), a pulmonary arterial line was inserted. Animals underwent CPB with a standard clinical neonatal circuit with cannulation of the ascending aorta and right atrium (Stöckert 2.6F and right-angled 20F cannula; Medtronic DLP, Grand Rapids, Mich), a hollow-fiber membrane oxygenator (Dideco SpA, Mirandola, Italy), and a twin roller pump (JOSTRA Medizintechnik AG, Hirrlingen, Germany). The bypass machine was primed with 350 mL whole blood. Animals underwent 70 to 120 minutes (mean 87 minutes) of hypothermic CPB (28°C) with 40 minutes of aortic crossclamping and cardioplegic arrest (4°C, St Thomas solution, 30 mL/kg). CPB was continued during rewarming, until rectal temperature was restored to 38°C and hemodynamic stability was achieved. Throughout CPB, the nonpulsatile flow was maintained between 75 and 100 mL/kg so that the mean perfusion pressure was adjusted between 40 and 50 mm Hg, with additional use of nitroglycerin for vasodilation as required. Protamine sulfate (1 mL/1000 IU heparin) was given immediately after CPB. Positive-pressure ventilation was recommenced after discontinuation of CPB.

Post-CPB Care

Routine intensive care vital signs (blood pressure, heart rate, central venous pressure, pulmonary arterial pressure, rectal temperature, and urinary output) and ventilator tidal volumes and

pressures were continuously monitored. An electric warming blanket was used; otherwise, no adjustments were made to temperature during the experiments. Hemoglobin was maintained at 5 to 7 g/dL with donor blood, and hematocrit was kept at around 20%. Throughout the experiments, a fluid containing 20-mmol/L potassium chloride, 20.5-mmol/L sodium chloride, and 2.31-mmol/L glucose was infused through a central venous line. Dobutamine and nitroglycerin were used according to hemodynamic conditions. The aim was to maintain a systolic arterial blood pressure of more than 70 to 80 mm Hg, a urinary output of more than 1 mL/(kg · h), adequate peripheral perfusion, and a nonacidotic state. Additional 20% glucose was infused in the IGF-1 group, with the rate adjusted to maintain the glucose levels above 4 mmol/L.

Methods of Measurement

$\dot{V}O_2$. $\dot{V}O_2$ was measured continuously by respiratory gas analysis with an open-circuit indirect calorimeter, Deltatrac II MBM-200 Metabolic Monitor (Datex Division Instrumentarium, Helsinki, Finland).^{11,12} This calorimeter contains a fast differential paramagnetic oxygen sensor to measure a difference between inspired and expired concentrations and the absolute concentration in the inspired gas, an infrared carbon dioxide sensor, and a gas dilution system to measure flow. The apparatus has been described in detail previously elsewhere.^{13,14} Briefly, all expired gas from the ventilator enters the 4-L mixing chamber, from which gas is sampled and analyzed to determine mixed expired oxygen (FE_{O_2}) and carbon dioxide (FE_{CO_2}) concentrations. The expired gas leaving the mixing chamber is then mixed with room air so that the total flow ($\dot{Q}$) is constant. Diluted carbon dioxide fraction (F^*CO_2) is measured, and the carbon dioxide production volume ($\dot{V}CO_2$) is calculated as follows:

$$\dot{V}CO_2 = \dot{Q} \times F^*CO_2 \quad (1)$$

The respiratory quotient (RQ), or the ratio of ($\dot{V}CO_2$ and $\dot{V}O_2$), is calculated by means of the Haldane transformation as follows:

$$RQ = \frac{1 - F_{IO_2}}{(F_{IO_2} - FE_{O_2})/FE_{CO_2} - F_{IO_2}} \quad (2)$$

where F_{IO_2} indicates the inspired oxygen concentration sampled at the inspiratory limb of the ventilator circuit.

The $\dot{V}O_2$ is subsequently calculated from the RQ as follows:

$$\dot{V}O_2 = \dot{V}CO_2/RQ \quad (3)$$

Gas volumes are corrected to standard conditions of dry gas, temperature and pressure. In this study, the artifact suppression mode was used. F_{IO_2} was less than 0.4 in all subjects during the study. Changes in minute volume and F_{IO_2} were avoided 15 minutes before measurement was taken. Calibration was performed before each experiment. The Deltatrac device measures $\dot{V}O_2$ every 1 minute, and the mean of at least 5 values was taken.

DO_2 , CO, oxygen extraction ratio, and blood lactate. Arterial and mixed venous blood samples were taken from the peripheral arterial and pulmonary arterial catheters. Blood samples were analyzed for oxygen, carbon dioxide, lactate, and glucose levels with a blood analyzer (Radiometer ABL System 615; Radiometer Medical A/S, Brønshøj, Denmark). CO was then calculated with the direct Fick method according to the following equation:

$$CO = \dot{V}O_2 / (CaO_2 - C\bar{v}O_2) \quad (4)$$

where CaO_2 and $C\bar{v}O_2$ are arterial and mixed venous oxygen contents, respectively. Do_2 was then calculated by the following equation:

$$Do_2 = CO \times CaO_2 \quad (5)$$

and oxygen extraction rate (ERO_2) was calculated by the following equation:

$$ERO_2 = \dot{V}O_2 / Do_2 \quad (6)$$

Study Protocol

Hemodynamic values, $\dot{V}O_2$, and rectal temperature were obtained, and blood samples were taken at the following times: after induction of anesthesia (baseline), 30 minutes after CPB, and then every 30 minutes until 6 hours after CPB. Intravenous infusion of IGF-1 at 1.2 mg/h was commenced 1 hour after the termination of CPB, when the subject was rewarmed and stabilized, and continued to 6 hours after the termination of CPB.

Statistical Analysis

Data are expressed as mean $\pm$ SE. Comparisons of the values between baseline and after CPB within the group were carried out with the unpaired 2-tailed *t* test. Comparisons of the changes of the values over the study period between the control and IGF-1 groups were performed with mixed linear regression for repeated serial measurements. The changes in each variable during the study period were analyzed with 1-way repeated measures of analysis of variance. Correlation between two data sets was assessed with the correlation coefficient.

Results

Figure 1 demonstrates $\dot{V}O_2$, CO, Do_2 , ERO_2 , central temperature, and arterial blood lactate levels during the study period in the IGF-1 and control groups.

Baseline Measures

Piglets weighed 6.9 ± 0.5 kg in the IGF-1 group ($n = 6$) and 6.5 ± 0.6 kg in the control group ($n = 6$, $P > .05$). CPB times were 93 ± 8 minutes in the IGF-1 group and 80 ± 4 minutes in the control group ($P > .05$). The baseline values of $\dot{V}O_2$ (7.55 ± 0.60 vs 7.77 ± 0.55 mL/[min $\cdot$ kg]), ERO_2 (0.46 ± 0.08 vs 0.48 ± 0.03), lactate (1.88 ± 0.68 vs 2.20 ± 0.34 mmol/L), and central temperature ($38.2^\circ\text{C} \pm 0.4^\circ\text{C}$ vs $38.5^\circ\text{C} \pm 0.4^\circ\text{C}$) were lower in the IGF-1 group than in the control group, whereas CO (0.29 ± 0.05 vs 0.23 ± 0.02 L/[min $\cdot$ kg]) and Do_2 (19.74 ± 3.93 vs 16.36 ± 1.43 mL/[min $\cdot$ kg]) were higher; however, none of these differences were considered to be of statistical significance ($P > .05$ for all).

Changes After CPB

The values of central temperature, $\dot{V}O_2$, Do_2 , CO, and ERO_2 at 30 minutes after CPB were lower than baseline for both the IGF-1 and control groups, except for CO in the IGF-1

group, which was slightly higher, but without statistical significance in all the values ($P > .05$). Blood lactate levels were significantly higher than baseline values after CPB for both groups ($P < .001$ for both). No correlations were found between the duration of CPB and $\dot{V}O_2$ immediately after CPB, at 1 hour after CPB, and at 6 hours after CPB. ($r = 0.2$ to 0.4 , $P > .05$ for all).

Comparison of Changes Between IGF-1 and Control Groups After CPB

In the IGF-1 group, $\dot{V}O_2$ initially increased after CPB to 8.1 mL/(min $\cdot$ kg) at 2 hours (1 hour after the infusion of IGF-1). The increase was insignificant relative to the first measurements at 30 minutes after CPB ($P > .05$). Between 2 and 6 hours, there was a significant fall in $\dot{V}O_2$ in the IGF-1 group ($P = .002$); $\dot{V}O_2$ in the control group also decreased during this period. The decrease in $\dot{V}O_2$ in the IGF-1 group was significantly greater than that in the control group ($P = .02$). During the same period, central temperature remained relatively stable in the IGF-1 group, whereas it increased in the control group ($P = .008$). Both CO and Do_2 were higher in the IGF-1 group throughout the study period. During the last 4 hours, CO and Do_2 showed increases in the IGF-1 group but remained at similar levels in the control group ($P = .016$ and $P = .049$, respectively). As a result, ERO_2 was significantly decreased in the IGF-1 group relative to the control group ($P = .012$). Lactate decreased significantly in both groups ($P < .001$), being significantly greater in the control group ($P = .015$). Nonetheless, it had returned to the normal range (<2.5 mmol/L) by the end of the study period in both groups. The average doses of dobutamine and nitroglycerin and the fluid infusion were similar in both groups. In the IGF-1 group, an additional 20% glucose infusion was needed so that the blood glucose was maintained at levels similar to those in the control group (>4 mmol/L, $P > .05$).

Discussion

This is the first study to assess the effects of IGF-1 on the balance between systemic $\dot{V}O_2$ and Do_2 during the early hours after CPB. Our data shows that intravenous infusion of IGF-1 significantly reduced $\dot{V}O_2$ while maintaining the central body temperature and was associated with increased CO and Do_2 during the first 6 hours after CPB. Therefore it improved the balance between $\dot{V}O_2$ and Do_2 , as indicated by a significant decrease in ERO_2 .

Effect of IGF-1 on $\dot{V}O_2$

It is well documented that $\dot{V}O_2$ increases during the early hours after CPB,¹⁵⁻¹⁹ and that the increase is related to central body temperature^{17,19} and to the systemic inflammatory response.¹⁸ The initial postoperative $\dot{V}O_2$ in our animals was lower than baseline in all the animals, as was central temperature, reflecting incomplete rewarming after

Figure 1. Values of central temperature (A, in °C), $\dot{V}O_2$ (B, in mL/[min · kg]), CO (C, in L/[min · kg]), $\dot{D}O_2$ (D, in mL/[min · kg]), $\dot{E}RO_2$ (E), and arterial blood lactate (F, in mmol/L) during first 6 hours after CPB in piglets receiving intravenous infusion of IGF-1 started (dashed line) 1 hour after CPB (filled circles, n = 6) and in control group (open circles, n = 6). Data points represent mean; error bars represent SE.

CPB. The subsequent increase in $\dot{V}O_2$ during the following 2 or 3 hours in both groups is consistent with our own and other previous studies.¹⁵⁻¹⁹ However, there was a significant decrease in $\dot{V}O_2$ within 1 hour of starting the intravenous infusion of IGF-1.

Circulating IGF-1 levels are uniformly low in hypercatabolic states in various diseases, including after surgery with

CPB.¹⁻⁵ This may be because the acquired growth hormone resistance fails to stimulate the synthesis and release of IGF-1, leading to the failure of the liver to produce IGF-1 in these circumstances.^{20,21} Administration of IGF-1 has been reported to attenuate protein catabolism and promote anabolism in postoperative⁶ and other critically ill subjects.^{7,9} Strock and colleagues⁷ reported that the decrease in IGF-1

levels coincided with the period of most pronounced hypermetabolic response in a rat model of burn injury, and that treatment with IGF-1 reduced metabolic rate and $\dot{V}O_2$ and increased body weight significantly during a period of 14 days. Our study shows similar effects of IGF-1 in subjects after CPB. Interestingly, this response was accompanied by a significantly lower temperature ($P = .008$) than in the control group, perhaps reflecting attenuated catabolism.

The mechanisms by which IGF-1 brings about this decrease in postoperative $\dot{V}O_2$ and metabolic rate in the postoperative animals cannot be explained by a direct effect on temperature control, because IGF-1 is not antipyretic. Rather, it is best explained by the substance's anabolic effects. While being stimulated by and mediating the growth stimulatory effect of growth hormone, IGF-1 exerts insulin-like metabolic effects with the cross-reaction with the insulin receptor on the energy substrates. It has been reported that administration of IGF-1 may increase protein synthesis⁶ as well as reduce protein breakdown,²² which may be associated with a reduction in $\dot{V}O_2$. In addition, the insulin-like effect of IGF-1 that promotes glucose as energy substrate by stimulating peripheral uptake and glucose oxidation instead of fat by suppressing lipolysis²³ may further contribute to the reduction of $\dot{V}O_2$, because glucose oxidation is less oxygen demanding than is fat oxidation.^{22,24} Most studies assessing the anabolic effect of IGF-1 have been performed through a period of several days^{6,7}; the significantly reduced $\dot{V}O_2$ in our more acute study may indicate the anabolic effect of IGF-1 during the early hours after CPB. Although the mechanisms remain a matter of speculation, IGF-1 may provide beneficial effects in terms of both oxygen transport and anabolism to accelerate postoperative recovery after CPB.

Effect of IGF-1 on Do_2

Do_2 is decreased after CPB primarily because of depressed cardiac function.^{25,26} The mechanism of the fall in cardiac function remains undefined but may be related to ischemia-reperfusion injury, direct trauma, cytokines, and other myocardial depressants.^{27,28} Administration of IGF-1 has been reported to confer cytoprotection against ischemia and reperfusion injury and thus to accelerate recovery of post-ischemic cardiac function.²⁵ In addition, IGF-1 may have distinct positive inotropic properties, leading to an increase in CO.^{10,25} These factors may contribute to the significant increases in CO and Do_2 in our study in the IGF-1 group relative to the control group. Unlike with inotropic drugs, however, the increase in cardiac contractility by IGF-1 may not come at the expense of increasing myocardial $\dot{V}O_2$, because it significantly increases myofilament free calcium sensitivity rather than increasing myocyte free calcium concentration.¹⁰ This unique property of IGF-1 may offer a significant therapeutic benefit in treating a myocardium with

limited Do_2 , such as is often encountered in patients after surgery with CPB. Overall, intravenous infusion of IGF-1 improved the balance of oxygen transport, as indicated by a significant decrease in ERO_2 relative to the control group. Assessment of blood lactate is increasingly used as a surrogate for tissue oxygen use, and although the decrease in blood lactate was significantly greater in the control group, it returned to the normal range in both groups.

Effect of IGF-1 on Blood Glucose Levels

The insulinlike effect of IGF-1 to stimulate glucose uptake and oxidation may be potentially beneficial in postoperative patients. Van den Berghe and associates²⁹ recently reported that normalization of blood glucose levels with intensive insulin therapy reduced mortality and morbidity among critically ill patients in the surgical intensive care unit, regardless of whether they had a history of diabetes, although the mechanisms remain a matter of speculation. IGF-1 has been shown to be 6% as potent a hypoglycemic agent as insulin.³⁰ Hypoglycemia remains a potential complication, although it has been reported that with continuous administration of IGF-1 the acute hypoglycemia may be less pronounced because of the transferring of free IGF-1 to its binding proteins.³¹ The blood glucose levels tended to decrease to low levels because of the relatively high dose of 1.2 mg/h in the piglets in our study. Thus careful attention to the prevention of hypoglycemia is essential when using IGF-1.

Conclusion

Intravenous infusion of IGF-1 improved oxygen transport by reducing $\dot{V}O_2$ as well as increasing CO and Do_2 during the first 6 hours after CPB in young piglets. This may have important clinical implications for the care of critically ill children after CPB surgery.

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