Normalization of HBOC-induced vasoconstriction by simultaneous vasodilator administration in conscious, instrumented swine

G.P. Dubé[1], M. te Lintel Hekkert[2], D. Merkus[2], P. Moon-Massat[3], D. Freilich[3], R. McCarron[3], D.J. Duncker[2]

[1]OPK Biotech, Cambridge, MA, USA; [2]Erasmus Medical Centre, Rotterdam, NL; [3]Navy Medical Research Ctr, Silver Spring, MD

Abstract

NORMALIZATION OF HBOC-INDUCED VASOCONSTRICTION BY SIMULTANEOUS VASODILATOR ADMINISTRATION IN CONSCIOUS, INSTRUMENTED SWINE

G.P. Dubé[1], M. te Lintel Hekkert[2], D. Merkus[2], P. Moon-Massat[3], D. Freilich[3], R. McCarron[3], D.J. Duncker[2]

[1]OPK Biotech, Cambridge, MA, USA.; [2]Erasmus Medical Centre, Rotterdam, NL; [3]Navy Medical Research Ctr, Silver Spring, MD, USA

Background: Most hemoglobin-based oxygen carriers (HBOCs) sequester nitric oxide resulting in vasoconstriction, elevated blood pressure (BP) and decreased cardiac output (CO). BP increases following HBOC-201 are usually transient and mild. Associated decreases in CO are normal adaptations to increased cardiac afterload. No hard evidence links vasoactivity to a safety imbalance in HBOC-201 clinical trials. Preclinical data demonstrate maintenance of blood flow to and oxygenation of brain, heart and kidney and clinical studies indicate normal coronary blood flow (CBF) during HBOC-201 administration to patients. However, some still perceive a need to minimize HBOC vasoactivity. Study aim: Explore strategies to reduce HBOC-201 vasoactivity.

Materials and Methods: Swine were chronically instrumented for pulmonary artery pressure (PAP), aortic pressure (AP), CO, CBF and heart rate (HR) in awake animals. One wk after surgery, swine were studied before HBOC-201 at rest and at five levels of treadmill exercise (1,2,3,4,5 kg/h, 2-3 min/level) resulting in HR≈85% of max. Hemodynamics were recorded continuously, arterial and coronary venous blood (pH, lactate) was collected and myocardial lactate consumption determined. The baseline exercise program was followed by 30 min of rest and infusion of HBOC-201 (1.3 g/kg) or HBOC-201 + intravenous vasodilator nitroglycerin (NTG) or adenosine (ADO) to maintain pre-HBOC MAP ± 5 mmHg. The exercise program was then repeated.

Results: CO was proportional to exercise intensity up to 2 fold above CO at rest due to increased HR. CBF increased with increasing exercise by up to 80%. Compared to control, HBOC-201 increased MAP (by 27mmHg), PAP (by 11mmHg), systemic vascular resistance (SVR, by 47%) and pulmonary vascular resistance (PVR, by 69%) at rest. Neither HBOC-201 or HBOC + vasodilator altered myocardial work (MW) at rest or during exercise. Following HBOC-201, CO was similar to control at rest and slightly lower than control during exercise. Although HBOC-201 increased coronary vascular resistance (CVR) by 22-24% during rest and exercise, CBF was similar to control. There was no indication of anaerobic myocardial metabolism before or after HBOC-201. NTG or ADO eliminated HBOC-induced decrease in CO and increases in SVR and PVR. However, NTG, but not ADO, eliminated the HBOC-induced increase in PAP.

Conclusions: Despite HBOC-201-induced increases in MAP and PAP, MW and myocardial metabolism were unaltered by HBOC-201, even during strenuous exercise. The HBOC-201-induced increases in MAP, PAP, SVR and PVR can be prevented via simultaneous infusion of NTG or ADO.

Introduction

Most hemoglobin-based oxygen carriers (HBOCs) sequester nitric oxide resulting in vasoconstriction, elevated blood pressure (BP) and decreased cardiac output (CO). BP increases following HBOC-201 are usually transient and mild. Associated decreases in CO are normal adaptations to increased cardiac afterload. No hard evidence links vasoactivity to a safety imbalance in HBOC-201 clinical trials. Preclinical data demonstrate maintenance of blood flow to and oxygenation of brain, heart and kidney (Mongan et al, 2009; Muir et al, 2011) and clinical studies (Serruys et al, 2008) indicate normal coronary blood flow (CBF) during HBOC-201 administration to coronary disease patients. However, some still perceive a need to minimize HBOC vasoactivity (Simoni et al, 2009; Chen et al, 2009). Accordingly, we conducted a study in conscious, instrumented swine to assess the effects of HBOC-201 (OPK Biotech, LLC) on hemodynamics, cardiac function and myocardial oxygenation as reported by a surrogate metabolic marker. We further compared the effects of HBOC-201 with those of HBOC-201 plus vasodilator co-infused to match the mean arterial blood pressure to that during HBOC infusion alone. The animals were studied at rest and at different levels of exercise during each pharmacologic treatment to create a metabolically challenging condition in the face of HBOC-201-induced vasoconstriction.

Methods

Swine were chronically instrumented for pulmonary artery pressure (PAP), aortic pressure (AP), left ventricular systolic pressure (LVSP), cardiac output (CO), coronary blood flow (CBF) and heart rate (HR) in awake animals. One week after surgery, swine were studied before HBOC-201 at rest and at five levels of treadmill exercise (1, 2, 3, 4 and 5 km/h, 2-3 min/level), resulting in HR ≈ 85% of maximum. Hemodynamics were recorded continuously, arterial and coronary venous blood (pH, lactate) was collected and myocardial lactate consumption determined. The baseline exercise program was followed by 30 min of rest and infusion of HBOC-201 (1.3 g/kg) or HBOC-201 + intravenous vasodilator nitroglycerin (NTG) or adenosine (ADO) to maintain pre-HBOC mean arterial pressure (MAP) ± 5 mmHg. The exercise program was then repeated.

An index of pulmonary vascular resistance was derived by dividing PAP by CO. Myocardial lactate consumption was derived by determining the difference between arterial and coronary venous blood lactate concentrations. MVO_2 was derived by determining the difference between arterial and coronary venous blood O_2 concentrations. An index of cardiac work was derived by determining the product of CO and LVSP.

References

1. Jahr, JS, Mackenzie, C, Pearce, LB, Pitman, A, and Greenburg, AG. HBOC-201 as an alternative to blood transfusion: efficacy and safety evaluation in a multicenter phase III trial in elective orthopedic surgery. *J Trauma* 2008:64:1484-1497.
2. Mackenzie, C.F. Dubé, G.P. Pitman, A.N., Shander, A. Do hemoglobin-based oxygen carriers have ischemia-related toxicities? 60th International Congress of the European Society for Cardiovascular Surgery, Moscow, Russia, 20-22 May 2011. Interact Cardiovasc Thorac Surg. 12: S73, 2011.
3. Mongan PD, Moon-Massat PF, Rentko V, Mihok S, Dragovich A, Sharma P. Regional blood flow after serial normovolemic exchange transfusion with HBOC-201 (Hemopure) in anesthetized swine. *J Trauma*. 2009 Jul;67(1):51-60.
4. Muir WW, Ilangovan G, Zweier JL, Moon-Massat PF, RentkoVT. Vital Organ tissue oxygenation after serial normovolemic exchange transfusion with HBOC-201 in anesthetized swine. Shock, 35:597-603, 2011.
5. Serruys, PW, Vranckx, P, Slagboom, T, et al. for the COR-0001 trial investigators. Hemodynamic effects, safety, and tolerability of hemoglobin-based oxygen carrier-201 (HBOC-201) in patients undergoing PCI for CAD. EuroIntervention Journal. 3: 600-609, 2008.
6. Simoni J, Simoni G, Moeller JF. Intrinsic toxicity of hemoglobin: How to counteract it. Artif Organs. 33:100-9, 2009.
7. Chen JY, Scerbo M, Kramer G. A review of blood substitutes: examining the history, clinical trial results, and ethics of hemoglobin-based oxygen carriers. Clinics (Sao Paulo), 64:803-13, 2009.

Results

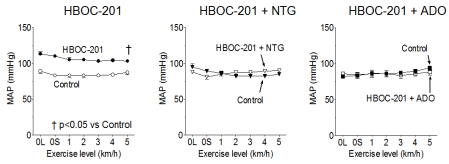

Figure 1. HBOC-201-induced increase in MAP is normalized by simultaneous NTG or adenosine infusion. HBOC-201 increased MAP 20-25 mmHg and systemic vascular resistance (SVR, not shown) at all levels of exercise. Simultaneous intravenous nitroglycerin (NTG) and adenosine (ADO) yielded MAPs and SVRs similar to those during HBOC-201 alone. Exercise itself had little effect on MAP.

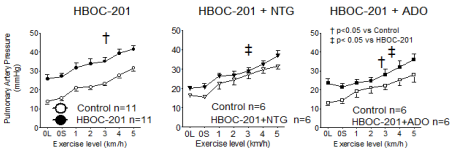

Figure 2. NTG, but not ADO, resolves HBOC-201-induced increase in pulmonary artery pressure. HBOC-201 increased pulmonary artery blood pressure (PAP) at rest and at all exercise levels secondary to increased pulmonary vascular resistance (PVR). NTG co-infusion normalized PAP. ADO co-infusion, however, was less effective in reducing PAP.

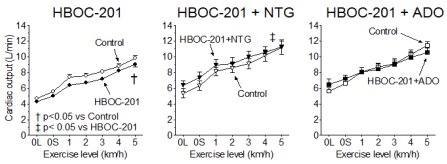

Figure 3. HBOC-201-induced decrease in CO is normalized by simultaneous NTG or adenosine infusion. HBOC-201 moderately depressed cardiac output (CO) over the full range of exercise levels and co-administration of NTG or ADO eliminated this effect. Exercise-induced increases in CO were attributable primarily to increased heart rate; stroke volumes were essentially unchanged by exercise.

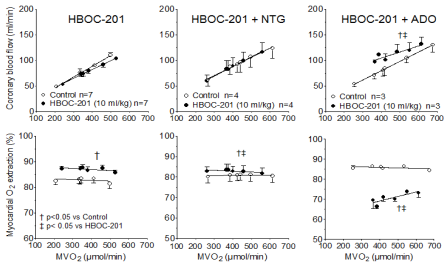

Figure 4. Coronary blood flow as a function of myocardial oxygen consumption. HBOC-201 had no effect on coronary blood flow (CBF) as a function of myocardial oxygen consumption (MVO_2). However, myocardial oxygen extraction (MO_2E) as a function of MVO_2 increased during HBOC-201 administration, possibly due to increased cardiac afterload. NTG co-infusion normalized MO_2E, possibly due to normalization of cardiac afterload, and adenosine sharply decreased MO_2E due to normalizing cardiac afterload and elevating CBF. Thus, ADO uncoupled CBF from MVO_2.

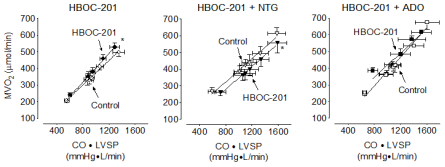

Figure 5. HBOC-201-induced increase in myocardial oxygen consumption is reversed by nitroglycerin and normalized by adenosine. HBOC-201 slightly increased MVO_2 as a function of cardiac work (CO•LVSP) compared to control (P<0.05), evident primarily over higher exercise levels. Co-infusion of NTG reduced MVO_2 to a level below that in control animals (P<0.05) and ADO co-infusion normalized MVO_2.

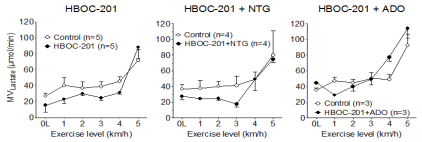

Figure 6. Myocardial lactate consumption is unaffected by HBOC-201. HBOC-201 had no effect on myocardial lactate consumption ($MV_{Lactate}$) compared to control. $MV_{Lactate}$ remained positive at rest and all exercise levels indicating that the myocardium maintained aerobic metabolism under all treatment conditions and exercise levels.

Discussion

The increase in mean arterial pressure during and following HBOC-201 infusion resulted in a modest decrease in cardiac output. This increase in cardiac afterload tended to increase myocardial work (although this effect did not reach significance) and increased myocardial oxygen consumption as a function of work. Although coronary blood flow was essentially unchanged by HBOC-201, myocardial oxygen extraction increased. The decrease in cardiac output and increase in myocardial oxygen extraction are both normal, physiological adaptations to an increase in cardiac afterload (both systemic and pulmonary). These adaptations limited the increase in cardiac work and maintained or increased oxygen utilization as a function of cardiac work, thereby facilitating maintenance of aerobic myocardial metabolism and averting signs of anerobic function (consumption rather than production of cardiac lactate). Furthermore, these adaptations and aerobic metabolism persisted through even strenuous exercise. Although co-infusion of vasodilators, nitroglycerin and adenosine could be administered to maintain MAP and PAP at or near pre-HBOC levels, and thereby preclude the physiological adaptations that occurred during infusion of HBOC-201 alone, vasodilator therapy was not necessary to maintain aerobic cardiac function and stable hemodynamics.

During both exercise and anemia, organisms respond by increasing cardiac output and redistributing flow to organs according to oxygen need. It is important to recognize that in coronary disease patients and the elderly, hemodynamic adaptations similar to those that occurred in the healthy swine of the current study may be limited. Fixed coronary stenosis and/or low coronary microvascular vasodilatory reserve may preclude an optimum or adequate increase in coronary flow to meet the demands of exercise or severe anemia. For this reason, it is recommended that treatment of anemia with HBOC-201 be limited to individuals under 80 yrs of age and without a history of cardiac disease (Jahr et al, 2008). Anemia in these individuals is more safely treated with packed red blood cells that have a higher efficacy than HBOC-201 to increase total hemoglobin concentrations (MacKenzie et al, 2011).

Conclusions

- Coronary blood flow was unchanged during HBOC-201 administration, consistent with previous preclinical and clinical studies.
- HBOC-201 administration, under conditions demonstrated to induce systemic and pulmonary vasoconstriction, increase blood pressure and decrease cardiac output, was well tolerated and supported aerobic cardiac function, even during strenuous exercise.
- HBOC-201-induced increases in MAP, PAP, SVR, PVR and associated hemodynamic and cardiac adaptations, can be prevented via simultaneous infusion of nitroglycerin or adenosine.
- Although not necessary for normal aerobic cardiac function in healthy animals (this study) and cardiac disease patients (Serruys et al, 2008) with normal hemoglobin concentrations, co-infusion of HBOC-201 and nitroglycerin or adenosine may provide additional protection to anemic patients having advanced age and/or a history of cardiac disease. New clinical studies would be required to validate this hypothesis.

Notices

- GPD is employed by OPK Biotech, LLC, manufacturer of HBOC-201.
- The views expressed in this presentation are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.
- Conducted in compliance with the Animal Welfare Act and in accordance with the "Guide for the Care and Use Committee; Use of Laboratory Animals," Institute of Laboratory Animals Resources, NRC, National Academy Press, 1996.
- BUMED congressional funding: 604771N.9737.001.A0315.
- Studies approved by NMRC/WRAIR IACUC or respective academic IACUCs.