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The use of esmolol in whole-body hyperthermia: cardiovascular effects

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Whole-body hyperthermia (WBH) is a well-described investigational adjunct to systemic chemotherapy for the treatment of advanced malignancies. The hemodynamic consequences of this physiologic state may include tachycardia, which can produce acute myocardial ischemia in patients with coronary artery disease. Ischemic heart disease is currently considered a contraindication to WBH. We chose to investigate the consequences of using a new β_1-adrenergic antagonist, esmolol, to attempt to control the tachycardia associated with WBH. After institutional approval and patient consent, nine consecutive patients with normal cardiac function presenting for WBH with carboplatin infusion were studied. Along with standard monitors, radial arterial and oximetric thermodilution pulmonary artery catheters were placed. Patients were sedated and heated in a radiant warmer (Enthermics). Spontaneous ventilation was maintained and hemodynamic data were gathered at 37°C, and at 41·8°C (before, during and after esmolol infusion). Heart rate and cardiac output increased (by 46% ($p = 0{\cdot}001$) and 35% ($p = 0{\cdot}04$) respectively) while mean arterial pressure and systemic vascular resistance fell (by 18% ($p = 0{\cdot}02$) and 44% ($p = 0{\cdot}006$) respectively) during hyperthermia. Heart rate was significantly reduced during esmolol administration (mean dose 180 μg/kg/min) in the absence of changes in cardiac index and calculated oxygen delivery. Ventricular filling pressures and stroke work were unchanged. No heart failure, pulmonary edema, or other adverse event was observed. Hemodynamic changes seen during esmolol administration were completely reversed 15 min after the infusion was stopped. We conclude that the administration of moderate doses of esmolol is safe for this population of patients undergoing WBH, and that this technique raises the question of whether patients with ischemic heart disease could safely undergo WBH.

Key words: Hyperthermia, whole-body, esmolol, beta-receptor blockade, effects, cardiovascular, effects, hemodynamic.

1. Introduction

Deliberate whole-body hyperthermia (WBH) has been shown to slow the progress of some cancers alone or as an adjuvant to chemotherapy or radiation therapy (Robins *et al.* 1990, Gautherie 1992, Dewhirst *et al.* 1982, Ohno *et al.* 1992). The methodologies for applying WBH are varied, including hot wax bath, hot water bath, hot water suit or blanket, hot air and microwave, as well as radiant heat. There has also been considerable variation in anaesthetic techniques applied, from

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general anaesthesia to sedation, and even no anaesthesia (Robins *et al.* 1985, van der Zee *et al.* 1987, Gautherie 1992). Some cardiovascular responses to hyperthermia are consistent and independent of methodologies used: heart rate, cardiac output, and total oxygen consumption all increase significantly. In contrast, changes in arterial blood pressure, central venous pressure, and pulmonary capillay wedge pressure, as well as reports of cardiac arrhythmias, are inconsistent. Myocardial work and oxygen consumption is significantly increased during hyperthermia (Sladen *et al.* 1981, Faithfull *et al.* 1984, van der Zee *et al.* 1987). Although, in patients without cardiovascular disease, the increased oxygen demand may be well tolerated due to a normal coronary reserve, pre-existing heart disease or coronary artery disease may lead to myocardial ischemia due to an increased oxygen demand beyond the capacity of the coronary circulation. With the onset of ischemia, the coronary perfusion may be compromised even further by a decreased diastolic compliance and increased end-diastolic pressures (Nathan 1993, Thys and Dauchot 1993). Because of the potentially deleterious effects of myocardial ischemia, most centers studying WBH require an extensive cardiovascular evaluation pre-treatment and have excluded any patient with pre-existing cardiovascular diseases (Faithfull *et al.* 1984, Robins *et al.* 1985, van der Zee *et al.* 1987).

Esmolol is a short-acting, cardioselective β_1-adrenergic antagonist (at usual clinical doses) without intrinsic sympathomimetic activity or membrane-stabilizing effects. The drug is metabolized by red blood cell esterases with a half-life of 9 min. Its metabolites have no clinical activity and are eliminated by the kidney. The effects of esmolol on cardiovascular parameters at rest and during exercise were found similar to those of propanolol, but they are reversible within 20 to 30 min after discontinuation (as opposed to several hours for propanolol) (Iskandrian *et al.* 1985, Royster 1993). This study was designed to determine the effective dose and to document any adverse effects of esmolol on the cardiovascular parameters of patients during WBH. The results of this study should provide data concerning the possibility of safely controlling HR during WBH with minimal impact on other hemodynamic parameters.

2. Materials and methods

After institutional human subjects committee approval and individual informed consent were obtained, we studied nine consecutive patients scheduled for whole body hyperthermia with carboplatin infusion. Four female and five male patients, ages 39–63 years and weighing 57–91 kg were enrolled. All patients were screened for significant heart or lung diseases with stress pulmonary function testing ($paO2 > 60$ mmHg breathing room air, and $FEV1/FVC > 0{\cdot}50$) and exercise nuclear ventriculography ($EF > 50\%$ with $> 5\%$ increase during exercise). Each patient had an indwelling subclavian central venous catheter in place prior to the procedure.

After sedation with midazolam 25–40 μg/kg IV, left radial arterial and right internal jugular venous catheters were placed under local anesthesia. A 7F balloon-tipped, flow-directed, thermodilution pulmonary artery catheter with oxygen saturation sensor (Oximetric, Abbot) was placed in the pulmonary artery via the internal jugular introducer after *in vitro* calibration. Precalibrated thermocouple temperature probes (Yellow Springs Instrument Co., Yellow Springs, Ohio) were placed on the anterior chest, anterior thigh, and axilla, as well as in the rectum and mid-esophagus. Blood temperature was recorded from the pulmonary artery cathe-

ter. Other monitoring included: 5-lead ECG (limb leads plus V5), pulse oximetry (SpaceLabs Medical, Inc., Redmond, Washington), and urine output via indwelling catheter. Cardiac output measurements were made in triplicate using 10 cc aliquots of 5% dextrose solution at room temperature (22–23°C). Lactated Ringer's solution was intravenously infused at 5·5–8·8 ml/kg/h during the treatment.

After baseline measurements of heart rate (HR), mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), arterial oxygen saturation (SpO_2), and venous oxygen saturation (SvO_2), the patient was placed in a radiant heating unit (Enthermics, Menomonee Falls, WI) with the head exposed. Inside the unit the radiant temperature was 65°C and the relative humidity 100%. Continuous digital recordings of temperatures from the skin, core, and blood probes were made during the entire procedure.

Patients received infusions of lidocaine (22–35 μg/kg/min) and thiopental (33–52 μg/kg/min); fentanyl was provided (up to 5 μg/kg) incrementally for discomfort. Patient comfort was continuously evaluated by one investigator (J.B.) and adequate analgesia maintained throughout the procedure. Spontaneous ventilation was maintained during the procedure; oxygen was supplied via nasal prongs at 3 l/min. When esophageal and blood temperature reached 41·8 ± 0·2°C, the patient was removed from the chamber and wrapped in insulating blankets to maintain a constant plateau temperature. An intravenous infusion of carboplatin (dose calculated according to the method of Egorin *et al.* (1984)) was begun after reaching target temperature and continued for the next 2 h. Hemodynamic data was obtained after 15 min at target temperature; then, esmolol 500 μg/kg was administered as a bolus and an infusion titrated over the next 5 min until HR was reduced by approximately 20%. After 15 min of steady-state esmolol infusion, hemodynamic measurements were repeated. Esmolol was then stopped and, 15 min later, a final set of measurements were made. After a total of 2 h at 41·8°C, the carboplatin and thiopental infusions were stopped; the patient was removed from the radiant warmer and actively surface cooled with a water mist and forced-air evaporation. The infusion of lidocaine was stopped at a core temperature of 38°C, and an anteroposterior chest radiograph was obtained. The patient was allowed to recover, and the jugular and arterial catheters were removed. After overnight observation, the patient was discharged from hospital.

Body surface area (BSA) was calculated by the method of Dubois and Dubois (1916); cardiac index (CI), systemic vascular resistance index (SVRI), pulmonary vascular resistance index (PVRI), stroke volume index (SVI), left and right ventricular stroke work indices (LVSWI, RVSWI), and oxygen delivery and consumption were calculated according to standard formulae†. Data were analysed using ANOVA with Tukey's *post hoc* test; $p < 0{\cdot}05$ was considered significant. All data are reported as mean ± standard error of the mean.

†Hemodynamic calculations as follows:
CI = CO/BSA; SVI = CI/HR;
SVRI = (MAP-CVP)(80)/CI; PVRI = (MPAP-PCWP)(80)/CI;
LVSWI = SVI(MAP-PCWP)(0·0136); RVSWI = SVI(MPAP-CVP)(0·0136);
O_2 delivery = (CI)(BSA)(CaO_2)(10), where $CaO_2 = 1{\cdot}36(Hb)(SpO_2) + (0{\cdot}003)(PaO_2)$
O_2 consumption = (CI)(BSA)(CaO_2-CvO_2)(10), where $CvO_2 = 1{\cdot}36(Hb)(SvO_2)$ + (0·003) (PVO_2);
PaO_2 and PvO_2 are estimated at 100 mmHg and 40 mmHg respectively;
Hb = hemoglobin concentration in gm/dl.

3. Results

The results are summarized in Table 1. During hyperthermia, HR increased 46% (136 ± 7 versus 93 ± 8, $p = 0.001$) and CI increased 35% (6·9 ± 0·4 versus 5·1 ± 0·6 l/min/m^2, $p = 0.04$) while MAP decreased 18% (77 ± 5 versus 94 ± 4 mmHg, $p = 0.02$), SVRI decreased 44% (810 ± 90 versus 1460 ± 180 dyne s m^2/cm^5, $p = 0.006$), and PVRI decreased 54% (72 ± 5 versus 154 ± 52, $p = 0.04$). Pulmonary artery pressures and cardiac filling pressures did not change with the onset of hyperthermia. SVI remained constant, but right ventricular stroke work (RVSWI) decreased by 38% (4·0 ± 0·8 versus 6·4 ± 1·5 g m/m^2, $p = 0.04$). Neither ST segment changes nor arrhythmias were noted. Oxygen delivery and consumption measurements (Table 2) showed evidence of adequate perfusion (oxygen extraction ratios ≤ 0·25).

The mean dose of esmolol required was 180 ± 20 μg/kg/min. HR decreased by an average of 23 min^{-1} or 17% (113 ± 4 versus 136 ± 7 min^{-1}, $p = 0.013$). During esmolol administration, no significant changes were observed in MAP (65 ± 4 versus 77 ± 5 mmHg, $p = 0.12$), MPAP, CVP, PCWP (13 ± 2 versus 10 ± 2 mmHg, $p = 0.34$), CI, SVI, SVRI, PVRI, LVSWI, RVSWI, oxygen delivery (1120 ± 90 versus 1310 ± 80, $p = 0.14$) or oxygen consumption. Within 15 min after esmolol

Table 1. Hemodynamic values during whole-body hyperthermia.

Mean±SEM ($n = 9$)	38°C	41·8°C	41·8°C + esmolol for 15 min	41·8°C, 15 min after esmolol stopped
HR (min^{-1})	93 ± 8	136 ± 7†	113 ± 4‡	138 ± 4
MAP (mmHg)	94 ± 4	77 ± 5†	65 ± 4	75 ± 6
MPAP (mmHg)	21 ± 2	17 ± 2	18 ± 2	17 ± 1
CVP (mmHg)	8 ± 1	9 ± 2	11 ± 2	10 ± 3
PCWP (mmHg)	11 ± 1	10 ± 2	13 ± 2	11 ± 2
CI (l/min/m^2)	5·1 ± 0·6	6·9 ± 0·4†	5·8 ± 0·5	7·1 ± 0·4
SVI (ml/m^2)	56 ± 8	52 ± 4	52 ± 5	51 ± 6
SVRI (dyne s m^2/cm^5)	1460 ± 180	810 ± 90†	790 ± 80	740 ± 60
PVRI (dyne s m^2/cm^5)	154 ± 52	72 ± 5†	60 ± 13	58 ± 21
LVSWI (g m/m^2)	41 ± 6	30 ± 3	25 ± 4	29 ± 3
RVSWI (g m/m^2)	6·4 ± 1·5	4·0 ± 0·8†	3·8 ± 0·6	3·3 ± 1·1

†$p < 0.05$ versus 38°C
‡$p < 0.05$ versus 41·8°C

Table 2. Oxygen transport during whole-body hyperthermia.

Mean±SEM ($n = 9$)	38°C	41·8°C	41·8°C + esmolol for 15 min	41·8°C, 15 min after esmolol stopped
SpO_2 (%)	98 ± 1	95 ± 2	96 ± 2	96 ± 2
SvO_2 (%)	74 ± 1	74 ± 2	73 ± 2	77 ± 2
Hemoglobin (g/dl)	8·8 ± 0·9	8·7 ± 1·1	8·7 ± 1·1	9·3 ± 0·8
O_2 delivery (ml/min)	1000 ± 120	1310 ± 80	1120 ± 90	1430 ± 110
O_2 consumption (ml/min)	230 ± 20	290 ± 30	280 ± 30	280 ± 20
O_2 extraction	0·24	0·22	0·23	0·20

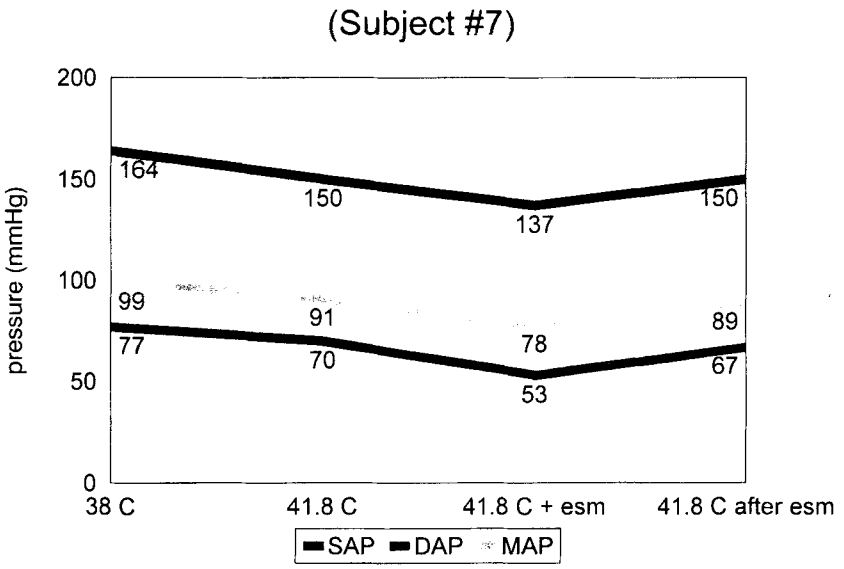

Figure 1. Blood pressure response to esmolol during WBH.

was stopped, the HR returned to its previous level; no other hemodynamic changes were observed. In post-treatment evaluation, no clinical or radiographic evidence of pulmonary edema was found, and no patient complications or adverse events were observed.

The changes in blood pressures and heart rate during the course of the treatment are also presented graphically for one typical patient (Figure 1).

4. Discussion

Our data demonstrate that, during WBH, the brief administration of esmolol resulted in a selective reduction in HR with little effect on other hemodynamic parameters. We also noted important differences in the measured hemodynamic responses to hyperthermia from those previous reported.

The hemodynamic changes associated with WBH were first examined by Faithfull *et al.* (1984) who showed significant increases in HR and CI, along with

Table 3. Significant differences among hemodynamic responses to WBH.

Variable	Current study	Faithfull *et al.* (1984)
Ventilation	Spontaneous	Controlled
Anesthetic	IV sedation	General endotracheal
MPAP (change from baseline)	−24% (n.s.)	+20% ($p < 0{\cdot}05$)†
PVRI (change from baseline)	−53% ($p < 0{\cdot}05$)	−40% ($p < 0{\cdot}001$)†
RVSWI (change from baseline)	−38% ($p < 0{\cdot}05$)	+263% ($p < 0{\cdot}001$)†

†p values versus beginning of warming (after anaesthetic induction) in original analysis.

decreases in SVRI and PVRI. Their data reflected an increase of 17% in MPAP and a doubling of RVSWI with hyperthermia; in our study MPAP was unchanged while RVSWI decreased (Table 3). The difference in stroke work is important when addressing concerns of potential right ventricular failure in these patients; radiant warming with sedation seems to unload the right ventricle much more than contact heating and general anaesthesia. These changes in right ventricular function may reflect the methodology used for inducing hyperthermia (hot air/water blanket versus our radiant warmer). However, another explanation is the difference in anaesthetic and ventilation techniques used. Faithfull *et al.* (1984) used methohexital, nitrous oxide and curare with controlled ventilation in their series, possibly producing changes in right-sided filling pressure and increasing pulmonary vascular resistance; whereas, we maintained spontaneous ventilation. They also did not report fluid management in their series and measured CVP in only 8 of their 30 subjects. It is possible that the new technology of radiant heating, with its attendant decrease in anaesthetic requirements (and no need for controlled ventilation), has altered the hemodynamic responses to hyperthermia. The use of sedation, while maintaining spontaneous ventilation, substantially lowers the intrathoracic filling pressures required to maintain cardiac output. Also, the presence of positive airway pressure in Faithfull's patients may have changed the compliance of the pulmonary vasculature sufficiently to account for their higher MPAP and RVSWI. More recently, Robins *et al.* (1985) reported some hemodynamic measurements in eight patients during WBH in a radiant device similar to ours. During sedation and spontaneous ventilation, stable MAP, MPAP, and PCWP were reported along with the expected increase in HR and CO.

The use of β-adrenergic blocking drugs is logical in patients at risk for myocardial ischemia. Tachycardia compromises diastolic coronary filling, and is significantly related to myocardial ischemia, while drugs blocking the cardiac β-receptors reduce HR and contractility, decrease MVO_2 and protect against myocardial ischemia (Slogoff and Keats 1985, 1988, Royster 1993). The use of β-receptor antagonists during hyperthermia was first reported in 1977. In a series of 29 patients under general endotracheal anaesthesia, pindolol was used in doses of 40 to 200 μg to control HR below 120 during hyperthermia to 42°C for 2 h. No hemodynamic measurements were reported (Euler-Rolle *et al.* 1978). Another report by Moricca *et al.* (1979) in patients anaesthetized with an unspecified barbiturate, nitrous oxide, and curare noted a pulse increase of 10 beats/min/°C. They used oxprenolol 2–6 mg to maintain a heart rate < 180, but again reported no hemodynamic measurements. The most interesting study of beta-blockade during WBH was performed in dogs by Robins *et al.* (1991). Three acutely instrumented, barbiturate-anaesthetized dogs were heated to 42°C with a radiant device similar to the one used in our series. After the infusion of 0·64 mg/kg propanolol over 25 min, HR fell by 12–47% and ejection fraction (determined by nuclear ventriculography) fell by 12–13%. They also noted 'changes in pulmonary vasculature demonstrating early pulmonary oedema' in their radionuclide studies. They interpret their results as representing a relative contraindication to drug-induced β-blockade during radiant heating WBH. We assume that Robins' group used propranolol because it was, at the time, the only β-antagonist available in intravenous formulation and that their results reflect the expected consequences of a nonspecific sympathetic blockade. Since esmolol is more specific for β_1-receptors, undesirable β_2-adrenergic blockade did not occur in our subjects.

Another issue of interest is whether prolonged administration of esmolol produces the same effects as seen in this study. One study (Ornstein *et al.* 1995) noted that the bradycardic effect of esmolol had a $t_{1/2}$ of 1·2 min while the hypotensive effect had a $t_{1/2}$ of 17·8 min. The authors attribute the slow onset of hypotension to esmolol-mediated inhibition of renin release and slow depletion of circulating levels. While their study was performed in isoflurane-anaesthetized, ventilated patients, it raises questions as to whether we achieved a steady-state MAP in our series. Further study of prolonged esmolol infusions may be appropriate.

Other issues have been debated concerning the cardiovascular physiology of the hyperthermic state. One argument for the necessity of high HR during hyperthermia has been proposed by van der Zee *et al.* (1987) and reiterated by Faithfull *et al.* (1984) and Robins *et al.* (1991). It is based on the premise that flow can be increased by increasing HR at a fixed SVI; this results in a smaller increment in ventricular work than increasing flow by increasing SVI at a constant HR. While this argument is valid, it presupposes that increased flow is a physiologic necessity. Although only global O_2 delivery and consumption were measured in this study, oxygen transport was more than adequate as reflected in the constant O_2 consumption and normal extraction ratios. Since hyperthermia results in a large increase in blood flow through cutaneous shunts, an increase in cardiac output should be necessary only to the extent needed to maintain vital organ perfusion in the face of a maximally dilated cutaneous vascular bed. We feel that this may be accomplished by the partial blockade of the usual sympathetic response to hyperthermia.

5. Conclusions

The present study demonstrates that: (1) in a population without cardiac disease, short-term, selective β_1-blockade with moderate doses of esmolol produces no adverse hemodynamic effects; and, (2) previous observations of hemodynamic changes with whole-body hyperthermia in anaesthetized, ventilated subjects may not be valid in sedated patients breathing spontaneously.

It may be determined by future studies that β_1-blockade will be useful in allowing patients with coronary artery disease to safely undergo whole-body hyperthermia as an adjunct to chemotherapy for advanced malignancies. Further study in animal models of myocardial ischemia rather than in patient populations at risk for myocardial infarction should be performed. Nonetheless, in patients exhibiting unexpected signs of myocardial ischemia and profound tachycardia while undergoing whole-body hyperthermia, esmolol may be a useful adjunct in controlling HR and minimizing potential myocardial injury while other measures (such as terminating the hyperthermic treatment) are being taken.

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