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Selective Endothelin-A Receptor Inhibition After Cardiac Surgery: A Safety and Feasibility Study

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Background. Increased synthesis and release of the bioactive peptide endothelin has been shown to change hemodynamics and postoperative recovery after cardiac surgery. However, the clinical effects of selective interruption of endothelin signaling have not been studied. Because the endothelin-A (ET-A) receptor subtype is the primary cardiovascular effector for endothelin, this study used the ET-A receptor antagonist sitaxsentan sodium (TBC11251Na) to evaluate: (1) dose-dependent changes in pulmonary artery pressure (PAP) and pulmonary (PVRI) and systemic (SVRI) vascular resistance index in patients undergoing on-pump coronary revascularization; and (2) whether ET-A administration was associated with increased adverse events.

Methods. Patients ($n = 44$, age, 62 ± 1 years) were randomized to receive vehicle ($n = 9$) or different bolus infusions of ET-A receptor antagonist: 0.1 ($n = 9$), 0.5 ($n = 9$), 1.0 ($n = 9$), and 2.0 mg/kg ($n = 8$) at separation from cardiopulmonary bypass (CPB). Adverse events were tabulated until hospital discharge. Results were expressed as changes from a composite baseline value, or from time 0 due to a high degree of inpatient measurement variability in the postoperative period.

Results. PAP increased by $27\% \pm 13\%$ from baseline (19 ± 1 mm Hg) in the vehicle group at 6 hours post-CPB

($p < 0.05$). PAP fell from this post-CPB vehicle value in a dose-dependent manner with the ET-A receptor antagonist; with a significant reduction observed at 2 mg/kg ($7\% \pm 8\%$ increase from baseline, $p < 0.05$). PVRI was reduced by $28.6\% \pm 16\%$ from baseline (249 ± 22 dyn \cdot s \cdot cm⁻⁵ \cdot m⁻²) in the 2 mg/kg ET-A receptor antagonist group at 30 minutes post-CPB and remained reduced up to 6 hours post-CPB ($p < 0.05$). SVRI was reduced from baseline (2770 ± 106 dyn \cdot s \cdot cm⁻⁵ \cdot m⁻²) by $51\% \pm 6\%$ in the 2.0 mg/kg ET-A receptor antagonist group at 30 minutes post-CPB ($p < 0.05$) and remained reduced up to 6 hours post-CPB. A total of 203 adverse events were tabulated in the postoperative period and were equally distributed across the five treatment groups, with no direct attributions to ET-A receptor antagonist treatment.

Conclusions. This unique study demonstrates that heightened endothelin-A receptor activation contributes to hemodynamic changes in patients after CPB. Selective inhibition of the endothelin receptor system can be successfully and safely performed in patients undergoing cardiac surgery and thereby reveals a potential, and clinically relevant therapeutic target.

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Endothelin-1 (ET) is a biopeptide that exerts potent and prolonged effects on the cardiovascular system [1–4]. Elevated levels of ET have been demonstrated in several pathologic conditions of the cardiovascular system. Increases in plasma ET also occur in the perioperative period after cardiac surgery requiring cardiopulmonary bypass (CPB), with associated greater inotropic requirements, coronary conduit (especially arterial) vasospasm, increased pulmonary vascular resistance, and increased postoperative morbidity [5–14]. Taken to-

gether, these findings suggest that the induction and release of ET in the early post-CABG period may be detrimental.

The biologic effects of ET occur through the occupancy and activation of two fundamental receptor types: the ET A receptor (ET-A) and ET B (ET-B) receptors [10, 14]. The ET-A receptor is the predominant subtype found within the vasculature and myocardium. Previous work from our laboratory has established that the ET-A receptor exerts negative inotropic effects [15, 16] and may cause significant pulmonary arterial vasoconstriction [17]. In

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Table 1. Measured Intraoperative Data^a

Group ^b	Baseline	0 Hr	0.5 Hr	6 Hr	24 Hr
CI (mm Hg)					
Placebo	2.1 ± 0.3	3.3 ± 0.9 ^c	3.3 ± 1.2 ^c	3.3 ± 1.2 ^c	3.3 ± 0.6 ^c
1.0 mg/kg	2.2 ± 0.6	3.2 ± 0.6 ^c	3.2 ± 0.9 ^c	3.2 ± 0.6 ^c	3.0 ± 0.6 ^c
2.0 mg/kg	2.0 ± 0.3	3.1 ± 0.6 ^c	3.5 ± 0.6 ^c	3.2 ± 0.6 ^c	3.1 ± 0.6 ^c
MAP (mm Hg)					
Placebo	78.9 ± 13.2	71.4 ± 4.5	79.6 ± 10.2	78.3 ± 5.1	85.3 ± 10.2
1.0 mg/kg	79.2 ± 10.8	70.3 ± 9.9	76.0 ± 13.2	76.4 ± 8.4	83.0 ± 11.7
2.0 mg/kg	80.5 ± 12.0	76.5 ± 16.5	70.3 ± 9.5 ^c	79.9 ± 12.0	77.4 ± 9.0
PAP (mm Hg)					
Placebo	18.5 ± 4.5	16.8 ± 4.5	18.7 ± 3.9	20.3 ± 3.9	17.7 ± 6.6
1.0 mg/kg	20.4 ± 2.4	19.0 ± 3.6	20.1 ± 2.1	20.5 ± 7.5	18.5 ± 6.9
2.0 mg/kg	19.9 ± 5.3	18.6 ± 3.1	20.5 ± 1.6	19.8 ± 4.5	16.6 ± 5.9
PVRI (dyne · s · cm ⁻⁵ · m ⁻²)					
Placebo	258.1 ± 125	206.5 ± 127	198.8 ± 116	244.4 ± 152	205.2 ± 185
1.0 mg/kg	210.2 ± 151	158.4 ± 70	194.3 ± 93	216.8 ± 118	209.2 ± 130
2.0 mg/kg	249.0 ± 120	151.7 ± 46	148.5 ± 76	165.3 ± 99	174.9 ± 82
SVRI (dyne · s · cm ⁻⁵ · m ⁻²) ^d					
Placebo	2693 ± 453	1655 ± 489 ^c	1835 ± 516 ^c	1781 ± 483 ^c	1954 ± 468 ^c
1.0 mg/kg	2589 ± 882	1592 ± 555 ^c	1821 ± 864 ^c	1672 ± 324 ^c	1931 ± 390 ^c
2.0 mg/kg	2890 ± 820	1783 ± 535 ^c	1330 ± 316 ^c	1794 ± 297 ^c	1759 ± 414 ^c
Plasma endothelin (fmol/mL, corrected for hemodilution)					
Placebo	2.8 ± 1.2	—	4.2 ± 3.3	4.7 ± 2.1	6.3 ± 2.1 ^c
1.0 mg/kg	4.1 ± 1.8	—	4.3 ± 3.0	6.5 ± 3.3	7.6 ± 3.9 ^c
2.0 mg/kg	3.3 ± 2.1	—	4.1 ± 2.2	6.0 ± 3.1 ^c	6.4 ± 3.4 ^c

^a Data expressed as mean ± standard deviation. ^b Sample sizes: placebo, n = 9; 1.0 mg/kg, n = 9; 2.0 mg/kg, n = 8. ^c *p* < 0.05 versus baseline. ^d Significant trend across doses based on non-parametric analysis.

CI = cardiac index; MAP = mean arterial pressure; PAP = pulmonary artery pressure; PVRI = pulmonary vascular resistance index; SVRI = systemic vascular resistance index.

the latter regard, we have shown that pulmonary vascular resistance increases after cardiac surgery requiring CPB were associated with changes in ET plasma levels [7, 8, 11].

In light of these observations, we hypothesized that during cardiac surgery, the release of ET with subsequent ET-A receptor activation directly contributes to pulmonary vascular resistance in the early postoperative period and that inhibition of the ET-A receptor would attenuate this effect. Accordingly, the current study was performed with the following objectives:

1. To administer a selective ET-A receptor antagonist in patients immediately after separation from CPB and determine whether a dose-dependent effect in pulmonary vascular resistance could be identified;
2. To determine whether ET-A receptor blockade would alter systemic hemodynamics over and above the effects on the pulmonary vasculature; and
3. To identify that delivery of a selective ET-A receptor antagonist would be safe, as defined as no increased adverse effects, in the context of cardiac surgery requiring CPB.

Patients and Methods

Patients

After approval by the Human Subjects Review Committee of the Medical University of South Carolina (HR11122), 44 consecutive patients undergoing elective coronary artery bypass (CABG) surgery requiring CPB provided informed consent to participate in the study. Although the study was conducted at two institutions, MUSC Medical Center and the Ralph H. Johnson Veterans Affairs Medical Center, the most procedures were performed at the latter institution. Because men comprise most of the patient population in this latter institution, this study was conducted in male patients only. All operations were performed by one surgeon (JSI).

The inclusion criteria included age between 18 and 80 years old, body mass index of less than 40 kg/m², left ventricular ejection fraction exceeding 0.35, and no heart failure symptoms according to New York Heart Association classification; if diabetic, be under proper control (fasting glucose <350 mg/dL or recent hemoglobin A_{1c} <9%); if hypertensive, be on a stable medical regimen with no significant changes within the past 30 days.

The exclusion criteria included emergency revascularization, stroke, or thromboembolic event within 3 months before surgery, previous myocardial infarction, or documented coagulopathy; hepatic dysfunction as defined by aspartate transaminase or alanine transaminase exceeding 1.5 times the upper limit of normal, and chronic renal insufficiency as defined by a creatinine exceeding 2.5 mg/dL or requirement for dialysis.

Operative Procedure

Standard induction and maintenance of anesthesia was accomplished with a combination of sufentanil, midazolam, and isoflurane. Appropriate radial artery and pulmonary artery monitoring catheters were placed. Before CPB, systemic heparinization was accomplished with a heparin dose of 400 U/kg. Additional heparin was administered during CPB to maintain an activated clotting time of more than 400 seconds. CPB was maintained at a cardiac index of 2.0 to 2.4 L/(min · m²) with a Stockert-Shiley Roller pump (Shiley Inc, Irvine, CA) using a Sarns membrane oxygenator (Terumo/Sarns, Ann Arbor, MI). The pump prime consisted of 1200 mL of normothermic, lactated Ringers solution, to which 500 mL of hetastarch, 25 mEq of sodium bicarbonate, and 1000 U of heparin were added. Retrograde autologous priming was performed whenever possible before initiation of CPB.

Initial cardioplegic arrest was accomplished with antegrade normothermic administration of a 250 to 500 mL of a solution of D₅/0.2 sodium chloride containing 29 mL of tromethamine (THAM) buffer, 34 mL of adenosine citrate phosphate dextrose, and 60 mEq of potassium chloride (120 mEq/L) in a 4:1 blood/crystalloid mixture. This was followed immediately with retrograde administration of 1000 mL of hypothermic cardioplegic solution. Every 20 minutes of cardioplegic arrest was maintained with 250 to 500 mL retrograde administration of the cardioplegic solution with a reduced potassium concentration (60 mEq/L) and a 500 mL terminal normothermic cardioplegic injection was given before cross-clamp removal. Patients were not actively cooled while on CPB and were rewarmed to a rectal temperature of 36.5°C before separation.

At the termination of CPB, heparin was neutralized with protamine in a 1:1 ratio. A nitroglycerin infusion was administered postoperatively for systemic hypertension (defined as a 20% increase over preoperative levels) and ST segment elevation or depression exceeding 1 mm. An epinephrine infusion was administered postoperatively to maintain a cardiac index of greater than 2.0 L/(min · m²) when needed.

Discharge criteria from the intensive care unit (ICU) included a complete wean from all vasoactive and inotropic infusions, extubation without pulmonary support, and no evidence of major organ failure. Discharge criteria from the hospital included stable sinus rhythm, no supplemental oxygen requirement, ambulation, and tolerance of oral intake.

Endothelin-A Receptor Antagonist

The selective ET-RA used in this study was sitaxsentan sodium (TBC11251Na), which has been described previ-

ously [14, 17, 18]. This study was performed under United States Food and Drug Administration IND#52,527. It has been demonstrated previously that this ET-RA quickly reaches a steady-state level (within 30 minutes) after intravenous administration and has a half-life of approximately 6 hours [18]. This laboratory has demonstrated previously in a large animal model of CPB that sitaxsentan effectively reduced pulmonary vascular resistance, but induced significant systemic hypotension in higher doses [17]. Sitaxsentan has been safely used in patients with primary pulmonary hypertension [14, 18]. On the basis of these past results, the present study tested a sitaxsentan dose range in an attempt to bracket the predicted dose to reduce pulmonary vascular resistance. The doses to be administered were a bolus of 0.1, 0.5, 1.0, and 2.0-mg/kg sitaxsentan formulated in sterile saline within 2 hours of systemic bolus infusion.

Study Protocol

After informed consent, the patients were randomized to five treatment groups by using a predetermined randomization coding scheme that was developed before the initiation of the study and maintained in a blinded fashion by the study coordinator (LF): group 1, placebo (saline vehicle bolus; group 2, 0.1 mg/kg; group 3, 0.5 mg/kg, group 4, 1.0 mg/kg, and group 5, 2.0 mg/kg of ET-A receptor antagonist).

The placebo or ET-A receptor antagonist was infused immediately after separation from CPB. This time point of infusion was designated as time 0. With this as the reference, the following measurement time points were used: baseline (after placement of arterial and pulmonary catheters, but before the onset of CPB), time 0 (immediately at cessation of CPB and after placebo/drug infusion), and 0.5, 6, and 24 hours post-CPB.

The hemodynamic measurements obtained at each of these time points were heart rate, mean arterial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac output, arterial and venous oxygenation, and central venous pressure. Cardiac outputs were measured by standard thermodilution techniques and were recorded as the average of at least two measurements. All pulmonary capillary wedge pressure measurements were obtained at end expiration in the ventilated and spontaneously breathing patients. At the designated time points, blood samples were collected to determine plasma ET level by using radioimmunoassay methods well described by this laboratory [7, 8, 11]. Diuretic, inotropic, and vasodilator requirements were recorded in the postoperative period. All adverse events were adjudicated, reviewed, and reported to the MUSC Institutional Review Board.

Data Analysis

Hemodynamic parameters and plasma ET levels at each time point were evaluated with a multiway analysis of variance (ANOVA). If the ANOVA revealed significant differences, pair-wise tests of individual group means were compared by Bonferroni adjusted probabilities.

Table 2. Demographics for Control and Endothelin-A Antagonist Treatment Subjects After Coronary Artery Bypass Grafting

Characteristic ^a	Group Mean	Placebo	0.1 mg/kg	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg
Males/females	44/0	9/0	9/0	9/0	9/0	8/0
Age (years)	62 ± 1	64 ± 2	61 ± 2	64 ± 2	59 ± 3	63 ± 3
Race						
Caucasian	40	9	7	7	9	8
African American	3	0	1	2	0	0
Filipino	1	0	1	0	0	0
BSA (kg/m ²)	2.1 ± 0.0	2.0 ± 0.1	2.1 ± 0.1	2.1 ± 0.1	2.0 ± 0.1	2.0 ± 0.1
Medications						
Hypertensive	1 (40)	89 (8)	78 (7)	100 (9)	89 (8)	100 (8)
Diabetic	41 (18)	56 (5)	22 (2)	33 (3)	78 (7)	13 (1)
Diuretic	8 (8)	22 (2)	22 (2)	11 (1)	22 (2)	13 (1)

^a Categorical values presented as number (%); continuous variables presented as mean ± standard error of the mean.

BSA = body surface area.

Categorical and preoperative variables were examined by using χ^2 analysis.

The changes in pulmonary and systemic vascular resistance were computed as follows. First, the change from baseline values was determined and a *t* test was used to determine any significant changes from relative baseline values. Next, pair-wise comparisons in the changes in these variables were performed using an adjusted *t* statistic. Finally, a nonparametric trend analysis was used to determine if a dose-response relationship could be detected. All statistical procedures were performed using Stata Intercooled 8 software (StataCorp, College Station, TX). Results are presented as mean ± standard error of the mean (SEM). Values of *p* < 0.05 were considered to be statistically significant, or as indicated in the results.

Analysis showed that that baseline indicators were identical between treatment groups, but a high degree of inpatient variability occurred in the postoperative period with respect to pulmonary artery pressure, pulmonary vascular resistance, and systemic vascular resistance (Table 1). In addition, nonparametric trend analysis showed evidence of a dose-response relationship for the pulmonary vascular resistance index and the systemic vascular resistance index. Thus, relative response curves were generated consisting of changes from a composite baseline value, and changes from time 0 were computed

for pulmonary artery pressure, pulmonary vascular resistance, and systemic vascular resistance. Expression of the data in these two forms allows end point assessment compared with the time of entry into the study (baseline) and from the exact time the study agent was given (time 0).

Results

Demographic and intraoperative clinical descriptive data for the 44 patients enrolled in this study are presented in Tables 2 and 3. This study included only men, with an equal distribution of African Americans. There were no significant differences in the preoperative use of angiotensin-converting enzyme inhibitors, calcium-channel blockers, or β -blockers across the treatment groups. Other perioperative statistics were identical across all treatment groups. No differences were noted in the dosage of nitroglycerine, epinephrine, or pressors used across the treatment groups over the various measurement times. Hemodynamic indices were highly similar at baseline before the initiation of the surgical procedures, and no significant differences were detected between the five treatment groups or when compared with a composite mean value.

A total of 134 grafts were performed in this study group: placebo, 25; 0.1 mg/kg, 29; 0.5 mg/kg, 30; 1.0

Table 3. Intraoperative Characteristics

Characteristic ^a	Group Mean	Placebo	0.1 mg/kg	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg
≥3 grafts	89 (39)	78 (7)	89 (8)	100 (9)	78 (7)	100 (8)
Cross-clamp time (hr)	1.1 ± 0.1	0.98 ± 0.11	1.1 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.2 ± 0.1
CPB (hr)	1.4 ± 0.1	1.3 ± 0.2	1.4 ± 0.2	1.5 ± 0.1	1.4 ± 0.1	1.5 ± 0.2
Surgery time (hr)	4.0 ± 0.2	4.0 ± 0.6	4.2 ± 0.3	4.0 ± 0.2	4.0 ± 0.3	4.1 ± 0.5
Ventilation time (hr)	16 ± 2	14 ± 3	18 ± 5	19 ± 2	14 ± 3	13 ± 3
ICU (hr)	70 ± 4	83 ± 7	61 ± 8	68 ± 13	83 ± 9	62 ± 11
Hospital stay (days)	7.4 ± 0.8	7.8 ± 1.6	6.0 ± 1.0	7.0 ± 0.9	8.9 ± 2.5	7.3 ± 2.2

^a Categorical data are presented as number (%); continuous values are presented as mean ± standard error of the mean.

CPB = cardiopulmonary bypass; ICU = intensive care unit.

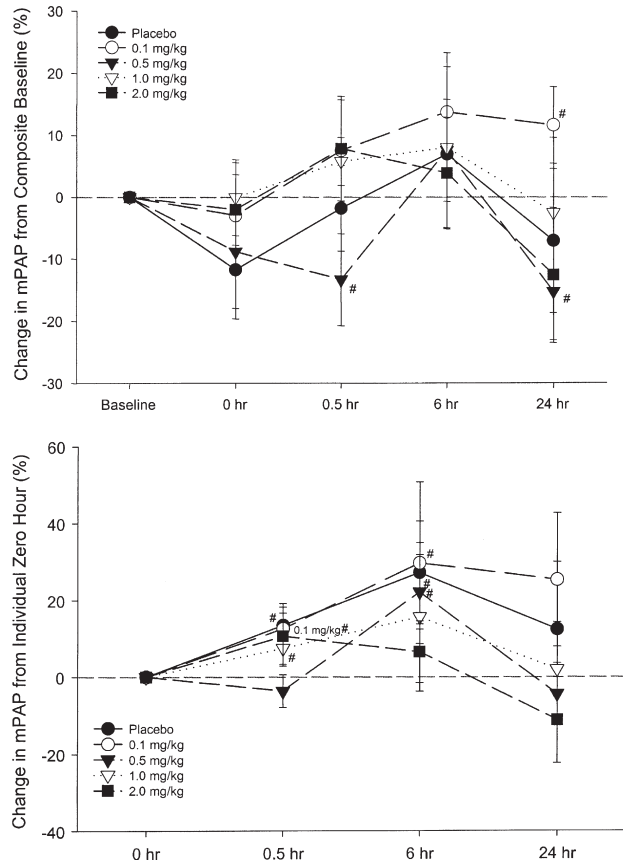


Fig 1. Changes in mean pulmonary artery pressure (mPAP) \pm standard deviation. (Top) Change from composite mean value. Trends were observed towards blunting of pulmonary artery pressures with higher antagonist doses. (Bottom) Change from time 0. Pulmonary artery pressure increased in the placebo (filled circle), 0.1 (open circle), and 0.5 mg/kg (filled triangle) groups at 6 hours after cardiopulmonary bypass, but this was not observed for the 1.0 (open triangle) and 2.0 mg/kg (filled square) groups. (# $p < 0.05$ from baseline [0 hour].)

mg/kg, 26; and 2.0 mg/kg, 24 ($p > 0.05$). All but 3 patients (placebo, 2; 2.0 mg/kg, 1) received a left internal mammary artery-left anterior descending graft. The left radial artery was used in 5 patients (0.1 mg/kg, 2; 0.5 mg/kg, 2; 1 mg/kg, 1). The right internal mammary artery was used in 1 patient (0.5 mg/kg). All patients were considered completely revascularized at the end of the procedure. Thus, patients randomized to the five treatment groups had very similar preoperative, intraoperative, and postoperative indicators.

Pulmonary artery pressure increased as a function of post-CPB time, but this trend was significantly blunted in the 2.0 mg/kg group. As shown in Figure 1, the change in pulmonary artery pressure from composite baseline actually moved in a negative direction at 0.5 and 24 hours in the 2.0 mg/kg group. As a function of time 0, pulmonary artery pressure increased in the placebo, 0.1, and 0.5 mg/kg group at 6 hours post-CPB, but this was not observed for the 1.0 and 2.0 mg/kg groups. This change in pulmonary artery pressure at 6 hours post-CPB is graph-

ically expanded in Figure 2, where pulmonary artery pressure increased in the placebo and low-dose ET-A receptor antagonist groups, but did not significantly increase in the higher-dose groups.

The change in pulmonary vascular resistance is summarized in Figure 3. Although pulmonary vascular resistance trended in an upward fashion in the placebo and low-dose groups, the change in pulmonary vascular resistance was attenuated to the greatest degree in the 2.0 mg/kg group. For example, as a function of a composite baseline value, 2.0 mg/kg demonstrated a significant reduction in pulmonary vascular resistance at all post-CPB time points.

Nonparametric testing demonstrated a dose-dependent effect on pulmonary vascular resistance ($p = 0.06$). Systemic vascular resistance was reduced in all groups as a function of baseline values (Fig 4), but the greatest reduction was observed in the 2.0 mg/kg group at 0.5 hours post-CPB. Thus, 2.0 mg/kg of the ET-A receptor antagonist produced the most significant effect on pulmonary artery pressure and vascular resistive properties in the post-CPB period.

The plasma ET level was measured in the systemic circulation throughout the surgical procedure and for 24 hours postoperatively. As anticipated, plasma ET levels increased in the post-CPB period, which could be most clearly observed as a function of baseline values as shown in Figure 5. The greatest early change in ET levels at time 0 was in the 2.0 mg/kg group, but this did not reach statistical significance. However, plasma ET levels increased as a function of post-CPB time in all groups with no significant difference between groups.

Adverse Events

A total of 203 adverse events were tabulated in the postoperative period and were evenly distributed in

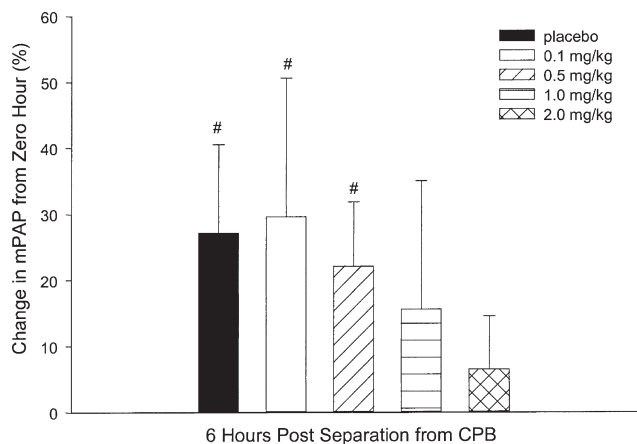


Fig 2. Change in mean pulmonary artery pressure (mPAP) \pm standard deviation at 6 hours after separation from cardiopulmonary bypass (CPB). Pulmonary artery pressure increased in the placebo (filled bar) and low dose ET-A receptor antagonist groups, but did not significantly increase in the higher dose groups. (Open bar = 0.1 mg/kg; diagonal pattern = 0.5 mg/kg; horizontal pattern = 1.0 mg/kg; diamond pattern = 2.0 mg/kg; # $p < 0.05$ from baseline [0 hour].)

number across the treatment groups ($p > 0.70$ by χ^2). None of these events were considered to be associated with the study protocol or drug groups. The most common adverse events noted were pain (35 events), edema (16 events), tachycardia (11 events), and hypertension (9 events).

Comment

The overall goal of this unique study was to demonstrate that sitaxsentan, a selective ET-A receptor antagonist, could be safely used in patients after cardiac surgery requiring CPB and that potential dose could be identified for a full-scale clinical effectiveness study. The results of this initial study demonstrated that a 2.0 mg/kg dose infused at the time of separation from CPB effectively blunted the rise in pulmonary vascular resistance in the early postoperative period and reduced systemic vascu-

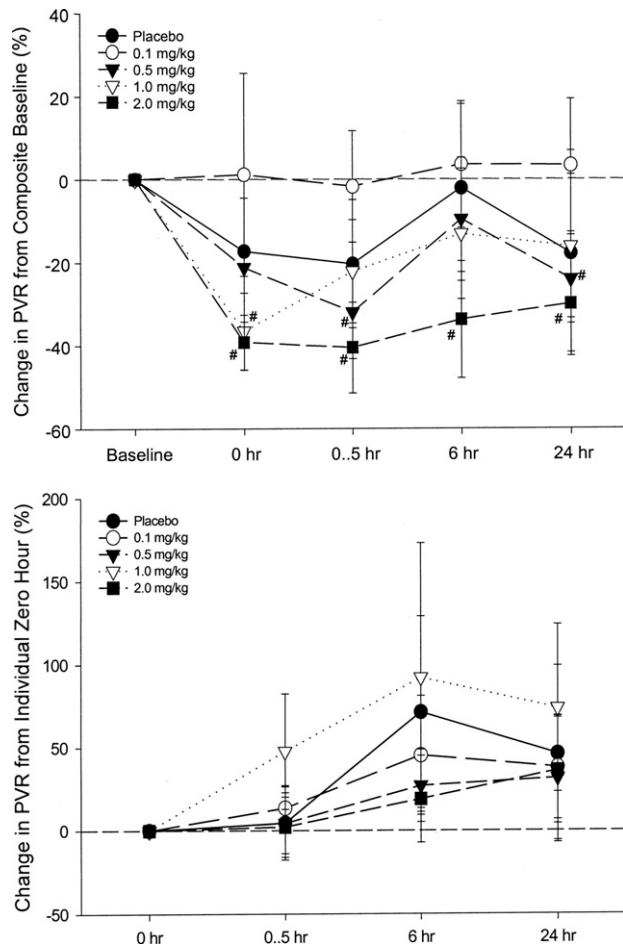


Fig 3. Changes \pm standard deviation in pulmonary vascular resistance (PVR). (Top) Change from composite mean value. Pulmonary vascular resistance was attenuated to the greatest degree in the 2.0 mg/kg group (solid square). (Bottom) Relative to time 0, pulmonary vascular resistance was not significantly increased across treatment groups. (Filled circle = placebo; open circle = 0.1 mg/kg; filled triangle = 0.5 mg/kg; open triangle = 1.0 mg/kg; # $p < 0.05$ from baseline [0 hour].)

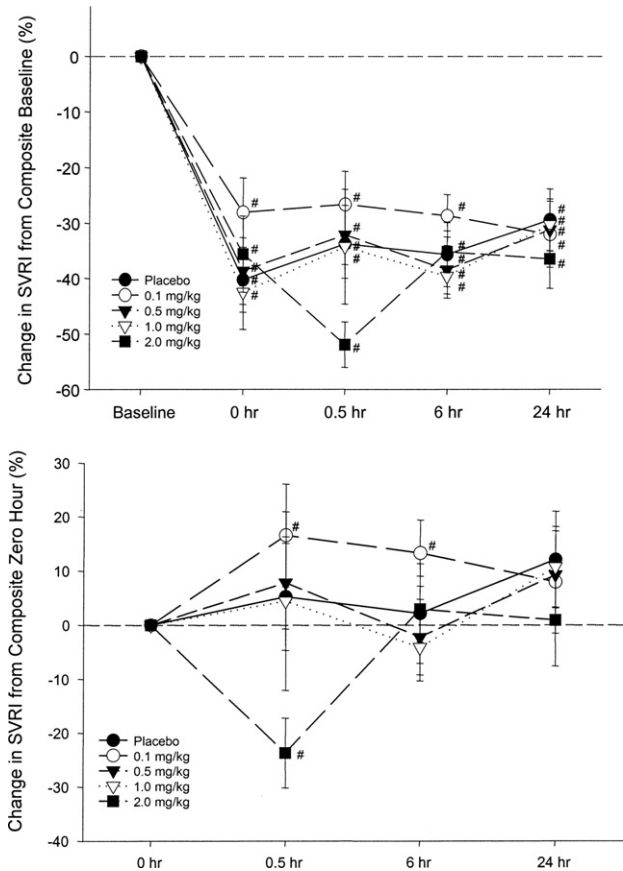


Fig 4. Changes \pm standard deviation in systemic vascular resistance index (SVRI). (Top) Change from composite mean value. Systemic vascular resistance was reduced in all groups, with no significant differences between groups. (Bottom) Change from time 0. In general, systemic vascular resistance was preserved across treatment groups after antagonist administration. (Filled circle = placebo; open circle = 0.1 mg/kg; filled triangle = 0.5 mg/kg; open triangle = 1.0 mg/kg; # $p < 0.05$ from baseline [0 hour].)

lar resistance to a transient degree at 30 minutes post-CPB. There were no doses of sitaxsentan that caused hemodynamic compromise or instability and no adverse events were associated with the protocol or treatment. Thus, the present study demonstrated that a selective ET-A receptor antagonist can be safely and effectively deployed in the postcardiac surgery setting.

The endothelins are a family of four similar vasoactive polypeptides. The most prevalent isoform is endothelin-1, a 21 amino acid biopeptide that exerts potent and prolonged effects on vasoconstrictive processes in the coronary, pulmonary, and systemic vasculature, and affects contractile processes in myocardium [1-4]. ET causes biologic effects through the occupancy and activation of two fundamental receptor types: the ET-A and ET-B receptors [10, 12]. The ET-A receptor, which is the predominant subtype found within the vascular smooth muscle and myocardium, causes intracellular calcium mobilization leading to changes in vascular tone and contractility [12, 13, 17]. The ET-B receptor has been

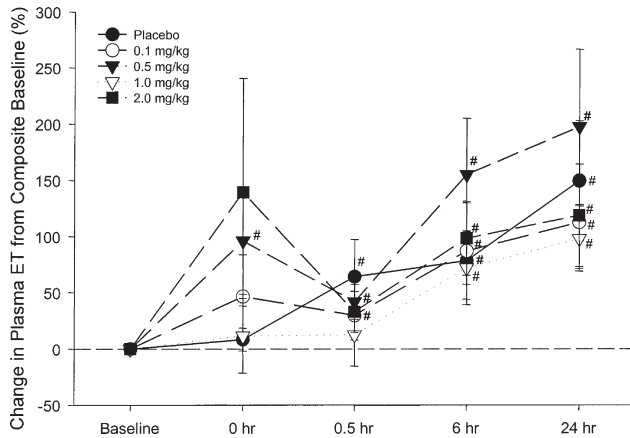


Fig 5. Changes in plasma endothelin (ET) levels. Plasma endothelin increased as a function of post-cardiopulmonary bypass time in all groups with no significant difference between groups. (Filled circle = placebo; open circle = 0.1 mg/kg; filled triangle = 0.5 mg/kg; open triangle = 1.0 mg/kg; # $p < 0.05$ from baseline [0 hour].)

primarily associated with vasorelaxation and the release of nitric oxide [19]. The ET-B receptor has also been postulated as the “clearance” receptor for ET in that it appears to regulate circulating levels of ET by controlling its production in an autocrine manner and by promoting its clearance from the circulation [14].

Right heart failure is a significant problem after cardiac surgery, particularly in certain clinical scenarios such as cardiac transplantation, mitral valve surgery in patients with pulmonary hypertension, and CABG. Important aspects of this scenario include decreases in right ventricular contractility and development of acute pulmonary hypertension with increases in pulmonary vascular resistance, imposing excessive afterload on the right ventricle. ET may contribute to all of these derangements. This laboratory has established previously that the ET-A receptor exerts negative inotropic effects in the context of cardiac failure and after simulated cardioplegic arrest [15, 16, 20].

Moreover, activation of the ET-A receptor has also been implicated to cause significant vasoconstriction of the pulmonary vasculature and thereby alter pulmonary vascular resistance properties and overall pulmonary function [17]. We have also shown that pulmonary vascular resistance increases after cardiac surgery requiring CPB and this was associated with changes in ET plasma levels [7, 8, 11]. These changes can be particularly pronounced in certain important patient subpopulations such as those with diabetes [21].

Additional studies have demonstrated that ET can increase vascular smooth muscle constriction in internal thoracic artery, radial artery, and saphenous vein bypass conduits [7, 12, 13]. These effects are more pronounced in the presence of atherosclerotic disease [12] and work synergistically with the vasoconstrictive effects of norepinephrine and serotonin [13]. Taken together, these findings suggest that the induction and release of ET in the early post-CABG period may negatively influence outcomes.

With exception of mechanical assist, management strategies for right heart failure have focused on increasing right ventricular contractility or minimizing right ventricular afterload, or both. In this latter regard, numerous agents are available for use as pulmonary vasodilators, including nitroglycerine, sodium nitroprusside, prostaglandin E1, nesiritide, sildenafil, and inhaled nitric oxide [22]. The low side effect profile and ease of administration of sitaxsentan, the ET-A receptor antagonist used in this study, suggests that this agent may be a safe and useful treatment adjunct to the available pharmacologic armamentarium for the treatment of early postsurgical right heart failure associated with pulmonary hypertension. In addition, its potential salutary effects on myocyte contractility and coronary conduit vascular tone justify further study for efficacy in postcardiac surgical patients.

The first ET antagonist to demonstrate clinical efficacy was bosentan, which exerts a relative ET-A/ET-B receptor selectivity of 70:1 [18]. Numerous studies have confirmed the efficacy of this agent in reducing symptoms from pulmonary hypertension [18]. This initial encouraging experience resulted in development and testing of other agents such as tezosentan, a nonselective ET-A/ET-B receptor antagonist. Clinical trials with tezosentan have shown unusual dose-dependent effects (improvements with mid-range doses compared with lower and higher concentrations), perhaps related to excessive vasodilatation and elevation of ET levels at higher concentrations [23, 24].

In the light of this experience, the postulate has arisen that selective ET-A receptor antagonism could offer superior clinical benefit to nonselective receptor blockade by reducing vasoconstriction mediated by the ET-A receptor while preserving the vasodilatory and ET clearance functions of the ET-B receptors. Currently, numerous selective ET-A receptor antagonists (ambrisentan, atrasentan, avosentan, clazosentan, darusentan, and sitaxsentan) are under clinical study [14]. Sitaxsentan is a selective ET receptor blocker with 6500 times greater affinity for the ET-A receptor subtype than the ET-B counterpart. Several studies in patients with pulmonary hypertension have shown encouraging improvements with this agent [14, 18], and in general, the hemodynamic effects with this selective agent have been more predictable than with nonselective ET antagonists.

In the present study, plasma ET levels were demonstrated to increase after discontinuation of CPB. The cause of this expected effect is multifactorial and may involve reduced ET clearance during CPB due to reduced pulmonary blood flow, endothelial cell injury from lack of pulsatile perfusion, and increased ET production as a result of reperfusion, surgery stress, and thromboxane release from activated platelets [10]. This underscores the importance of preservation of the ET clearance role of the ET-B receptor and may explain the more consistent dose-response effects associated with selective ET-A receptor antagonism.

The present study evaluated the potential utility sitaxsentan, a selective ET-A receptor antagonist, in postcardiac surgical management. From the results of this first phase, it

is recommended that the dosage of 2 mg/kg, which lowered pulmonary vascular resistance and was not associated with specific adverse effects, be carried forward to the second study phase, an efficacy/outcomes trial in patients at higher risk (eg, diabetes, pulmonary hypertension) for development of postoperative right heart failure.

The results demonstrated from this study are subject to several important limitations. First, the fraction of inspired oxygen levels in the ventilated patients were not actively controlled during measurement acquisition but were weaned as tolerated by standard ventilator weaning protocols. Because pulmonary vascular resistance is oxygen sensitive, this may have influenced the measurement results.

Second, thermodilution cardiac output measurements have been shown to vary by as much as 20% when taken at varying points in the respiratory cycle owing to "thermal noise" resulting from cyclic variations in pulmonary artery pressure [25]. Although the cardiac index measurements did not vary significantly over the groups and time studies, the results should be interpreted with some caution.

Finally, the calculation of pulmonary vascular resistance is sensitive to pulmonary vascular tone and dimensions but is flow-dependent, and conditions of high alveolar pressure or high pulmonary vascular tone can cause artifacts [26]. These points should be taken into consideration in the interpretation of the data.

In conclusion, the present study results confirm the safety and potential efficacy of selective ET-A receptor blockade in the cardiac surgical patient and justify its larger scale investigation as a novel therapeutic agent in the management of acute right heart failure and pulmonary hypertension in the immediate post-operative period.

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DISCUSSION

DR JOHN W. HAMMON, JR (Winston-Salem, NC): John, that was an excellent paper. I want to congratulate you and your group, particularly Frank Spinale, for putting this information together, and I do think this is something that will be valuable for us in the future in some form. The work that has gone on with endothelin, which is really a very, very powerful vasoconstrictor and has significant detrimental effects in patients, particularly those at very high risk for surgery, has been very well known for some time. The treatment regimen that you give with an infusion of a receptor antagonist for the endothelin A subtype receptor appears to be safe and appears to not have detrimental effects, and I think that must be the primary thrust of your presentation as a safety study for this potential therapy.

I do believe that you need to establish efficacy in treating higher-risk patients in terms of mitral valve replacement, patients with bad ventricles, and perhaps patients that are undergoing transplant that are having problems with elevated pulmonary vascular resistance and would challenge you to always use pulmonary vascular resistance as opposed to PA pressure as an outcome measure since it incorporates the effect of elevated or depressed cardiac output.

Many of us use ultrafiltration, either modified or simple ultrafiltration, during surgery or immediately after the pump run to remove cytokines from the plasma, and I was wondering if you used these in your patients and what effect this has on endothelin levels in the plasma. Thank you.

DR IKONOMIDIS: Thank you, Dr Hammon, for those pertinent comments. The first point that you made was about establishment of efficacy, and in fact, we have embarked on that trial looking at patients who are older with depressed left ventricular function, numerous cardiac procedures and numerous comorbidities, and especially elevated preoperative pulmonary pressures, to specifically address efficacy as you so rightly indicated.

With regards to ultrafiltration, we generally don't use ultrafiltration in lower-risk patients. There is evidence in the literature that ultrafiltration does clear endothelin to some extent from the circulation. Comparing the effects of ultrafiltration to use of a specific antagonist, there is evidence that the specific antagonist may be more efficacious in terms of its effects on the pulmonary vascular bed.

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