[redacted] Date: 21 February 2006

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To: CBER/Office of Blood Research and Review/Division of Hematology
1401 Rockville Pike; HFM-392
Rockville, Maryland 20857

Subject: IND 12504:HBOC-201 (Polymerized Bovine Hemoglobin –B): Request for consultative review of efficacy of HBOC-201 vs. lactated Ringer's solution in a porcine hypovolemic shock model

Study examined:

Protocol KO04-04: A RESUS clinical trial IND-enabling study to compare the efficacy and safety of HBOC-201 (HBOC) and lactated Ringer's (LR) solution in a swine hemorrhagic shock model with uncontrolled hemorrhage and blunt traumatic brain injury (TBI).

Executive summary, and recommendations:

Model. The subject study was done in a lethal model of acute hemorrhage and TBI in which provision of definitive resuscitative care was delayed 30 (Short Delay: SD) or 75 minutes (Longer Delay: LD) until simulated arrival to ER/OR/ICU. Interim "field" treatment with HBOC (10 ml/Kg/infusion); LR (20 ml/kg/ infusion) or no fluid (control) was provided during these delays (SD: 1 infusion; LD: 4 infusions). Survival and cardiovascular (CV) status were monitored for 6 hours following trauma. It is a model particularly vulnerable to right –sided overload, and the pulmonary vascular hypertension provoked by whole blood during definitive resuscitation necessitated a confounding prophylactic use of keterolac.

Results. In the SD scenario, survival to 30 minutes was 100% in all cohorts. In the LD scenario, survival to 75 minutes was significantly improved by intervention with 4 infusions of either

HBOC or LR (70-90% vs. 30% absent fluid intervention; appreciably prolonged mean survival times vs. control, as well).

However, I was not able to evaluate, unconfoundedly, relative survival to 6 hours (HBOC: 62% vs. approx 10% for LR or control) – or the value of any of the multiple CV parameters monitored throughout this study. That is, a different population was monitored after "hospital arrival", namely only the sub-set of pigs which received keterolac (a potent and long-acting thromboxane synthase inhibitor) after such arrival.The prognostic/therapeutic implications of changes in CV status was also indeterminate, to me, since only trajectories of survivors was plotted in this study (a retrospective segregation to decedents vs. survivors and their relative CV status over time was not performed). As noted, only a subset of the original populations continued to be tracked after "hospital arrival".

Keterolac was used to prevent lethal pulmonary artery hypertension (PAH) and cardiovascular collapse provoked by whole blood transfusions during definitive resuscitation. As argued below (see Keterolac issue) it is expected to blocks most, if not all, of any residual pulmonary pressor and other vaoconstrictor activity of previously infused HBOC. Accordingly, the ostensibly impressive superiority of emergency treatment with HBOC over LR or control on survival to 6 hrs [62% vs 10% as noted above ($p< 0.01$); mean survival time: 4.2 hours vs. 1-2 hours ($p<0.001$)] is suspect.

<u>Recommendations:</u> It is recommended that –since use of keterolac is not envisioned for the proposed clinical trial– this model not be considered as support for emergency use of HBOC *per se*. Effect of HBOC, absent keterolac pretreatment, on survival and/or neurologic sequelae at 6 hours, and beyond, remains unknown. It does suggest superiority of HBOC + keterolac over LR + keterolac as emergency therapy prior to definitive treatment if — absent data on longer-term survival/ neurologic status — survival time to 6 hrs is the only criterion.

Although in my opinion the study does not support clinical testing of HBOC-201 *per se*, it could be informatively revisited for the purposes of:

1 Deriving pulmonary vascular resistance (since cardiac output, PAP, and PA capillary wedge pressures determinants were all periodically monitored), and determining status of pulmonary and systemic vascular resistance prior to and after keterolac. The study report is silent on variability of effect, if any, of Keterolac, at the dosage used, on total systemic or pulmonary resistance Since timing of keterolac and whole blood transfusions varied from pig to pig, it is, furthermore, not appropriate to exclusively plot mean of data at fixed post-trauma time points as sponsor has previously done.

2. Segregating pigs into surviving and decedent cohorts and plotting the trajectories of their cardiovascular and physiologic parameters to inform prognostic/therapeutic implications of changes in cardiovascular status.

<u>Overview:</u>

<u>Background:</u>

HBOC-201 is an investigational hemoglobin-based oxygen carrier, namely ultrapurified, glutaraldehyde-polymerized, modified bovine hemoglobin (hemoglobin concentration 13±1 g/dL) carried in a balanced electrolyte solution. It is intended to replace RBCs for emergency "field" treatment of hemorrhagic shock. Naval Medical Research Center, in collaboration with Biopure Corp, proposes to evaluate HBOC-201 as a resuscitation fluid in the pre-hospital setting in the urban trauma situation. Their rationale is that a hemoglobin substitute would serve to restore both effective vascular volume and, unlike normal saline or LR, O2-carrying capacity. Sponsor hypothesized that HBOC-201 would - relative to LR - improve hemodynamics, tissue oxygenation, and survival while decreasing the overall fluid and blood transfusion volume requirements for such. To increase likelihood that parity or even superiority to LR would be encountered in the context of a smaller total resuscitation volume, the intravenous bolus infusion "dosages" of HBOC were ½ that of LR, namely 10 ml/Kg vs. 20 ml/Kg, respectively,

They submitted a Phase 3 trauma trial, to be conducted under §50.24. It would compare pre-hospital resuscitation with HBOC-201 vs. normal saline (standard of care).

To try to address CBER clinical hold issues, sponsor submitted the subject study of the behavior of HBOC-201 vs. LR vs. neither in a pig hemorrhagic/traumatic brain injury (TBI) shock model of high mortality absent timely and appropriate resuscitation.

The Model:

Features

This is a model of acute severe hemorrhagic shock /TBI in which definitive resuscitative treatment was delayed for 30-minutes (Short Delay: SD) or 75-minutes (Longer Delay: LD) until simulated arrival at a hospital ER/OR/ICU. Either HBOC or LR was infused during the delays. The trajectory was lethal if bleeding was allowed to persist for 75 minutes with only oxygen as support. Upon "hospital arrival", standard medical/surgical care for hemorrhagic shock was administered to survivors (optimized mechanical ventilation; normal saline, whole blood, and/or mannitol prn; hemostasis of the lacerated liver).

In addition to survival and fluid requirements for resuscitation, a variety of cardinal CV and physiologic parameters were monitored to 6 hours post-trauma. These included: mean arterial pressure; pulmonary artery/capillary wedge pressures; cardiac output; total peripheral vascular resistance; tissue oxygenation; intra-cerebral pressure; lactic acid and base excess; and PT, PTT, and fibrinogen Brain histopathology was also assessed. Conspicuously absent was veterinary follow-up beyond 6 hours- although survival in the LD scenario controls is only about 10% despite standard normal saline or whole blood restitution and surgical repair, it was over 60% for the HBOC cohort.

Central venous pressure and pulmonary vascular resistance (PVR) were not monitored. However, all the parameters needed to derive PVR were periodically or continuously recorded (i.e., cardiac output, PAP, and pulm. art.capillary wedge pressure). It is recommended that sponsor re-visit data and derive PVR. Stroma-free Hgb preparations have very appreciable renal, pulmonary, and – as evident in the large increase in SVRI in the subject study – other systemic vasoconstrictor activity. It should be expected that, based on the literature, that administration of a thromboxane inhibitor e.g., keterolac, would block most, if not all, of any residual pulmonary pressor and other vaoconstrictor activity of previously infused HBOC.

Induction /extent of trauma:

In the hands of the sponsor, this is a model of reasonably reproducible trauma since blood loss and hemodynamic status at 15 minutes - when pre-hospital intervention with HBOC or LR was initiated - were comparable across the six treatment cohorts based on the small coefficients of variation. At such time, cardinal pressures (arterial, cerebral perfusion and pulmonary artery/capillary wedge) as well as total periph.vascular resistance, cardiac output, transutaneous tissue oxygenation, and mixed venous oxygen saturation were depressed 20-50% and end-tidal CO2; mixed venous oxygen saturation; and cerebral cortex tissue oxygen by up to 75%. As expected, certain parameters e.g., heart rate and lactate, were uniformly elevated as sequelae of the exsanguination

Cardiovascular monitoring:

It bears recognizing that this is an anesthetized model and a variety of physiological CV parameters and homeostatic reflexes to preserve such are undoubtedly affected. However, in my experience and to my understanding, isoflurane, in that regard, is preferred over pentobarbital anesthesia (and is what I used in developing/monitoring a rat model of heart failure secondary to acute massive MI.: DeFelice, A. et al. 1989. Am. J Physiol 257:H289-96).

The cardinal CV parameters monitored included: cardiac output; cerebral blood flow; blood gases/pH; total peripheral vascular resistance; base excess, and end-tidal carbon dioxide; brain tissue oxygenation; and critical pressures (i.e., systemic and pulmonary; LV end-diastolic; cerebral perfusion; and intracranial). Central venous pressure and blood volume were, however, prominently absent. Pre-resuscitation blood loss and volumes of fluid administered/required prior to and during hospital simulation were recorded. Surprisingly, central venous pressure and blood volume were not monitored, which may be just as well since neither would be tracked " in the field" to guide intravenous therapy. Injection of labeled microsphere into the left ventricle for monitoring cerebral blood flow is valid only if there is adequate mixing in the LV. Evidence of such was not provided. Cardiac output was reliably monitored via the pulmonary artery by thermal dilution. I note, in passing, that blood flow to a variety of other tissues could also have been readily monitored with the microsphere technique (DeFelice et al, *ibid*).but evidently were not.

I am not familiar with the combined oxygen sensor/ Doppler flow probe used to monitor brain tissue (cerebral cortex) oxygenation/blood flow at, and contralateral to, the injury site via craniotomies. I note that the changes in both parameters are so slight and variable as to be uninformative, to me at least.

The vasodilatory response to adding CO_2 to the inhalation unit, as measured by changes in Sagital Sinus O_2 saturation and laser Doppler cerebral blood flow, was evaluated periodically (0, 120, 360 min). Sponsor acnowledges that this was not especially informative given the small and statistically insignificant changes in SS O_2 sat. The CO_2 challenge caused acute apnea and hypotension in some cases, and significant unrelated mortality prior to the scheduled 2 and 6 hr time points yielded few time points on which to base mean behavior.

Importantly, prothrombin and partial thromboplastin times (PT; PTT) as well as fibrinogen and platelets/ platelet function were monitored

Utility of Trajectory CV parameters as portrayed:

It would have been more informative to compare trajectories of cardinal CV parameter in surviving vs expiring pigs – in both SD and LD scenarios, and regardless of experimental resuscitation regimen - for insight into factors associated with mortality, and with protection. However, the data were not retrospectively segregated into surviving and terminal sub-groups. Rather, the less informative mean value (± SD) of survivors as a function of time and treatment was depicted, and does not afford impressions of prognostic parameters, viewed in isolation or as sets.

Blinding:

As noted above, this was not performed. However, there appear to have been relatively discrete objective clinical criteria triggering need for supplemental HBOC or LR infusions prior to simulated hospital arrival, and need for normal saline or whole blood interventions after "arrival"

Statistical Analysis/Power:

The sponsor calculated a sample size to address the primary outcome of interest i.e., survival to 6 hours. Given an alpha of 0.05 (one-sided), with 8 animals per group, sponsor asserts that study had sufficient power to detect only large (e.g., 75%) differences between treatment groups Accordingly, this study was under-powered to detect very important differences in survival (e g., 25-50%). Two separate analyses were conducted: Fisher's Exact Test for proportion surviving to 6 hours; and time to event (Kaplan-Meier, Cox proportional hazards regression), and sponsor asserts results were "highly consistent".

Sponsors assert that, based on prior research, the sample size was adequate to detect moderate to large (e.g., ≥ 25%) between group differences for secondary hemodynamic and physiologic outcomes including cerebral blood flow, CO2 reactivity, brain tissue oxygenation. This seems reasonable However, as I have noted data was not segregated to compare the CV trajectory of survivors vs. terminal pig sub-sets.

Trial Design (Dosing, Resuscitation, End-Points):

Resuscitation:

"Pre- hospital": After ten minutes of exsanguination, pigs were randomly allocated to one of six treatment groups. Two delays to hospital arrival were simulated: 30 minutes (Short Delay) and 75 minutes (Longer Delay). There were three cohorts in each simulation based on fluid received (HBOC-201; LR) or not received (controls) prior to simulated "ER/OR/ICU" arrival. Interim resuscitation with either HBOC-201 at 10 ml/Kg/infusion or LR at 20-ml/Kg/ infusion) began at 15 minutes In the LD cohort, additional infusions were provided at 30, 45, and/or 60 minutes as dictated by the animals clinical condition per discrete "trigger points" namely MAP< 60 mmHg; and/or HR > baseline (time 0) value. Thus SD pigs received 1 infusion, and LD pigs up to 3 more. Controls received no fluids until simulated hospital arrival. All pigs were ventilated with 100% oxygen from 15 minutes until simulated hospital arrival.

"Arrival at hospital". Definitive stabilization care was implemented PRN upon "hospital arrival" (Sponsor's table 1.), namely: to increase FiO2, infuse normal saline; infuse whole blood (up to three times, and proceeded by administration of keterolac), adjust ventilation, and administer up to 2 doses mannitol. Such care was applied prior to and after repair of the liver and asserted to depend on status of blood pressure, heart rate, hemoglobin, lactic acid, CO2, and cerebral pressures (intracranial; perfusion).

Resuscitation after simulated hospital arrival was not blinded. However, the timing (approx. 30-minute intervals) and volume of normal saline and/or whole blood (10 ml/Kg; a total of three maximum) appear to have been dictated by the veterinary status of the pig (vital signs, blood gases, lactic acid and hemoglobin). As I am neither veterinarian nor physician, I cannot comment on what care is "consistent" with veterinary or clinical ER/OR/ICU practice, and appropriateness of the trigger points used. [In the pivotal LD cohort there were also objective criteria, as noted, for triggering supplemental infusions of HBOC or LR at 30, 45, and/or 60 minutes prior to definitive resuscitation].

The model was intended to compare effects of HBOC vs. LR on survival and, secondarily, hemodynamic status when administered prior to a delayed definitive resuscitation attempt. Three cohorts were used in both SD and LD scenarios according to fluid received or not received in the "field" - namely HBOC (10 ml/Kg) or LR (20 ml/Kg) vs. none - all on a background of mandatory oxygen support. Neither was given as part of subsequent standard resuscitative treatment. In the SD scenario, one HBOC or LR infusion was administered 15 minutes prior to hospital "arrival" at 30 minutes. In the LD scenario, up to three more infusions of either fluid could be delivered at 30, 45, and/or 60 minutes based on veterinary criteria. The primary end-point in both the SD and LD scenarios was survival to simulated hospital arrival (SD: 30 min; LD: 75 min), and to 6-hours. Cardiovascular trajectories, as well as tissue oxygenation (brain; thoracic and thigh sc.) and markers of brain neuronal and glial injury were secondary as noted.

The Keterolac Issue: Keterolac was needed to prevent lethal pulmonary hypertension (PAH) and cardiovascular collapse otherwise seen after the whole blood transfusion (triggered if hemoglobin was ≤ 7 mg/Dl). All pigs needed whole blood tranfusions (up to two, the max. no. Allowed). The PAH was attributed by sponsor to RBC-provoked thromboxane generation by pulmonary WBCs. The expected blocking effect of ketorolac on the dose-related pressor (vasoconstrictor) activity of HBOC but not lactated ringer's in the LD scenario in this study confounds any interpretation of relative activity of emergency HBOC vs. LR pre-treatment on subsequent definitive resuscitation. Both the marked renal vasoconstriction and fall in GFR provoked by stroma-free hemoglobin in isolated kidneys were blocked 70% by pre-treating the rats with the thromboxane synthetase inhibitor OKY-046 (Lieberthal et *al.*, Biomat Artif Cells Immobil biotechnol 1992. 20 (2-4): 663-7). These authors observed these deleterious renal effects with unmodified, glyoxalated, or pyridoxyalated Hgb preparations at concentrations "well below that necessary to effectively improve oxygen content" (Lieberthal *et al* Life Sci. 1987 41(23) 2525-33.)

Lieberthal *et al* (1987; 1992) reported that unmodified and modified stroma-free hemoglobin has vasoconstrictor activity at concentrations less than necessary to effectively improve blood oxygen content; and demonstrated, both directly and by use of a thromboxane-synthase inhibitor, that this acivity is thromboxane_-mediated. Furthermore, Rabinovici *et al* (1992) reported, in a head to head study, that Hgb produced vasoconstriction under conditions where LR or normal saline revealed no such activity

RESULTS:

I confine my comments primarily to behavior in both the SD and LD cohorts *prior to* simulated hospital arrival where results are not confounded by use of Keterolac. The relative cardiovascular status and survival after such "arrival" was monitored in the context of the pervasive use of ketorolac since all pigs received at least one whole blood transfusion and Keterolac prophylactically.

A. **Blood losses and fluid requirement: SD and LD**

Blood losses:SD. Blood loss at 15 minutes, just prior to interim treatment with either HBOC or LR was approx. 22 ml/Kg in all cohorts. Blood loss was also comparable at 30 min in the SD scenario.

Blood Losses: LD.Total blood loss in the Long Delay scenario was nearly identical for pigs resuscitated with HBOC or LR (both approx.75 ml/Kg). This was nearly twice that lost by controls (mean : 40 ml/Kg) - not surprising, since the exsanguinations at the liver remained uncontrolled, and many of the controls were dead by the time the other cohorts were due for their third (45 minute)_or fourth (60 minutes) infusion of HBOC or LR

Pre-hospital fluid requirements: In the LD scenario, the LR and the HBOC cohorts each received 4 infusions at 20 and 10 ml/infusion, respectively, i.e., the maximum possible. Accordingly, the total of approx 80 ml/Kg of LR and the 40 ml/ kg of HBOC, afforded full or partial restituition, respectively, for the 75 ml/Kg of blood lost by pigs in each cohort. and it is in that context that definitive resuscitation was attempted.

Pigs were oliguric at time of "hospital arrival" as expected given the marked hypotension.

B. Survival and Hemodynamic status

SD Scenario:

Behavior before "hospitalization".

Survival:

There was 100% survival to start of definitive resuscitation at 30 minutes, even in the control cohort, which received no fluid intervention.

Hemodynamic status:

There were some apparent improvements in CV parameters of HBOC-treated pigs relative to that observed in the control and LR groups. These prominently included appreciable restorations in: cerebral perfusion pressure; contralateral brain oxygen partial pressure; mean systemic and pulmonary artery pressures; end-tidal CO_2; transcutaneous tissue oxygenation; and sagittal sinus O_2 saturation. Cardiac output, however, remained depressed in all cohorts. Systemic vascular resistance at 30 minutes approached pre-trauma values, even in controls, and in the HBOC group actually exceeded baseline.

Behavior after "hospitalization"

I make no attempt to tie pre-"hospital" to post-"hospital" trajectories because of differences in population and treatment. That is, only pigs that received keterolac were tracked both prior to and after hospital "arrival" and attempted definitive resuscitation. Their earlier behavior is collapsed with that of pigs monitored only up to hospital arrival, pigs which, presumably, subsequently died after whole blood transfusion absent protection with keterolac. Trajectories of pigs that survived vs. pigs, which expired, were not segregated retrospectively and plotted. Consequently, I could not determine prognostic utility of any parameter – and salutary effects, if any, of treatment on such.

I can note, however that by 6 hours and despite attempts at resuscitation via standard interventions prn, survival was down to approx 50% in both the HBOC and LR cohorts vs. 100% in the control cohort. Lack of significance at the $p < 0.05$ level speaks to the lack of power to detect such a clinically important difference in relative survival (n= only 3 for control pig cohort). This can be compared to the 6 hour HBOC survival in the LD scenario (see immediately below) where pigs received four infusions prior to hospital arrival: 62% vs ca. 10% for control or LR cohorts Ostensibly, emergency treatment with four HBOC infusions tends to be only slightly better, in terms of survival to 6 hours, than one; however extent and duration of hemorrhage and untreated survival differ in the SD and LD scenarios, and study design does not afford insight into Dose-Response for HBOC (if such applies to fluid replacement in hypovolemic shock).

LD Scenario:

Behavior before "hospitalization".

Survival

Emergency field treatment with 4 infusions of HBOC and LR in the 75 minute interval prior to "hospital arrival" significantly prolonged survival to such time: 94% (15/16); 71% (10/14); and 30% (3/10) for HBOC, LR, and control cohorts respectively ($p \leq 0.01$). A majority of the control pigs succumbed in the 30-50 minute interval.

Hemodynamic status

Insights into the prognostic utility of any CV parameter – and salutary effects, if any, of treatment on such vis a vis survival – could have been provided by plotting, retrospectively, the trajectories of pigs which survived vs. pigs which expired rather than the "Kaplan-Meyer" type of survivor portrayal provided. This can be informative in models of lethal CV compromise (DeFelice *et al.* Echocardiography of aortic regurgitant rabbits FASEB J 7(3-4) A752. 1993). However, this was not done even in this pre-hospital interval where there was a striking difference in survival, and results were not compromised by Keterolac. A less informative (to me) view of the trajectory of survivors in the 0-75 minute interval – especially the 30-50 minute interval of highest lethality in the controls- nevertheless revealed rather abrupt inflection points and or slope changes for cardiac index: mean arterial, pulmonary arterial wedge (a surrogate for LV end-diastolic filling), intra-cranial and cerebral perfusion pressures; saggital sinus oxygen sat.and lactate; and serum lactate/base deficit. I interpret the changes in slope of those parameter in that lethal 20-minute as reflecting an "unmasking" of the status of pigs at less immediate risk of imminent death vs. those dropping out during this interval. And suggest such parameters are prognostic in this model, but, again, pigs were not retrospectively stratified as to survival.

The relative CV status of the survivors (which is all that is plotted) at 75 minutes (15, 10, and 3 pigs in the HBOC, LR, and controls, respectively) is not especially informative to me. Only the status of survivors is plotted, and it does not obviously distinguish either the surviving (HBOC and LR) from the nearly depleted (control). I would recommend that sponsor re-visit data and do a retrospective plot of survivors vs. non-survivors in all cohorts to more accurately identify prognostic markers and relative effects, if any, of HBOC vs. LR on such.

Behavior after "hospitalization"

Survival:

6-hour survival of pigs receiving emergency treatment with HBOC in this LD scenario was significantly greater than that of the LR or control cohorts (HBOC: 62%; mean survival time 4.2hours. LR and control: ca. 10%, and mean survival time of ca. 1-2 hrs). Two observations undermine the confidence I place in this therapeutic superiority: all pigs received keterolac prior to subsequent whole blood transfusions: and the fluid requirements during definitive resuscitation (both) of the HBOC cohort were, based on mean number of saline and whole blood infusions were 2-4 times greater than those associated with the LR and control cohorts. Again, data for survivors vs. decedents vis a vis fluid requirements was not segregated to inform whether survival was inferior in LR and control cohorts despite comparable attempts to restore effective blood volume. Of course, LR and control may have received fewer fluids during attempted definitive resuscitation simply because they were dying off more quickly than pigs in the HBOC-treated cohort.

Since sponsor monitored cardiac output, and pulmonary artery/ capillary wedge pressures throughout the study, it is recommended that the sponsor re-visit the primary data, and derive pulmonary vascular resistance. It is critical to determine - especially in this LD scenario where HBOC showed ostensibly impressive survival benefit – whether keterolac reversed, partially or fully, the adverse pulmonary vasoconstrictor activity of the latter. Clearly, HBOC promoted mean pulmonary artery pressure appreciably (to approx 16 mmHg vs. 8 mmHg in control: Sponsor's Fig 12, p. 2870]) Incidentally, this is the same mean 8 mmHg pressor activity associated with the lethal whole blood transfusions in pigs unprotected with ketorolac (Sponsors Figure 3,p 2858). Evidently, these pigs are prone to right-sided failure, as normally, these would not be considerd, at least by me, to be egregious increases.

Recommendations:

These are provided in the Executive summary.

It is cardinal that we know, in this model, not only effect of HBOC-210 *per se* on hemodynamic status and survival before definitive veterinary resuscitation of hemorrhagic shock, but after such, including effect on neurologic status. The only neurological status monitored in the subject study was histopathology at autopsy.e.g. neuronal necrosis (NN). Since histopath. does not immediately follow injury sponsor concedes NN is skewed by survival and does not accurately represent true differences in incidence and severity of NN (and I might add all other biomarkers monitored , including white matter degeneration, WBC infiltrates, and the several immunohistochemistries (GFAP: MAP-2), none of which distinguished , to me , the various cohorts

The study does support *prima facie* the emergency use of HBOC-210 prior to definitive resuscitation with whole blood and normal saline if preceded by treatment with keterolac. However, it is not at all clear from the hemodynamic status, as depicted, which parameters - including tissue oxygenation - were prognostic, and effect, if any, of HBOC on such parameters. That is, at study end, there was no segregation into surviving and decedant cohorts to identify - retrospectively, and by re-playing their trajectories side-by side - those parameters whose preservation, or reversal, had survival benefit.