

Consensus Statement: Defining Minimal Criteria for Reporting the Systemic Inflammatory Response to Cardiopulmonary Bypass

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ABSTRACT

The causal factors of the systemic inflammatory response to cardiopulmonary bypass (CPB) were correctly identified in the early 1990s: "... activation of complement, coagulation, fibrinolytic, and kallikrein cascades, activation of neutrophils with degranulation and protease enzyme release, oxygen radical production, and the synthesis of various cytokines from mononuclear cells" [Butler 1993]. Why therefore have clinical advances to curb the systemic inflammatory response proven such a disappointment? Part of the problem is that cardiac surgery has never taken intellectual ownership of this issue, borrowing its diagnosis from critical care medicine and failing to define the minimal criteria that should be measured when reporting on the systemic inflammatory response. An evidence based review of the current literature by many of the coauthors on this paper found that the majority of studies on the systemic inflammatory response did not measure a single one of the causal factors listed above - thus hindering our ability to identify mechanisms of causation and identify drug targets [Landis 2008]. A panel of experts convened at the Outcomes XII meeting, Barbados 2008, drafted the present consensus document in order to provide a framework to guide future studies and interdictions of the systemic inflammatory response. Herein, we have recommended: 1) mandatory reporting of minimal CPB and perfusion criteria that may affect outcomes, 2) reporting of a minimal set of causal inflammatory markers linked to adverse sequelae, and 3) reporting of at least one clinical end-point of organ injury, from a list of end-points and markers of organ injury that balance practicality with clinical meaningfulness. It is our collective belief that this document will serve as a foundation for furthering our understanding of the influence of CPB practice with the systemic inflammatory response by standardizing the reporting of research findings in the peer-reviewed literature.

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Definition of the Systemic Inflammatory Response

The systemic inflammatory response is broadly defined as an inflammatory state of the whole body without a proven source of infection. The criteria agreed upon in 1992 by The American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference to diagnose the Systemic Inflammatory Response Syndrome (SIRS) in adults are as follows [Bone 1992]:

"SIRS is diagnosed when two or more of the following are present:

- Fever of more than 38°C or temperature less than 36°C
- Heart rate of more than 90 beats per minute (not appropriate in children)
- Respiratory rate of more than 20 breaths per minute or a PaCO₂ level of less than 32 mm Hg (4.3kPa)
- Abnormal white blood cell count <4 x 10⁹ cells/L or > 12 x 10⁹ cells/L or >10% bands)"

A clear distinction needs to be drawn between markers used to aid the diagnosis of SIRS, and markers responsible for causing SIRS. There are few studies in the cardiothoracic literature that have had the statistical power to use SIRS, as defined above, as a hard end-point. However, critical care criteria are often inappropriately utilized as continuous variables in cardiothoracic surgery reports. For instance, leukocyte count as a continuous variable is commonly presented as a marker of the systemic inflammatory response, despite its more appropriate use as a binary cut-off for diagnostic purposes. In our opinion, the activation state of white cells, or release of destructive cytokines and proteases from white cells, is likely to be much more instructive with respect to causation of the systemic inflammatory response and end-organ injury [Weiss 1989; Clark 1991; Eppinger 1995; Anttila 2006]. The present consensus statement is therefore aimed at defining criteria that should be included in studies about the systemic inflammatory response: what are the minimal set of CPB and perfusion details to be included in a research report? Which markers are causally involved in the systemic inflammatory response and therefore clinically relevant? And in the final part of the guidelines, can we identify "Goldilocks" end-points of organ injury (not too hard, not too soft: in other words, markers that are clinically meaningful but practical to measure)?

Mandatory Description of CPB Equipment and Perfusion Techniques Used

Two different but concurrent mechanisms are critical in initiation of SIRS during CPB. The first is blood and its component activation due to contact with the foreign surface of the bypass machine, then causing a secondary systemic host response and ischaemia reperfusion injury due to inadequate tissue perfusion during CPB. Many fixed and variable factors of CPB and perfusion technique may influence inflammatory outcomes.

Fixed components, such as open versus closed venous reservoirs, use of active suction, arterial line filters, and type and coating of the oxygenator and tubing may affect the extent of blood component activation and embolic load [Brown 2000; Jones 2002b, 2002a; Allen 2005; De Somer 2002]. We recommend mandatory description of CPB coating, the type of circuit used (closed, open venous reservoir, mini system), the type of tubing and oxygenator used, type of arterial line filter and prebypass filter type and size, and the type of pump used (roller, centrifugal, use of venous suction, and use of pulsatile flow).

Many foundational characteristics of CPB, while often linked to adverse sequelae and especially to the underlying mechanisms of SIRS, are rarely noted in research reports dealing with the inflammatory response, including: Blood pressure, flow, temperature, glucose levels, oxygen delivery, extent of hemodilution, and duration of CPB [Schwartz 1995; Stensrud 1999; Ranucci 2006, 2005; Haugen 2007; Brown 2000; Habib 005].

In addition to systemic factors, physical manipulation of grafts and the aorta may impact on local generation of coagulation factors and emboli. Procurement related endothelial injury to grafts and excessive clamping force used during aortic cross clamping may each have deleterious effects on clinical outcomes [Poston 2006; Burris 2008; Hammon 2006]. The panel therefore recommends mandatory reporting of the type and number of grafts performed and how they were handled during procurement (open/closed harvest, whether flushed and with what, or distended, or “pipe cleaned”). The type and number of cross clamps should also be specified.

The use or non use of cell salvage for handling pleuro-pericardial blood has an influence on systemic activation of coagulation factors and cells/platelets in blood [Allen 2007; Aldea 2002; Shann 2006]. The increased awareness of the dangers of blood transfusion has resulted in a dramatic reduction in the use of packed red cells, fresh frozen plasma, platelets and cryoprecipitate in cardiac surgery. All these products are associated with the risk of inflammatory response [Spiess 2004; Furnary 2007; Banbury 2006]. Patients receiving these products may introduce bias into the study and their use needs to be specified, and dealt with in the methods (modifying study entry criteria) or analysis (stratification of results, or adjustment).

Finally, the type of anesthesia and use of drugs pre- and peri-operatively should be defined, since these may materially affect the systemic inflammatory response [De Hert 2005; Kincaid 2005; Radaelli 2007; Goudeau 2007; Levy 2008].

Table 1 summarizes the minimal CPB and perfusion criteria that should be reported.

What markers should be monitored when researching the systemic inflammatory response?

A major weakness of current research is that markers relevant

Table 1. Mandatory Description of CPB Equipment and Perfusion Techniques Used

CPB Equipment	*type of circuit (closed, open venous reservoir, mini system) tubing (type and coating) active/passive venous suction pump type (roller or centrifugal, brand and model) flow type (pulsatile, non-pulsatile) oxygenator (type and coating) arterial filter and pore size pre CPB filter and pore size
Protocols And Techniques	duration of CPB priming volume type + amount of cardioplegia (colloids, crystalloids, etc.) type of anesthesia (volatile vs. venous) temperature management (where measured, active/passive cooling/heating and separation temperatures) pH management target flow and pressures (lowest and average pressure during CPB) heparinization protocol lowest DO2 during CPB and average DO2
Surgical Technique	graft (type, number, open/closed harvest) graft handling (how flushed, distended, pipe cleaned?) cannulation site aortic management (x-clamp, side biting clamp, epi-aortic scanning)
Blood Management	cardiotomy suction protocol use of cell saver (processing of residual blood, volume, timing) transfusion (PRBC, FFP, platelets, cryoprecipitate)
Drug Use	use of antifibrinolytics or other hemostatic drugs. At what concentration? was ACEI used + % of patients on ACEI before operation? % of patients on platelet inhibition pre-op? Which inhibitor?

*Report all details of equipment, protocols and techniques specified on the list, since these can affect outcomes (the systemic inflammatory response). Fixed hardware (like type of oxygenator employed) can be listed in Methods. Variables (such as transfusion requirement) should be summarised in the text or tables.

to the systemic “inflammatory” response to CPB have not been defined. The literature is replete with reports that claim to study the systemic “inflammatory” response, yet fail to measure a single marker of inflammation and monitor only “convenience metrics” (variables easily identified through administrative or billing records), such as length of hospital stay. Inferences drawn from such reports may lead to faulty assumption that have nothing to do with the inflammatory response, since neither causal markers nor clinically meaningful end-points were considered.

CAUSAL MARKERS

Major Criteria

Typically, classical inflammatory cytokines and chemokines have been monitored, like IL-1 and IL-8, along with acute phase proteins like hs-CRP, IL-6, and TNF α [McBride 1995; Verrier 2004; Rinder 1999, 2007]. The present recommendation suggests broadening the list to include other cytodestructive and

vasoactive mediators released from activated white cells and complement pathways:

- Classical cytokines (e.g. IL-1, etc.)
- Chemokines (e.g. IL-8, MCP-1, etc.)
- Acute phase proteins (e.g. hs-CRP, IL-6, TNF α , etc.)
- Regulatory cytokines (e.g. IL-10, IL-12)
- Complement factors (e.g. C4a, C3a, C5a, C5b9 complex)
- Leukotrienes (e.g. LTB4, PAF, etc.)
- Proteases (e.g. elastase, myeloperoxidase, cathepsin G, MMPs)

A number of factors from the coagulation cascade and their secondary activation products cross over into the inflammatory response and should be included [Kamiya 1993; Wachtfogel 1993; Kaplanski 1998; Lidington 2000; Wojciak-Stothard 2001]:

- Intrinsic coagulation cascade (e.g. Kallikrein, Thrombin [F1.2 and TAT])
- Activation products of intrinsic coagulation (e.g. kinins)
- Extrinsic coagulation cascade (e.g. tissue factor)
- Regulatory factors (e.g. Activated protein C, protein C inhibitor)

Markers of leukocyte activation and study of extravascular migrating leukocytes will be important to include as causal markers of the systemic host response [Seekamp 1993; Diego 1997; Hill 1996; Evans 2008]:

- extravasated leukocyte populations (e.g. bronchoalveolar lavage cells)
- activation markers (e.g. CD11b, CD18, L-selectin shedding)

In the absence of overwhelming sepsis the usefulness of monitoring leukopenia as a marker of the inflammatory response is questionable. Unless leukocytes are activated, disgorge their products, or accumulate extravascularly, it is not likely that systemically elevated leukocyte numbers are clinically meaningful. Racial variation in leukocyte endothelial margination exists further decreasing specificity. The consensus of the panel at Outcomes XII was that leukocyte count should NOT be used as a marker of the systemic inflammatory response.

With respect to brain injury, the panel cautioned that popular markers, such as S100B, tau and enolase, had limited value as markers of brain injury but no value as causal inflammatory markers. In order to evaluate alterations in surgical techniques or pharmaceutical interventions with anti-inflammatory potential, the following causal markers of brain injury were recommended for study [Taylor 1998; Kamiya 1993; Stump 2007; Murkin 2007]:

- microparticles (gaseous and particulate emboli)
- edema (brain & retinal edema)

In addition to the major criteria listed above it is also reasonable to measure causal inflammatory markers from the list of minor criteria below:

CAUSAL MARKERS

Minor Criteria

Reactive oxygen species may contribute to the systemic inflammatory response [Weiss 1989; Shappell 1990; Entman 1992; Rothlein 1994]. These species are short-lived and would usually be measured indirectly by their oxidation adducts.

- systemic adducts (e.g. MDA, TBARs)
- urinary adducts (F2-isoprostanes)
- flow cytometric evaluation of ROS (e.g. fluoresceine diacetate)

Hemolysis contributes to oxidant stress, endothelial dysfunction and is a causal factor in systemic hypertension, pulmonary hypertension and renal injury in other hemolytic conditions (e.g. sickle cell). Intravascular hemolysis, due to shearing of the erythrocytes in the CPB circuit, is also commonly associated with CPB [Tanaka 1991; Davis 1999; Christen 2005]. It is therefore reasonable to measure markers of intravascular hemolysis in studying the systemic inflammatory response [Minnecci 2005; Kato 2006; Hsu 2007].

- hemolysis (ferricyanide, plasma free hemoglobin, haptoglobin)
- LDH (isoenzymes 1 or 2)

Circulating markers of endothelial activation, circulating endothelial cells (CECs) and circulating endothelial progenitors (EPCs) are all potential markers of the systemic inflammatory response, although they remain to be validated as such [Toussoulis 2008; Cribbs 2008; Rabelink 2004; Scheubel 2003]. The value of shed endothelial adhesion molecules (e.g. sE-selectin, sICAM, sVCAM-1) as markers of endothelial activation is questionable [Malik 2001]. Endothelial function tests by non-invasive techniques such as flow mediated dilation, peripheral arterial tonometry and plethysmography may provide a more robust measure of clinical endothelial dysfunction following CPB, but remain difficult to perform in a clinical setting.

Fibrinolysis and blood loss: whereas there is some evidence that plasmin may exert direct platelet and chemoattractant effects during the systemic host response to surgery [Shigeta 1997; Syrovets 1997], the panel agreed that blood loss as measured by chest tube drainage should NOT be included as a marker of inflammation.

How many causal markers to measure? What criteria?

If one accepts the principle that the systemic host response to surgery consists of a multi-system disorder, then it stands to reason that more than one pathway of activation should be monitored when judging the clinical usefulness of a potential intervention [Butler 1993; Landis 2007a, 2007b].

The panel recommends that A MINIMUM OF TWO causal markers of the systemic host response should be measured: either 2 major criteria or 1 major and 1 minor criterion. Recommended major and minor criteria are summarised in Table 2.

Very few studies in the current literature would satisfy the stringent criteria of measuring more than one marker in different pathways. However, it would seem to be an inescapable truth that a multi-system disorder will require a multi-targeted intervention to be clinically significant, either through a combination of pharmacological interventions (e.g. anti-complement, anti-leukocyte, anti-coagulant, anti-cytokine), circuit modification strategies and/or changes in clinical practice aimed at minimizing localized trauma to vessels or organs. If progress is to be made towards achieving clinically meaningful interventions against the systemic host response, then multiple causal pathways must be monitored and targeted simultaneously. For examples of robust studies that satisfy most of the recommended cri-

Table 2. Causal Systemic Inflammatory Markers

Major Criteria* (at least 1 marker from these three major categories)	
Vasoactive mediators	↑cytokines chemokines acute phase proteins complement factors
Coagulation factors	kallikrein + kinins, thrombin tissue factor
Activated leukocytes	activation markers cytotoxic products extravascular leukocytes
Minor Criteria	
Oxidant stress	oxidative adducts fluorescent detection
Emboli	gaseous or particulate emboli
Hemolysis	plasma free hemoglobin
Fibrinolysis	plasmin, D-Dimers
Activated endothelium	endothelial progenitors endothelial dependent vasodilation

*Measure a minimum of 2 inflammatory markers (2 Major; or 1 Major+1 Minor)

†Must specify time-point(s) at which chosen inflammatory markers were measured

teria, including clinical end-points as described below, refer to Giomarelli et al 2003, Rubens et al 2005 and Goudeau et al 2007 [Giomarelli 2003; Rubens 2005; Goudeau 2007].

CLINICAL END-POINTS

In order to link causal inflammatory markers to adverse clinical outcomes, the panel recommended that studies quantifying the systemic inflammatory response should measure at least 1 major clinical end-point. Ideally studies would be powered to measure traditional clinical end-points (STS Adult Cardiac Surgery Database: www.sts.org) such as:

- Death (index admission or 30-days)
- MI
- ARDS
- renal injury requiring dialysis
- stroke
- multi organ failure

However, we recognize that in practice it is not always feasible to power a study for rare adverse end-points, such as stroke, nor is there a clear value in reporting a composite endpoint. The problem is compounded when evaluating combinatorial drug therapies or multimodal interventions, in which case ballooning patient numbers would rapidly render studies non-feasible. Hence, the panel identified surrogate end-points of organ injury and measures of hospital stay/resource utilization that were deemed clinically meaningful but practical to measure and not too rare (Table 3). We hope that identification of such convenient clinical end-points will encourage investigators to identify

Table 3. Clinical End-points and Markers of Organ Injury

Major Criteria*	
Clinical End-points	death (index admission, 30 day) MI ARDS dialysis stroke multi-organ failure
Markers of Organ Injury	CK-MB, troponin change in LVEF ECG changes of infarct alveolar arterial oxygen gradient intrapulmonary shunt lung water oliguria (<0.5mL/Kg/Hr) delta serum creatinine GFR need for CVVHF neuropsychological testing encephalopathy delirium, confusion brain oxygen saturation DW-MRI S-100B (in CSF) gut ischemia by colonoscopy/gastroscopy neonates/infants: fluid accumulation on-pump
Hospital Stay/Resource Utilization	time on ICU inotrope requirements non-invasive ventilatory support pharmacological renal support wound infection

*Measure a minimum of 1 major criteria from the list of clinical end-points above

combinations of drugs and/or clinical management changes with potential anti-inflammatory benefits, at least to guide the initial phases of research.

CONCLUSION

If one accepts the principle that the systemic inflammatory response to cardiac surgery consists of multiple host defense pathways simultaneously activated, then it stands to reason that more than one pathway of activation should be monitored, especially when judging the clinical usefulness of an intervention. The purpose of this consensus document was to define minimal criteria relating to equipment and perfusion techniques that should be reported, causal inflammatory markers that should be measured and to identify useful and appropriate clinical end-points that may be monitored - our recommendations are summarized in the Figure. Specifically, we have recommended: 1) mandatory reporting of minimal CPB and perfusion criteria that may affect outcomes (Table 1) and 2) reporting of causal inflammatory markers (minimum of two) that may link

Summary of Recommendations:

1. **Minimal description of CPB equipment and perfusion techniques used. See Table 1.**
2. **Report a minimum of 3 criteria (3 major criteria or 2 major and 1 minor). See Tables 2 & 3:**

i.e.

- 3 major** (2 inflammatory and 1 clinical end-point or marker of organ injury)
or
2 major (1 inflammatory and 1 clinical end-point or marker of organ injury) and **1 minor** criteria.

exposures to outcomes (Table 2) and 3) reporting of at least one clinical end-point of organ injury, from a list of apt end-points and markers of organ injury that are practical to measure yet clinically meaningful (Table 3).

ACKNOWLEDGEMENTS:

We acknowledge participants at the 2008 Outcomes XII conference, Barbados, May 21-24, who contributed to discussions on the systemic inflammatory response.

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GLOSSARY

ACEI	- inhibitors of angiotensin-converting enzyme
APC	- activated protein C
APC-PCI	- activated protein C-protein C inhibitor complex
ARDS	- adult respiratory distress syndrome
CD11b	- leukocyte integrin adhesion receptor, alphaM subunit
CD18	- leukocyte integrin adhesion receptor, beta2 subunit
CK-MB	- creatinine kinase-myocardial band
CPB	- cardiopulmonary bypass
CRP	- C reactive protein
CSF	- cerebro spinal fluid
CVVHF	- continuous venovenous hemodiafiltration
DO2	- oxygen delivery
DW-MRI	- diffusion weighted magnetic resonance imaging
GFR	- glomerular filtration rate
F1.2	- prothrombin fragment F1.2
FFP	- fresh frozen plasma
ICU	- intensive care unit
IL	- interleukin
LDH	- lactate dehydrogenase
LTB4	- leukotriene B4
MCP	- monocyte chemoattractant protein
MDA	- malondialdehyde
MI	- myocardial infarction
MMP	- matrix metalloproteinase
PAF	- platelet activating factor
PRBC	- packed red blood cells
ROS	- reactive oxygen species
S100B	- S100 calcium binding protein B
TAT	- thrombin-antithrombin complex
TBARS	- thiobarbituric acid-reactive substances
TNF	- tumor necrosis factor