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

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ABSTRACT

The lack of established cause and effect between putative mediators of inflammation and adverse clinical outcomes has been responsible for many failed anti-inflammatory interventions in cardiopulmonary bypass (CPB). Candidate interventions that impress in preclinical trials by suppressing a given inflammation marker might fail at the clinical trial stage because the marker of interest is not linked causally to an adverse outcome. Alternatively, there exist examples in which pharmaceutical agents or other interventions improve clinical outcomes but for which we are uncertain of any anti-inflammatory mechanism. The Outcomes consensus panel made 3 recommendations in 2009 for the conduct of clinical trials focused on the systemic inflammatory response. This panel was tasked with updating, as well as simplifying, a previous consensus statement. The present recommendations for investigators are the following: (1) Measure at least 1 inflammation marker, defined in broad terms; (2) measure at least 1 clinical end point, drawn from a list of practical yet clinically meaningful end points suggested by the consensus panel; and (3) report a core set of CPB and perfusion criteria that may be linked to outcomes. Our collective belief is that adhering to these simple consensus recommendations will help define the influence of CPB practice on the systemic inflammatory response, advance our understanding of causal inflammatory mechanisms, and standardize 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 [Bone 1992] consisted of the manifestation of 2 or more of the following conditions:

- Fever >38°C or a temperature <36°C;
- Heart rate >90 beats/minute (not appropriate in children);
- Respiratory rate >20 breaths/minute or a $PaCO_2$ level <32 mm Hg (4.3 kPa);
- Abnormal white blood cell count: $<4 \times 10^9$ cells/L, $>12 \times 10^9$ cells/L, or >10% immature (band) forms.

Investigators and researchers should remember that although these parameters are used to aid in the diagnosis of SIRS, they are rarely causative of SIRS. In the cardiothoracic field, we are fundamentally concerned with identifying causal markers of inflammation and then interdicting them. The trauma experienced after cardiac surgery with cardiopulmonary bypass (CPB) is also quite distinct from the trauma experienced in critical care medicine. The present consensus statement is an attempt to take control of the intellectual property of the inflammatory response as it applies to the field of cardiothoracic surgery and to recommend simple criteria that should be included in the design and

reporting of studies in this arena. We are guided by the principle that a comprehensive set of host defensive pathways are activated simultaneously through the combined insult of operative stress and the exposure of blood to air and components of the extracorporeal bypass circuit. These defensive pathways include: (1) intrinsic coagulation, (2) fibrinolysis, (3) hemolysis, (4) classic complement pathway activation, (5) oxidant stress, (6) chemokine and cytokine elaboration, (7) kinin activation, (8) leukocyte activation, and (9) endothelial activation [Butler 1993; Edmunds 1993; Landis 2008a]. Recent reviews and meta-analyses have collectively alluded to the phenomenon as "blood activation." Interventions—whether they be circuit modifications, pharmacologic regimens, alterations in operative technique, or combinations thereof—must dampen "blood activation" to be clinically effective [Landis 2009; Ranucci 2009]. We recognize that effective dampening of such a multipronged inflammatory response may ultimately require a combination of 2 or more interventions; therefore, our recommendations emphasize the need to study practical end points (so as to avoid unachievable sample sizes) and to identify networks of causation. The recommendations have been condensed into 3 practical tables that define the following study criteria:

- Markers causally involved in the systemic inflammatory response and therefore clinically relevant (Table 1);
- End points of organ injury that are clinically meaningful but practical to measure. (Table 2);
- The minimal data set for CPB and perfusion that should be included in a research report (Table 3).

WHAT MARKERS SHOULD BE MONITORED WHEN RESEARCHING THE SYSTEMIC INFLAMMATORY RESPONSE?

A major weakness of current research is that markers relevant to the systemic inflammatory response to CPB have not been defined. The literature is replete with reports that claim the systemic "inflammatory" response was studied, yet fail to describe the measurement of a single marker of inflammation. These studies monitored 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 assumptions that have nothing to do with the inflammatory response, because neither causal markers nor clinically meaningful end points were considered.

We recommend that all clinical studies include the measurement of at least 1 inflammation marker. Such measurements are especially important when considering a new anti-inflammatory intervention. Recently, an evidence-based review carried out on behalf of the International Consortium for Evidence-Based Perfusion (ICEBP) found that in <4% of drug trials that investigated the systemic inflammatory response were investigators able to link biochemical changes in inflammatory pathways with any change in clinical outcome [Landis 2008b]. The literature therefore yields only scant support for clinically effective pharmacologic interventions, with steroids and antifibrinolytic agents leading the field with equivocal class IIa or class IIb American Heart Association/American College of Cardiology–style provisional recommendations.

Table 1. Causal Markers of Systemic Inflammation*

Vasoactive mediators	Cytokines
	Chemokines
	Acute-phase proteins
	Complement factors
Coagulation factors	Kallikrein and kinins
	Thrombin
	Tissue factor
Activated leukocytes	Activation markers
	Cytodestructive products
	Extravascular leukocytes
Oxidant stress	Oxidative adducts
	Fluorescence detection
Emboli	Gaseous or particulate emboli
Hemolysis	Plasma free hemoglobin
	Haptoglobin
Fibrinolysis	Plasmin, d-dimers, thromboelastography
Activated endothelium	Endothelial progenitors
	Endothelial-dependent vasodilation

*Researchers are encouraged to incorporate measurement of at least 1 causal inflammation marker. Such measurement should be considered mandatory when the intervention does not have an established anti-inflammatory mechanism. Refer to text for examples of possible inflammation markers, broadly defined.

It is perhaps telling that the first meta-analysis of the anti-inflammatory properties of aprotinin took place only after the drug was withdrawn from the market [Brown 2009]. Putative anti-inflammatory benefits were promoted ahead of the scientific evidence base and ahead of more important clinical-safety considerations, such as weight-based dosing [Fritz 1983; Royston 2001]. The rise and fall of aprotinin, therefore, stands as a cautionary tale for clinicians and industry. The paucity of evidence revealed by both the ICEBP study and the aprotinin meta-analysis merely highlights the urgent need to expand the evidence base with well-designed clinical trials that link causal inflammation markers to clinical outcomes.

In the past, inflammatory cytokines and chemokines, such as interleukins (interleukin 1 [IL-1], IL-8), and acute-phase proteins (high-sensitivity C-reactive protein [hs-CRP], IL-6, and tumor necrosis factor α [TNFα]) have typically been monitored [McBride 1995; Rinder 1999; Verrier 2004; Rinder 2007; Perry 2009; Shaw 2009]. The present recommendation suggests broadening the list to include other cytodestructive and vasoactive mediators released from activated white cells and the complement pathways:

- Classic cytokines (eg, IL-1, IL-18);
- Chemokines (eg, IL-8, monocyte chemoattractant protein 1 [MCP-1]);
- Acute-phase proteins (eg, hs-CRP, IL-6, TNFα);

Table 2. Clinical End Points and Markers of Organ Injury*

Hard clinical end points	Death (index admission, 30-day)
	Myocardial infarction
	Acute lung injury
	Dialysis
	Stroke
	Multiorgan dysfunction requiring mechanical support
Markers of organ injury	
Heart	CK-MB, troponin
	Change in LVEF
	ECG changes of infarct
Lung	Arterial PO_2 on 100% oxygen
	Gas exchange adequate for extubation
	Alveolar arterial oxygen gradient
	Intrapulmonary shunt
	Lung water
Kidney	Oliguria (<0.5 mL/kg per h)
	Change in serum creatinine
	Glomerular filtration rate
	Need for CVVHF
Brain	Neuropsychological testing
	Encephalopathy
	Delirium, confusion
	Brain oxygen saturation
	DW-MRI
	S100B in CSF
Gut	Gut ischemia by colonoscopy/gastroscopy
Pediatric	Fluid accumulation on pump
Hospital stay/resource utilization	Time in ICU
	Vasopressor use
	Inotrope requirements
	Noninvasive ventilatory support
	Pharmacologic renal support
	Wound infection

*Measure at least 1 clinical end point from this suggested list. CK-MB indicates creatine kinase isoenzyme MB; LVEF, left ventricular ejection fraction; ECG, electrocardiogram; CVVHF, continuous venovenous hemodiafiltration; DW-MRI, diffusion-weighted magnetic resonance imaging; S100B, S100 calcium-binding protein B; CSF, cerebrospinal fluid; ICU, intensive care unit.

- Regulatory cytokines (eg, IL-10, IL-12);
- Complement factors (eg, C4a, C3a, C5a, C5b9 complex);
- Leukotrienes (eg, leucotriene B4 [LTB4], platelet-activating factor [PAF]);
- Proteases (eg, elastase, myeloperoxidase, cathepsin G, matrix metalloproteinases [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 (eg, kallikrein, thrombin [prothrombin fragment F1.2 and thrombin–antithrombin complex]);
- Activation products of intrinsic coagulation (eg, kinins);
- Extrinsic coagulation cascade (eg, tissue factor);
- Regulatory factors (eg, activated protein C, protein C inhibitor).

The leukocyte count, markers of leukocyte activation, and studies of migrating extravascular leukocytes will be important to include as causal markers of the systemic host response [Seekamp 1993; Hill 1996; Diego 1997; Evans 2008; Ng 2009]:

- Leukocyte count (preferably the differential count);
- Extravasated leukocyte populations (eg, bronchoalveolar lavage cells);
- Activation markers (eg, CD11b, CD18, L-selectin shedding).

With respect to brain injury, the panel cautioned that although popular markers such as S100B (S100 calcium-binding protein B), tau, and enolase had a limited value as markers of brain injury, they had no established value as causal inflammation markers (except for S100B in cerebrospinal fluid). For the evaluation of alterations in surgical techniques or pharmaceutical interventions with anti-inflammatory potential, the panel recommended the following causal markers of brain injury for study [Kamiya 1993; Taylor 1998; Murkin 2007; Stump 2007]:

- Microparticles (gaseous and particulate emboli);
- Edema (brain and retinal edema).

Reactive oxygen species (ROS) 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 via their oxidation adducts. Such species include the following:

- Systemic adducts (eg, malondialdehyde, thiobarbituric acid–reactive substances);
- Urinary adducts (F2-isoprostanes);
- Flow cytometric evaluation of ROS (eg, fluorescein diacetate).

Hemolysis contributes to oxidant stress and endothelial dysfunction and is a causal factor in systemic hypertension, pulmonary hypertension, and renal injury in other hemolytic conditions (eg, sickle cell). Intravascular hemolysis, due to shearing of the erythrocytes in the extracorporeal circuit, is inevitably associated with CPB [Tanaka 1991; Davis 1999; Christen 2005]. It is therefore reasonable to measure markers of intravascular hemolysis when studying the systemic

Summary of Recommendations:

1. **Measure at least 1 inflammation maker, defined in broad terms. See Table 1.**
2. **Report at least 1 clinical end point, drawn from a list of practical yet clinically meaningful end points. See Table 2.**
3. **Report a core set of CPB and perfusion criteria that may be linked to outcomes. See Table 3.**

Figure 1. Summary of recommendations. CPB indicates cardiopulmonary bypass.

inflammatory response [Minneci 2005; Kato 2006; Hsu 2007]. Such markers include the following:

- Hemolysis markers (ferricyanide, plasma free hemoglobin, haptoglobin);
- Lactate dehydrogenase (isoenzyme 1 or 2).

Circulating markers of endothelial activation (circulating endothelial cells and circulating endothelial progenitor cells) are potential markers of the systemic inflammatory response, although they remain to be validated as such [Scheubel 2003; Rabelink 2004; Cribbs 2008; Tousoulis 2008]. The value of shed endothelial adhesion molecules (eg, soluble E-selectin, soluble intercellular adhesion molecules [sICAMs], soluble vascular cell adhesion molecule 1 [sVCAM-1]) as markers of endothelial activation is questionable [Malik 2001]. Endothelial-function tests that use such noninvasive techniques as flow-mediated dilation, peripheral arterial tonometry, and plethysmography may provide a more robust measure of clinical endothelial dysfunction following CPB, but they remain difficult to perform in the clinical setting.

With respect to fibrinolysis and blood loss, although some evidence suggests 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 was nonspecific and should not be included as a marker of inflammation. Fibrin-degradation products (eg, fibrin d-dimers) and thromboelastography provide more-specific markers of fibrinolytic pathway activation, and they may be included as inflammation markers.

Table 1 provides a broad list of causal inflammation markers that can be selected for inclusion in reports.

WHAT CLINICAL END POINTS OR MARKERS OF ORGAN INJURY SHOULD BE MEASURED?

To link causal inflammation markers to adverse clinical outcomes, the panel recommended that studies quantifying the systemic inflammatory response measure at least 1 major clinical end point. Ideally, studies would be powered to measure traditional hard end points (Society of Thoracic Surgeons Adult Cardiac Surgery Database; see http://www.sts.org), such as:

- Death (index admission or after 30 days);
- Myocardial infarction;
- Acute lung injury/respiratory distress syndrome;
- Renal injury requiring renal-replacement therapy;
- Stroke;
- Multiorgan dysfunction requiring mechanical support.

We recognize, however, that it is not always feasible in practice to power a study for rare adverse end points, such as stroke, nor is there a clear value in reporting composite end points. The problem is compounded when evaluating combination drug therapies or multimodal interventions, in which the number of patients required for a study renders it unfeasible. Hence, the panel identified surrogate end points of organ injury and measures of hospital stay and resource utilization that were deemed clinically meaningful but that were practical to measure and not too rare (Table 2). We hope that identification of such convenient clinical end points will encourage investigators to identify combinations of drugs or clinical-management changes with potential anti-inflammatory benefits, at least to guide the initial phases of research.

Examples of robust studies already published that satisfy most of the recommended criteria, including clinical end points as described above, include those of Giomarelli et al [2003], Rubens et al [2005], Goudeau et al [2007], and Gunaydin et al [2009].

MANDATORY DESCRIPTION OF CPB EQUIPMENT AND PERFUSION TECHNIQUES USED

Two different but concurrent mechanisms are critical in the initiation of SIRS during CPB. The first is activation of blood components by contact with the foreign surface of the extracorporeal circuit, leading to a secondary systemic host response and ischemia-reperfusion injury due to inadequate tissue perfusion during CPB. Many fixed and variable factors of CPB and the perfusion technique may influence inflammatory outcomes.

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

Table 3. Mandatory Description of Cardiopulmonary Bypass (CPB) Equipment and Perfusion Techniques Used*

CPB equipment	Type of circuit (closed, open venous reservoir, minisystem)
	Tubing (type and coating)
	Active/passive venous suction
	Pump type (roller or centrifugal, including brand and model)
	Flow type (pulsatile, nonpulsatile)
	Oxygenator (type and coating)
	Arterial filter and pore size
	Pre-CPB filter and pore size
Protocols and techniques	CPB duration
	Priming volume
	Amount and type of cardioplegia (colloids, crystalloids, etc)
	Type of anesthesia (volatile versus venous)
	Temperature management (where measured, active/passive cooling/heating, and separation temperatures)
	pH management
	Target flow and pressures (lowest and mean pressure during CPB)
	Heparinization protocol (dose, maximum and minimum ACT/KCT, and machine used)
	Hematocrit
	Glucose concentration
	Lactate concentration
	Lowest DO_2 during CPB and mean DO_2
Surgical technique	Graft (type, number, open/closed harvest)
	Graft handling (how flushed; distended, pipe-cleaned?)
	Cannulation site
	Aortic management (cross-clamping, side-biting clamp, epiaortic 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?)
	Preoperative use of nicorandil
	Was an ACEI used? Percentage of patients on ACEI before operation? Percentage on platelet inhibition preoperatively? Which inhibitor?

*Report all details of equipment, protocols, and techniques specified on this list, because these variables can affect outcomes (the systemic inflammatory response). Fixed hardware (such as type of oxygenator used) can be listed in the "Methods" section. Variables (such as transfusion requirement) should be summarized in the text or in tables. ACT indicates activated clotting time; KCT, kaolin clotting time; DO_2, oxygen delivery; PRBC, packed red blood cells; FFP, fresh frozen plasma; ACEI, angiotensin-converting enzyme inhibitor.

size, and the type of pump used (roller, centrifugal, use of venous suction, use of pulsatile flow).

Although CPB itself is considered a cause of SIRS and is often causally linked to adverse outcomes, the fundamental characteristics of CPB are rarely mentioned in research reports dealing with the inflammatory response. Such characteristics include arterial pressure, pump flow, inflow temperature, blood glucose management, oxygen delivery, extent of hemodilution, lactate concentration, and CPB duration [Schwartz 1995; Stensrud 1999; Brown 2000b; Habib 2005; Haugen 2007]. Suboptimal perfusion has been highlighted as a special area of concern in the inflammatory response [De Somer 2009]. The difficulty in maintaining adequate tissue perfusion in clinical practice is demonstrated by the fact that up to 20% of all cardiac procedures show evidence of hyperlactatemia, a recognized risk factor for an adverse

outcome [Maillet 2003; Ranucci 2006a]. Minimal and average oxygen delivery (DO_2) values should therefore be reported. Carbon dioxide–derived parameters (carbon dioxide production [VCO_2], respiratory quotient, and the DO_2/VCO_2 ratio) also show good correlation with tissue perfusion and may be reported [Ranucci 2005; Ranucci 2006b].

In addition to systemic factors, physical manipulation of the heart, the great vessels, and bypass grafts may have an impact on the local generation of coagulation factors and emboli. Excessive clamping force used during aortic cross-clamping and endothelial injury to bypass conduits during their harvest and preparation may each exert deleterious effects on clinical outcomes [Hammon 2006; Poston 2006; Burris 2008]. The panel therefore recommends mandatory reporting of the type and number of bypass grafts performed and how they were handled during procurement (eg, open versus closed harvest, whether they were flushed and with what, whether they were distended or "pipe-cleaned"). The type(s) of cross-clamps and the number of cross-clamp applications should also be specified.

Using cell-salvage techniques to process cardiotomy blood has an influence on the systemic activation of coagulation factors and cellular components of the circulation [Aldea 2002; Shann 2006; Allen 2007; Gunaydin 2009]. The increased awareness of the hazards associated with homologous blood transfusion has led to a dramatic reduction in cardiac surgery of the use of packed red cells, fresh frozen plasma, platelets, and cryoprecipitate—all of which are associated with the risk of inflammatory response [Spiess 2004; Banbury 2006; Ferraris 2007; Furnary 2007]. Because the use of blood products may represent a source of bias in a study, their use needs to be stated explicitly and dealt with in the methods (via modifying the criteria for study entry) or analysis (via stratification of results or their adjustment).

Finally, the anesthetic and other drugs administered in the perioperative period should be stated, because these drugs may materially affect the systemic inflammatory response [Falase 1999; De Hert 2005; Kincaid 2005; Goudeau 2007; Radaelli 2007; Levy 2008].

Table 3 summarizes the minimal CPB and perfusion criteria that should be reported.

The reporting of so many fixed and variable criteria relating to CPB equipment and perfusion protocols is clearly a daunting prospect. Assistance in this regard has accompanied a new initiative: Perfusion Standards of Reporting Trials (PERFSORT). PERFSORT aims to simplify and standardize reporting of perfusion parameters in the literature and to track emerging clinical standards of perfusion internationally. The main product of PERFSORT is the production of a database that is freely downloadable (see http://www.perfsort.net). Authors submitting their articles for publication also submit their perfusion data via this database. They will then be supplied with a statement regarding the PERFSORT compliance percentage. The original data will then become incorporated into a Web site for downloading as an electronic supplement to the publication. In addition, the database will be imported into a single worldwide perfusion database, which should facilitate evidence-based analyses of worldwide perfusion practices. Considered an evolving process, PERFSORT will be subject to periodic changes as new evidence emerges. PERFSORT is relevant to single-patient case reports, patient series, and multicenter studies.

CONCLUSION

The purpose of this consensus document was to define minimal criteria relating to the equipment and perfusion techniques that should be reported, list the causal inflammation markers that should be measured, and identify useful and appropriate clinical end points that may be monitored. Figure 1 summarizes our simple recommendations. Specifically, we have recommended the following: (1) reporting of results for 1 causal inflammation marker (mandatory if the intervention does not have an established anti-inflammatory mechanism of action) (Table 1); (2) reporting of at least 1 clinical end point of organ injury, from a list of apt end points and markers of organ injury that are practical to measure, yet are clinically meaningful (Table 2); and (3) reporting of a core set of CPB and perfusion criteria that may affect outcomes (Table 3).

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