

Invited Editorials

20 Years On: Is It Time to Redefine the Systemic Inflammatory Response to Cardiothoracic Surgery?

R. Clive Landis

Edmund Cohen Laboratory for Vascular Research, Chronic Disease Research Centre, University of the West Indies, Barbados

Abstract: The “systemic inflammatory response” has never been defined from a cardiothoracic surgery perspective, but borrowed its definition from the critical care field at a landmark 1992 definition conference on sepsis. It is unclear why the diagnostic criteria for the Systemic Inflammatory Response Syndrome (SIRS) were adopted in isolation, ignoring other potentially more useful definitions for Severe Septic Shock or Secondary Multiple Organ Dysfunction Syndrome. The 1992 SIRS definition for sepsis has since been updated at a conference in 2001 advocating PIRO (Predisposition, Infection, host Response, Organ dysfunction) as a hypothetical model to better link sepsis with clinical outcome. PIRO is readily adaptable to cardiothoracic surgery and provides the precedent and road map for how to update a definition. The need is obvious since the current definition of SIRS is widely disregarded in heart surgery: a dwindling proportion (14%) of articles on the systemic inflammatory response even mention SIRS and 0% monitored SIRS criteria in the past decade in an evidence-based review of anti-inflammatory interventions. The name “inflammatory response” is also problematic; it is too nar-

row and might be replaced with host response (the R in PIRO) to better convey the wide spectrum of host defensive pathways activated during heart surgery (i.e., complement, coagulation, fibrinolysis, kinins, cytokines, proteases, hemolysis, oxidative stress). A variant on PIRO could allow these elements of the host Response (R) to be anchored within the context of Premorbid conditions (P) and the inevitable Insult (I) from surgery, to better link risk exposures to Organ dysfunction (O) in heart surgery. The precedent of PIRO suggests the following steps will be required to redefine the systemic inflammatory response: 1) buy-in from the leading societies for cardiothoracic surgery, anesthesia, and perfusion on the need for a re-definition conference, 2) assigning relative risk scores to different premorbid exposures, operative insults, and host response factors on clinical outcome, 3) validation of the risk model in a prospective cohort, and 4) development of algorithms or “apps” to facilitate rapid diagnosis and staging of care at bedside. **Keywords:** inflammation, systemic-CPB, inflammatory response, complications and management-CPB, outcomes. *JECT. 2015;47:5-9*

THE PURPOSE OF A DEFINITION: LESSONS FROM SEPSIS

It is instructive to reflect on what is considered the purpose of a definition, set out in the proceedings of the 2001 re-definition conference on sepsis (1); this was considered two-fold: first, to facilitate bedside diagnosis for the rapid clinical staging of critically ill patients, and, second, to provide simple entry criteria for clinical trials. The proceedings went on to state that: “facilitating bedside diag-

nosis should have primacy over research entry criteria.” The systemic inflammatory response to heart surgery, as currently understood, does not satisfy either one of these criteria. Indeed, it has never been formally defined and appears to have evolved organically as a concept from review articles written around the time of the 1992 Systemic Inflammatory Response Syndrome (SIRS) definition conference, from which the only formal definition was subsequently borrowed.

The only formal definition therefore derives from the 1992 American College of Chest Physicians (ACCP)/ Society of Critical Care Medicine (SCCM) Consensus Conference definition for SIRS (2). SIRS is defined when any two diagnostic criteria relating to abnormal temperature, heart rate, respiratory rate, and leukocytes are present (Table 1). The 1992 ACCP/SCCM conference was a monument in the field of sepsis and fully achieved its

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Address correspondence to: R. Clive Landis, Edmund Cohen Laboratory for Vascular Research, Chronic Disease Research Centre, University of the West Indies, Barbados BB11115. E-mail: clive.landis@uwichill.edu.bb
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Table 1. Clinical diagnosis of the SIRS.

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

1. Fever $>38^{\circ}\text{C}$ or temperature $<36^{\circ}\text{C}$
 2. Heart rate >90 beats per minute (not appropriate in children)
 3. Respiratory rate >20 breaths per minute or a $\text{PaCO}_2 <4.3$ kPa (32 mm Hg)
 4. White blood cell count $<4 \times 10^9$ cells/L or $>12 \times 10^9$ cells/L or $>10\%$ bands
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goal: “to provide both a conceptual and a practical framework to define the systemic inflammatory response to infection, a progressive, injurious process that . . . includes sepsis-associated organ dysfunctions as well.”

It should not be forgotten that this definitions conference was convened for the diagnosis and treatment of sepsis and that SIRS of non-infectious origin merited a mere mention under “other” in a single illustration. It is a shame, looking back, that SIRS was adopted for heart surgery in isolation from other definitions at the 1992 conference that might have been more relevant to the field, such as the definition for “Severe Septic Shock”: “Sepsis (SIRS) induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status” or the definition for “Secondary MODS”: “Secondary MODS develops, not in direct response to the insult itself, but as a consequence of the host response,” which resonate powerfully with the field of cardiothoracic surgery.

ORIGINS OF THE SYSTEMIC INFLAMMATORY RESPONSE: A MURKY HISTORY

Most researchers would cite the classic Butler, Rocker, and Westaby review of 1993 (3) as the origin of the systemic inflammatory response to heart surgery. This paper has stood the test of time and is as relevant today as it was 20 years ago. It provided a logical theoretical framework to link elements of the activated host response with the risk of organ injury and proposed pathophysiological disease mechanisms that have not been challenged or significantly improved upon to the present day. The paper was noteworthy in that it recognized the broad scope of the response, which was much more than a mere manifestation of “inflammatory cytokines,” involving the following pathways: “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.” The pathways activated in the host response to surgery have been detailed in seminal publications both before and after the 1993 review (4–8). It is also noteworthy that despite being published after the 1992 ACCP/SCCM definition conference, the Butler, Rocker, and Westaby paper made no mention of SIRS.

The first record of SIRS being advocated for use in heart surgery appears to originate from a commentary written in 1996 by Ken Taylor (9), arguably the father of the systemic inflammatory response with his pioneering work in 1975 on the cortisol response during heart–lung bypass (10). His commentary, however, urged caution and recognized three limitations for incorporating SIRS into heart surgery: 1) the definition was very broad (e.g., moderate tachycardia and pyrexia $>38^{\circ}\text{C}$ was sufficient to include a patient in the syndrome), 2) SIRS is seen in all patients undergoing open heart operation groups but the severity of the response was variable, ranging from mostly mild to severe life-threatening hemodynamic instability, and 3) SIRS needed to be studied in its own right in the cardiac surgery setting, not relying on research from other disciplines like critical care medicine. Later studies have confirmed that SIRS is indeed too non-specific for use in the heart surgery field and if interpreted literally, up to 40% of all patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) would meet the inclusion criteria for SIRS (1,11–13). It is by failing to rise to the challenge laid down by Ken Taylor, by failing to take intellectual control of the definition that has led to 20 years of drift and disappointing outcomes (14–16), with the only formal definition, SIRS, falling into desuetude and no objective scoring system having taken its place.

EXISTING DEFINITION WIDELY DISREGARDED IN THE FIELD: THE NEED FOR INTELLECTUAL CONTROL

A plot of PubMed citation trends shows how the concept of the systemic inflammatory response predated the concept of SIRS in heart surgery by about a decade (Figure 1). The first citations on the systemic inflammatory response appeared in 1985 compared with SIRS in 1996. Although SIRS provided the only formal and measurable definition, it never gained much traction in the field of heart surgery; hovering around 10% to 13% of papers mentioning SIRS in relation to the systemic inflammatory response, falling to even lower levels in recent years. A critical review of anti-inflammatory interventions conducted by the STS Perfusion Writing Group (17) examined 1600 papers describing interventions to limit the systemic inflammatory response published between the years 2002 and 2011; to be included, studies had to measure at least one inflammatory marker and one clinical outcome as defined by the “Outcomes 2010 Consensus Statement.” A sub-analysis presented in Table 2 of 98 papers that qualified for final inclusion reveals that 14% made any mention anywhere in the text of SIRS, 32% measured just one criterion for SIRS, 9% measured at least two criteria, and 0% monitored SIRS using the four 1992 diagnostic criteria. The likelihood to measure any single

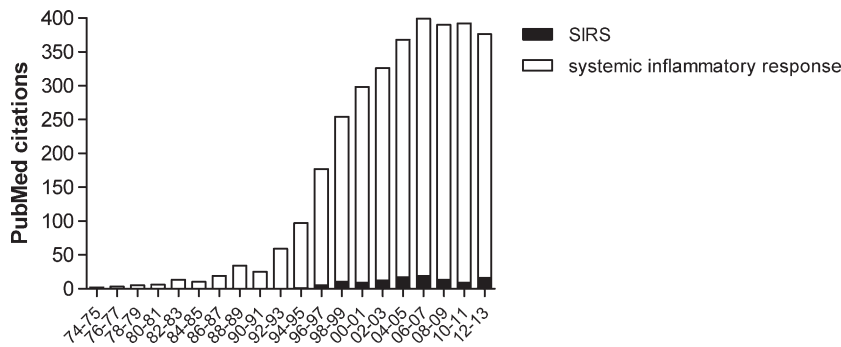


Figure 1. Citation trends for SIRS 1974–2013. The illustration shows the number of citations in PubMed for SIRS (black bars) compared with the systemic inflammatory response (open bars) in cardiopulmonary bypass surgery, plotted in two-year increments for years 1974–2013.

criterion for SIRS was similar between those papers that mentioned SIRS in the text (5/14 = 36%) and those that did not (26/84 = 31%). Hence, any criteria measured were incidental to the objective determination for SIRS, a damning indictment for a medical definition fallen into desuetude and a call to arms to take intellectual control of the definition after 20 years. The median sample size in the inflammation literature, $n = 40$, was also of major concern, with most studies lacking the statistical power to evaluate hard end points, like death, stroke, or myocardial infarction (MI). In the absence of a relevant and practical definition to link the systemic inflammatory response with organ injury, different groups have been left to adopt their own interpretations. For example, “Severe SIRS” with involvement of organ injury is a concept put forward by groups that have adopted organ injury thresholds from other scoring systems such as ODIN (Organ Dysfunctions and/or Infection) or APACHE (Acute Physiology And Chronic Health Evaluation) (12,18,19).

THE PRECEDENT AND ROAD MAP OF PIRO: AN OPPORTUNITY TO ESTABLISH A NEW DEFINITION

PIRO is the acronym for: Predisposition, Infection, host Response, Organ dysfunction, first introduced in the proceedings of the 2001 sepsis re-definition conference

Table 2. SIRS in the evidence base.

Reference of SIRS	Number of Papers	%
SIRS mentioned anywhere in the text	14	14/98* = 14.3%
Measurement of a single SIRS criterion	31	31/98 = 31.6%
Measurement of any two SIRS criteria	9	9/98 = 9.2%
Monitoring of all four SIRS criteria	0	0/98 = 0%

*Ninety-eight papers comprised the evidence base in a critical review of randomized control trials investigating attenuation of the systemic inflammatory response to cardiopulmonary bypass (17).

endorsed by the SCCM, the European Society of Intensive Care Medicine (ESICM), the American College of Chest Physicians (ACCP), the American Thoracic Society (ATS), and the Surgical Infection Society (SIS) (1). According to Mitchell Levy, lead author of the 2001 proceedings, “. . . the specific criteria [for SIRS] proposed in the 1992 consensus definitions are widely considered to be too nonspecific to be of utility in diagnosing a cause of the syndrome . . .” Hence the purpose of PIRO was to update the 1992 ACCP/SCCM criteria for SIRS in sepsis with a scoring system more closely anchored to organ dysfunction. Interestingly, the PIRO model had distinct echoes of a figure in the original Richard Bone paper in 1992 depicting Secondary MODS (2). The illustration for Secondary MODS has been faithfully reproduced in Figure 2, but annotated to show the origins of PIRO: P for Predisposition, I for Insult, R for host Response and O for Organ dysfunction. The I for Insult was revised by Levy et al. (1) to denote “Infection” for sepsis, but the hypothetical purpose for developing PIRO applies equally well to sepsis as it would to the inflammatory response to heart surgery: “A hypothetical model for staging sepsis, which, in the future, may better characterize the syndrome on the basis

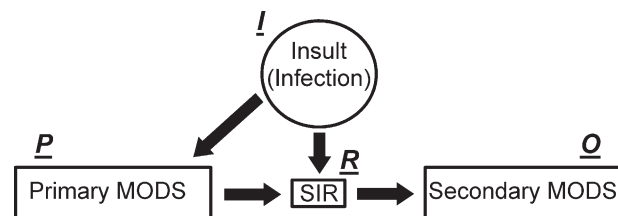


Figure 2. PIRO: close alignment with model for Secondary MODS The PIRO model was proposed by Levy et al. (1) at the 2001 SCCM/ASICM/ACCP/ATS/SIS re-definition conference. However, it echoes an illustration from the original 1992 ACCP/SCCM definition conference by Bone et al. (2) for the development of secondary MODS. The illustration from Bone et al. (2) has been reproduced here and annotated to demonstrate how PIRO aligns with the hypothetical model for developing secondary MODS. Key: MODS, multiple organ dysfunction syndrome; Secondary MODS, develops not in direct response to the insult itself, but as a consequence of the host response (2); SIR, systemic inflammatory response; P, predisposition/premorbid condition; I, insult (or infection in the case of sepsis); R, host response; O, organ injury.

of predisposing factors and premorbid conditions, the nature of the underlying infection, the characteristics of the host response, and the extent of the resultant organ dysfunction.” PIRO is therefore a ready-to-wear definition that could be adapted for use in cardiothoracic surgery to re-define the systemic inflammatory response.

VALIDATING A NEW DEFINITION FOR USE IN CARDIOTHORACIC SURGERY

In the original 1992 paper, Richard Bone noted with remarkable prescience that his definition should require periodic updating and objective risk weighting: “The assignment of criteria for measuring organ dysfunction should not occur a priori, but should result from an empirical process in which specific variables are tested against outcome. By doing so, the predicted accuracy of individual variables, groups of variables, and levels of abnormality can be defined in a manner that reflects current clinical practice.” The hypothetical PIRO scoring system for sepsis has undergone just such an empirical validation in a landmark study by Michael Howell in 2011 (20).

The first step in the Howell validation study was a derivation cohort of patients with clinically suspected infection ($n = 2132$), which was used to create an objective PIRO score for in-hospital mortality (using such covariates as age, race, comorbidities, infection, etc.) (20). In this risk model for sepsis, the highest PIRO scores were assigned to covariates such as pneumonia, tachypnea, hypotension, oliguria, and hyperlactatemia. Many of the same-risk covariates would undoubtedly be considered in any cohort examining PIRO in heart surgery, but clearly the nature of the insult would be different. In sepsis, the I for Infection included just three covariates: pneumonia, soft skin infection, and other infection. In heart surgery, the I stands for Insult and would include, in addition to infection, a range of other operative insults relating to choice and complexity of surgery, extracorporeal bypass, graft procurement, and perfusion variables (21). The purpose of the derivation cohort is to establish objective odds ratios for mortality for each covariate by multivariate regression analysis. In the Howell study in sepsis, each covariate was assigned a weighted integer value and the predictive accuracy of the PIRO score was then validated in a separate validation cohort (20).

An alternative approach that could be taken is the Analytical Hierarchy Process (AHP), a technique used in other health care settings for the systematic assessment of new technologies where clinical evidence is not yet available or incomplete (22–24). In this approach, for example, an expert panel could be tasked with categorizing various risk exposures and insults into low, medium, high, or very high risk categories for organ injury due to the systemic inflammatory response.

By following a similar empirical road map for heart surgery as in sepsis, whether by a cohort or AHP approach, a variant of PIRO could be created, risk weighted, and validated for predicting mortality, hence fulfilling the recommendations in the original 1992 SIRS definition paper and the recommendations of Ken Taylor in 1996, who cautioned that the SIRS concept would need validating for use in heart surgery. A newly minted PIRO for heart surgery would provide a logical framework to incorporate as yet undiscovered risk factors, such as new surgical and extracorporeal perfusion techniques, genetic screening techniques to expose predisposition, and biomarkers for organ injury and the host response. These risk factors could be added in a process of continuous refinement to reflect current practice.

STEPS TOWARD A NEW DEFINITION

The precedent for PIRO in sepsis suggests the following steps will need to be taken to redefine the systemic inflammatory response: 1) a consensus conference to seek the endorsement of surgeons, anesthesiologists, perfusionists, and the critical care field, 2) risk assignment for premorbid factors, operative insults, and host response factors on clinical outcome, 3) proof of concept of the proposed PIRO model or a related model, and 4) development of algorithms or apps to facilitate diagnosis and staging of care at bedside. At the end of this process, we would hope to have proven the hypothesis, as articulated by Levy for sepsis: “that improvements in the management of critically ill patients with serious infections will follow the development of a staging system for sepsis that can better characterize the syndrome on the basis of predisposing factors and premorbid conditions, the nature of the underlying infection, the characteristics of the host response, and the extent of the resultant organ dysfunction.”

Steps 1 to 3 would follow the empirical road map already laid out by Levy and Howell (1,20), who developed and validated the PIRO scoring system respectively. However, even after completing these steps, adoption of a variant PIRO scoring system would remain incomplete since the scoring system is likely to be complex and potentially unwieldy. Again quoting Levy, “Diagnostic criteria will be judged successful if clinicians regard them as an aid for decision making at the bedside.”

Hence, a final step 4 would be needed to develop practical bedside algorithms or apps to help cope with a potentially large number of perioperative variables contributing to I for insult, an anticipated plethora of biomarkers tracking the activated systemic host response (R), and as yet undiscovered genetic screening techniques contributing to P for predisposition. The algorithm would need to integrate and automate all available evidence to produce

a single risk score for bedside prediction of mortality, facilitating rapid decision making, guiding appropriate treatment, and providing objective entry criteria for clinical trials.

CONCLUSION

As cautioned by Mitchell Levy when he re-defined the 1992 SIRS definitions for sepsis: “Establishing working definitions for a syndrome is inherently an imperfect process and one that requires periodic updating on the basis of new insights into pathophysiology or the availability of new diagnostic tests.” The time has come to begin this process for the systemic inflammatory response in heart surgery, by first taking intellectual control of the definition, proposing an alternative definition, and subsequently through development and validation of a modified scoring system, lead to the rapid staging of clinical care.

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