Neuroanesthesia and Intensive Care

Multiple organ dysfunction syndrome: a narrative review

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Purpose: To review multiple organ dysfunction syndrome with respect to: 1) clinical measurement systems; 2) molecular mechanisms; and 3) therapeutic directions based upon molecular mechanisms.

Methods: The Medline, Cochrane, and Best Evidence databases (1996 to 2000), conference proceedings, bibliographies of review articles were searched for relevant articles. Key index words were multiple organ failure, multiple system organ dysfunction, sepsis, septic shock, shock, systemic inflammatory response syndrome. Outcomes prospectively defined were death and physiological reversal of end organ failure.

Results: Multiple organ dysfunction/failure (MODS) is the most common cause for death in intensive care units. The recognition of this syndrome in the last 30 yr may be due to advances in early resuscitation unmasking these delayed sequelae in those that would have died previously. Multiple organ dysfunction occurs after shock of varied etiologies and may be the result of unbridled systemic inflammation. As yet, therapy directed to prevent or improve MODS has not dramatically altered outcomes.

Conclusion: Multiple organ dysfunction may serve as useful measure of disease severity for risk adjustment and outcome marker for quality of care and therapy provided. Anesthesiologists treating shock patients will note the subsequent development of MODS in the critical care unit and may be required to provide anesthetic support to these patients.

Objectif : *Passer en revue la documentation sur le syndrome de défaillance multiviscérale en regard : 1) des systèmes de mesure clinique; 2) des mécanismes moléculaires et 3) des indications thérapeutiques fondées sur ces mécanismes.*

Méthode : *On a consulté les bases de données de Medline, Cochrane et Best Evidence (1996 à 2000), les actes de conférences, les bibliographies d'articles de revues afin de trouver des articles pertinents. Les mots-clés ont été multiple organ failure, multiple system organ dysfunction, sepsis, septic shock, shock, systemic inflammatory response syndrome. L'évolution, en prospective, est la mort ou le renversement physiologique de la défaillance organique.*

Résultats : *Le syndrome de défaillance/déficience multiviscérale (SDMV) est la cause la plus fréquente de mort des malades à l'unité des soins intensifs. La reconnaissance de ce syndrome au cours des 30 dernières années tient sans doute aux progrès réalisés en réanimation précoce qui ont permis de dévoiler des séquelles à retardement chez ceux qui seraient morts auparavant. La défaillance multiviscérale survient après un choc de causes diverses et peut être le résultat d'une foudroyante inflammation généralisée. À ce jour, le traitement visant à prévenir ou à réduire la manifestation du SDMV n'en a pas beaucoup modifié l'évolution.*

Conclusion : *La défaillance multiviscérale peut servir de mesure utile de la sévérité d'une atteinte au moment de juger des risques et de marqueur de l'évolution en vue des soins de qualité et d'une thérapie à administrer. Les anesthésiologistes qui traitent des malades en choc devront noter l'évolution du SDMV à l'unité des soins intensifs, car ils pourraient être appelés à y fournir un soutien anesthésique.*

MULTIPLE organ dysfunction syndrome/failure (MODS) is the unwanted outcome of successful shock resuscitation. Shock is defined as inadequate organ perfusion even after adequate fluid resuscitation often presenting as persistent hypotension or need for vasoactive drugs to augment blood pressure. Only those patients not immediately dying from hemorrhage or infection are alive long enough to demon-

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Accepted for publication January 16, 2001.

strate MODS. The first case reports of MODS are only 25 yr old .[1–3] As a syndrome, MODS is defined as altered organ function in the setting of sepsis, septic shock, or systemic inflammatory response syndrome. The affected organ systems involved are: respiratory, cardiovascular, renal, hepatic, gastrointestinal, hematological, endocrine, and central nervous system. The goal of this review is a discussion of MODS with respect to 1) clinical measurement systems; 2) molecular mechanisms; and 3) therapy based upon molecular mechanisms. At present, insufficient trials exist to warrant a systematic review with graded recommendations upon the treatment of MODS. Consequently, this is a narrative review. This review should act as an update for clinical anesthesiologists on the possible patient outcomes after their resuscitative care. We anticipate that anesthesiologists may in the future administer mediator targeted anti-inflammatory therapy which may become as routine as perioperative antibiotics in patients with MODS. As yet, specific anesthetic considerations for MODS (other than those considerations for each isolated organ) do not exist. The specific effects of anesthetics on the inflammatory response (over and above the effects of the original disease process, stress, or surgery) have been recently reviewed[4] and will not be summarized here. Rather than a comprehensive listing of biological compounds involved in inflammation, this review focuses upon biological concepts and their current clinical implications.

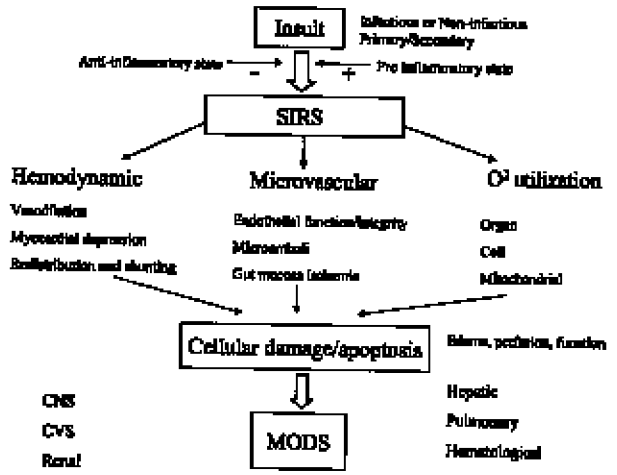

FIGURE 1 Illustrates the common physiological characteristics of multiple system organ failure and the variety of end organs/systems affected. Note that the changes induced are irrespective of the original etiology (i.e., infectious/non infectious). Individual patients vary to the extent of MODS depending on the balance of the specific injury with their individual response.

Clinical measurement systems

A consensus conference by the American College of Chest Physicians and the Society of Critical Care Medicine in 1992 proposed that the acronym MODS be adopted and defined MODS as the presence of altered organ function in a severely ill patient so that homeostasis cannot be maintained without intervention.[5] A variety of more specific definitions are used to classify organs as dysfunctional using easily obtained laboratory or physiological markers[1] (see Table I). A variety of mechanisms can generate MODS (mechanical tissue injury, microbial invasion, endotoxin release, ischemia-necrosis, ischemia-reperfusion).[6]

MODS scoring systems can be classified using general physiological critical care scores i.e., Acute Physiological and Chronic Health Evaluation;

TABLE I Parameters and scores used in assessing organ dysfunction

Parameter	*SOFA*[9]	*Score*	*MODS*[10]	*Score*	*LODS*[11]	*Score*
Respiratory	PaO_2/FiO_2 and ventilation	0 to 4	PaO_2/FiO_2	0 to 4	PaO_2/FiO_2, ventilation and CPAP	0–3 0–3
Coagulation	platelet number cell number	0 to 4	platelet number	0 to 4	platelet, white blood	
Hepatic	bilirubin	0 to 4	bilirubin	0 to 4	bilirubin, prothrombin time	0–1
Cardiovascular	blood pressure and vasopressor use	0 to 4	heart rate central venous pressure, blood pressure	0 to 4	heart rate and blood pressure	0–5
Central nervous system	Glascow Coma Scale	0 to 4	Glascow Coma Scale	0 to 4	Glascow Coma Scale	0–5
Renal	Creatinine urine output	0 to 4	Creatinine urine output	0 to 4	Creatinine urea urine output	0–5
Aggregate score	Add worst daily scores	0 to 24	Add worst daily scores	0 to 24	Add worst daily scores	0–22

(APACHE), Simplified Acquired Physiological Score (SAPS), Mortality Probability Model (MPM)[7] or specific organ score to describe dysfunction/failure (i.e., Multiple organ dysfunction score; MODS), Sepsis-related Organ Failure Assessment (SOFA), Logistic Organ Dysfunction System (LODS). The specific organ dysfunction scores classify organs as failed (i.e., yes or no)[8] or dysfunctional using an ordinal scale (i.e., graded score).[9–11] The aggregate score quantitates severity in any one organ and the overall severity of organ dysfunction. The aggregate score can then be interpreted as a likelihood of predicted mortality based upon the observed mortality in those study patients used to construct the original scoring system. Thus for the MODS score, an increase of one unit is scaled to reflect a change of mortality from 5% to 6%. As well, some organ dysfunction (cardiac, central nervous system) may have greater prognostic significance[12] and will provide more prognostic insight. Ideally, scoring systems should be simple, demonstrate good inter and intra observer reliability, be generalizable over time and in different intensive care units, and be independent of therapy provided.[7] In setting an overall prevalence, it has been estimated that up to one half of the mortality in intensive care units are attributable to MODS.[13–14] Because organ failure is not homogeneously defined and scoring systems not standardized, the incidence of MODS, the specific cost for supportive care, and the attributable mortality for a patient under your care is not well defined.[15] There exists no rationale to favour one scoring system or another. As well, the scoring systems do not tell the clinician when specific organ dysfunction is reversible or irreversible. Practically, a simple count or organs affected and the duration of the dysfunction will stratify mortality within broad ranges between 60% to 98% depending on age with dysfunction in three or more organs for at least a week.[16]

Although scoring systems have been traditionally used as a disease severity classification tool, they have value as measurements of clinical outcome during the process of care.[17] The advantage of using MODS as an outcome is that it may be a less biased measurement of the original injury and subsequent care provided. In North America, withdrawal of therapy is common.[18] Death due to withdrawal of therapy may have important social and ethical determinants that overlay the biological determinants of death. Differences in outcomes may also be measured in those patients not dying and related to resource consumption. Table II outlines potential uses of MODS scores.

TABLE II Outlines potential uses of multiple organ dysfunction syndrome scores

Baseline severity assessment score	Admission severity of organ failure
Score at any one time	Evolution over time of organ failure
Aggregate score over time	Cumulative severity of organ failure
Change in score	Organ failure attributable change
Combine score with mortality	Mortality adjusted severity of organ failure
Score aggregated by institution	Quality of care performance marker

Molecular mechanisms

In this section, we will review past and current theories about the causes of MODS. The reader should be sensitized to the fact that past discarded or less popular theories were adopted and formed the basis of accepted clinical care. Thus prior to basing therapy upon any new etiological theory, more clinical evidence that is now available is required.

Initially, the etiology of MODS was thought to be uncontrolled infection. The treatment of sepsis or septic shock with antibiotics and source of infection control was considered the major therapeutic aim.[19] Infection as the sole etiology is not in accord with the varied causes of MODS[20] such as pancreatitis, burns, major surgery, ischemia/reperfusion, and trauma. As well, in many patients an infectious agent is not isolated.[21] The impetus for considering a unifying hypothesis for MODS is reinforced by the similarity in the noted organ disturbances (see Figure 1) and systemic physiological changes (hemodynamic, microvascular, and oxygen utilization).

The unifying infectious etiology identified the gut as a potential source of bacteria (host for 10^8 aerobes and 10^{11} anaerobes in the colon) or at least circulating products of bacteria. Decreased gut perfusion and subsequent damage to the mucosal and immunological gut barriers may allow the translocation of endogenous bacteria or their products into the systemic circulation. This "second hit" augments the initial injury.[22] More recently the intestinal mucosa is considered to be another source of inflammatory mediators activated by hypoperfused mucosa.[23] Measurement of intramucosal pH (tonometry) can stratify mortality risk[24] but attempts to augment gut perfusion are not considered to be useful therapy in altering MODS outcomes in septic patients.[25,26] Gut sterilization in the prevention of ventilatory acquired pneumonia is an extension of the concept of an endogenous gut bacterial reservoir. However, for ventilatory acquired pneumonia, the route of infection is considered to be oral/integument rather than systemic as in MODS.[27]

The widespread use of invasive cardiac monitoring reveals the association between indices of perfusion (cardiac output, systemic vascular resistance) and oxy-

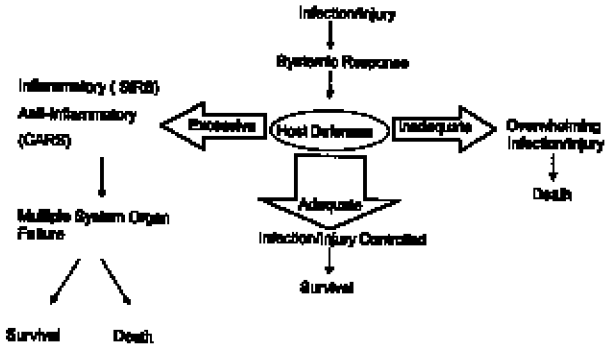

FIGURE 2 Illustrates the balance between insufficient inflammatory response leading to death and excessive (anti-inflammatory or inflammatory) leading to MODS. Survival without MODS requires a balanced host response which is an additional consideration in understanding the effect of disease insult.

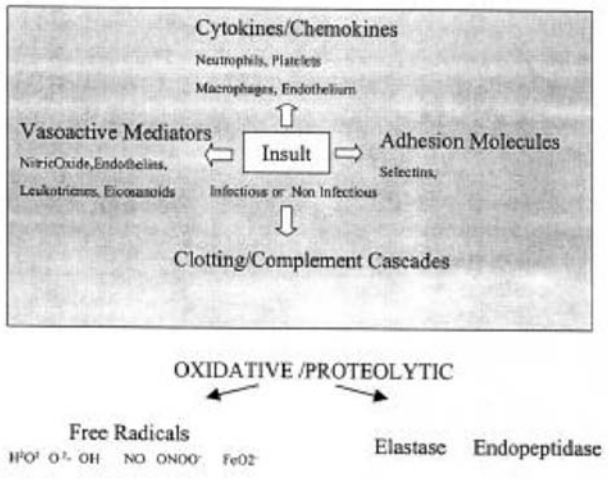

FIGURE 3 Illustrates the variety of mediators and inflammatory products that are active in propagating the inflammatory response. Neutrophils activated by tissue injury both recruit other neutrophils (chemokines), bind to endothelial cells (adhesion molecules), and produce cytokines to enhance the production of free radicals and proteolytic enzymes. This sustained inflammatory state must be balanced by expression of anti-inflammatory cytokines and programmed cell death (apoptosis).[58] Both timing of expression and complexity of inflammatory products underline the difficulty in therapeutic intervention.[42]

gen consumption in patients with MODS.[28] Survivors have higher cardiac index, lower systemic vascular resistance, and higher oxygen consumption than non-survivors.[29] Critical values are a cardiac index greater than 4.5 $L \cdot min^{-1} \cdot m^2$, oxygen delivery index greater than 600 $ml \cdot min^{-1} \cdot m^2$, and oxygen consumption greater than 170 $ml \cdot min^{-1} \cdot m^2$.[30] Although many studies have demonstrated that survival is associated with attaining threshold critical values, attempts to enhance the hyperdynamic response with pharmacological agents (dobutamine, dopexamine) have not shown a consistent response in more than 18 randomized control trials.[31] The dependency of oxygen consumption upon delivered oxygen may be an artifact of measurement.[32]

Another consideration for oxygen is the balance between tissue damaging oxidizing agents and their neutralization with anti-oxidants. Reactive oxygen species are involved in the formation of reactive nitrogenous and ferric species and direct cellular destruction, and act as secondary messengers in the inflammatory cascade.[33] The balance between reactive oxygen species/reactive nitrogenous species may be important in determining the progression of organ dysfunction.[34–36] A significant proportion of the increase in total oxygen consumption may be enhanced use by phagocytic cells.[37]

Finally, inflammation has become the most current etiological explanation of MODS. Inflammation is the activation of circulating cells (leukocytes), the endothelium, the liver, and multiple mediator networks that are normally held in balance by corresponding anti-inflammatory mediators. Chemotactic agents attract, adhesion molecules focus, and cytotoxic agents assist these cells in driving the process. MODS (see Figure 2) occurs when either the host's inflammatory or anti-inflammatory response to injury (or both) are excessive; death may occur if the host response to injury is either excessive or insufficient.[38] In broad terms, following a noxious insult there is an initial response mediated by liver, neutrophils, macrophages and the endothelium. Hepatic inflammatory proteins such as C reactive protein are opsonins of degraded proteins and nucleic acids derived from injured cells which would be potentially metabolized to more toxic substances.[39] The macrophage response includes the release of a variety inflammatory mediators (e.g., Tumour Necrosis Factor [TNF], Interleukin-1, Interleukin-6); these mediators then upregulate receptors on neutrophils (e.g., L –Selectin) and endothelial cells (e.g., P-Selectin, E-Selectin, Intercellular Adhesion Molecule-1, Vascular Cell Adhesion Molecule-1 Cellular) and stimulate transmigration. Adhesion molecules can be considered as aids to the retention of neutrophils as these large cells are transiently retained in the microvasculature by purely mechanical factors.[40] With transmigration other effector molecules (reactive free radical species, endopeptidases) are released that cause

organ damage and further recruit activated neutrophils to the site of injury.[41]

Cytokines are important inflammatory mediators with the following actions: 1) directing a T lymphocyte response; 2) inducing enzyme production in distant sites (e.g., endothelium: nitric oxide, liver: C reactive protein); and 3) altering cell surface adhesion molecules. Cytokines can be broadly classified as: 1) growth factors (e.g., Transforming Growth Factor ß); 2) leukocyte chemotactic chemokines (e.g., Interleukin-8); 3) modulators of lymphocyte function (e.g., Interleukin-4); and 4) modulators of inflammatory response (e.g., Interleukin-6 as a pro-inflammatory mediator and Interleukin-10 as a anti-inflammatory mediator). A large body of work has demonstrated that the clinical manifestations of sepsis arise through the activation of a complex cascade of host-derived mediator molecules.[42] Indiscriminate injury from these mediators may be the underlying mechanism to MODS.[43] The possible mechanisms of injury are: 1) excessive production of free radicals; 2) induction of elastase or endopeptidases; and 3) elevation of circulation soluble peptides that activate programmed cell death (apoptosis). However opposing this etiological concept is that the serum concentration of these pleiotropopic mediators do not always directly correlate with mortality.[44] For example, an alternate potential mechanism for ischemia and reperfusion injury may be small vessel obstruction by microthombi.[45]

The schema shown in Figure 3 is not all-inclusive, but outlines various aspects of the inflammatory response in which the down-regulation of mediators might be of benefit given their association with MODS and death.[46] The therapeutic challenge in attempting to modulate these pathways is that the number of mediators are numerous, their expression varies over the time of the illness, and their measurement using serum assays or biological assays may not be reflective of *in vivo* activity.[42] As well, the modulating effects of overall health status[47] and genetic pleomorphism may significantly confound outcomes. For example there is differential organ expression of endothelial adhesion molecules in response to pro-inflammatory cytokine signalling with such organs as the lung.[48] The production of hepatic inflammatory proteins such as fibrinogen is genetically modulated.[49] From an epidemiological perspective, postoperative septic patients that are high TNF producers have higher mortality and MODS than low TNF producers.[50] Knowledge of the individual inflammatory reaction to noxious stimuli may allow tailored therapy. Gene therapy using recombinant technology could potentially enhance an under expressed anti- or pro-inflammatory state. As well, targeting DNA or mRNA could block overproduction of specific proteins.[51]

Therapeutic directions based upon molecular mecha - nisms

The use of anti-inflammatory agents for the symptomatic relief of infection dates back to the use of ASA to reduce fever.[52] One of the early randomized controlled clinical trials conducted to evaluate the effect of an anti-inflammatory agent on the severity and incidence of sepsis in a high-risk population[53] concluded that methylprednisilone was associated with a poorer outcome and increased mortality rates when compared with placebo. Many other anti-inflammatory agents, ranging from *iv* ibuprofen[54] to an inhibitor of the pro-inflammatory cytokine TNF[55] have since been evaluated for the treatment of septic shock, but none have proved to be successful therapeutic interventions to date. When MODS is established, extensive medical support is required until the excessive inflammatory response dampens. These supportive therapies may include mechanical ventilation (for acute lung injury), *iv* pressors or fluids (for cardiac failure), hemodialysis (for acute renal failure), total parenteral nutrition (for acute gut injury) or sedation (for acute brain dysfunction). It is hoped that early intervention with selective anti-inflammatory therapy or with a combination of the appropriate agents at different times (according to the severity of MODS) will reduce inflammation, preserve organ function, and result in an increase in survival rates and a decrease in the utilization of hospital resources.

Our knowledge of the complex interactions that occur during an inflammatory response to infection is still lacking. Issues still to be addressed include how to achieve the appropriate balance between an inadequate response and an excessive one (both can lead to death!). For example, should the inflammatory response associated with hemorrhagic shock or gram-negative bacteremia be down-regulated to the same extent? In addition, how should patients who are diagnosed with MODS at different times in the course of their illness be treated? Anti-inflammatory therapy may be similar to other time-sensitive treatments (e.g., thrombolysis for acute myocardial infarction and stroke), where only a finite window of time exists in which a specific treatment will therapeutic.

The theoretical intervention points for MODS therapy directed at inflammation are: 1) cell adhesion retardation; 2) inflammatory mediator reduction (translation/transcription inhibition); 3) neutralizing (polyclonal or monoclonal) antibodies directed at cytokine/ vasoactive / coagulation / complement mediators; 4) cytokine/ vasoactive / complement / coagulation mediator receptor inhibitors; 5) anti-inflammatory protein induction (preconditioning, substrates, products, or genes); and 6) anti-oxidants and anti-proteases.[51]

Cloned proteins and monoclonal antibodies are among the new therapeutic agents being developed that may regulate specific steps of the inflammatory response. Bedside tests to rapidly measure specific elements of the inflammatory cascade (e.g., Interleukin-6) are also under development. Tumour Necrosis Factor is detectable within 30 min, Interleukin-1 within three hours and Interleukin-6 within six hours.[56] A recent meta-analysis suggests polyclonal but not monoclonal immunoglobulin decreases mortality in sepsis.[57] The first demonstration of a monoclonal antibody in sepsis decreasing MODS has just been announced (Press release American Thoracic Society Meeting Toronto May 2000). Thus it may become possible to adjust anti-inflammatory therapy in response to specific biochemical changes in the cascade.[58,59] The ultimate extension of this approach would see patients with MODS receiving moment-to-moment titration of specific anti-inflammatory agents, with the type and amount of medication administered based on continuous bedside measurements of inflammatory mediators. Outcomes may relate to specific organ dysfunction rather than overall global mortality.

Acknowledgements

We would to acknowledge the staff at the Royal University Hospital, Saskatoon and University Hospital, Edmonton for the thoughtful questioning which prompted this review.

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