Is MOF an outcome parameter or a transient, adaptive state in critical illness?

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Purpose of review
The term 'multiorgan failure' (MOF) carries the negative connotation of major homeostatic breakdown and severe malfunction. However, this traditional paradigm may not be necessarily accurate. This review will investigate the rationale for no longer considering MOF to be simply a 'failed' pathophysiological state.
Recent findings
Multiorgan failure is characterized by a hypometabolic, immunodepressed state with clinical and biochemical evidence of decreased functioning of the body's organ systems. Notwithstanding these findings, evidence for cell death is scarce and organ recovery is frequently the rule in surviving patients without pre-existing organ disease. Decreased mitochondrial activity appears to play a key role in the processes underlying MOF, both as a victim and a player. Reduced ATP production will compromise normal metabolic functioning. To protect itself from dying, the cell may adapt by decreasing its metabolic rate, and this is clinically manifest as organ dysfunction. Mitochondrial modulation may thus represent an important therapeutic target.
Summary
The concept of MOF could be revisited as a transient state of metabolic shutdown analogous to hibernation. Avoiding the detrimental effects of inappropriate and counter-adaptive iatrogenic interventions is an important cornerstone of therapeutic management.

Keywords
mitochondria, mortality, multiorgan failure, outcome

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Introduction

Following on from its first description in the early 1970s [1], multiorgan failure (MOF) has been defined as 'a progressive dysfunction of two or more organ systems following an acute threat to systemic homeostasis' [2]. Alas, a myriad of overlapping definitions have been proposed [3], thereby complicating comparison between studies and perhaps adding confusion rather than clarity.

Multiorgan failure represents a significant challenge, not only medically and economically, but ethically as well. Clinical management currently focuses upon the support of failed organs until they spontaneously recover, rather than any particular 'cure'. This, however, generates huge costs from prolonged hospital stay [4] and poses a significant long-term economic burden from ongoing morbidity. Importantly, we now recognize that both mortality and morbidity often result from the complications of iatrogenic intervention (e.g. ventilator-induced lung injury), rather than a direct consequence of the disease process itself. We also are faced with the ethical/moral dilemma of premature withdrawal of life-prolonging support in a potential survivor versus unnecessarily prolonging life (and hope) in a patient irrefutably destined to die. It is thus crucial to identify whether MOF is a simple, nonadaptive, irrecoverable pathological process or an adaptation to severe, prolonged inflammatory stress that is transient and carries the potential for full recovery. The aim of this article is to attempt to better understand the pathophysiological entity of MOF, and how this impacts upon clinical management and outcome.

Is multiorgan failure a major killer?

Multiorgan failure is associated with a high mortality, whatever the initial insult. Apart from sepsis [5], MOF is responsible for more than 60% of deaths occurring 1 week after severe trauma [6], 50% of deaths from pancreatitis [7] and 30% of deaths in patients with burn injury [8] and in ICU patients admitted postcardiac arrest [9]. The higher the number of failed organs, the higher the mortality [10,11]. Even in survivors, the longer-term quality of life is inversely related to the severity of

MOF [12]. Within the temporal and spatial balance of MOF, failed organs do not carry the same individual weight. Renal, central nervous system [13], haematological and hepatic impairment [10,14] are associated with worse outcomes than respiratory or haemodynamic dysfunction. Typically, the neurological system is often the first to become dysfunctional, followed by abnormalities of the respiratory, cardiovascular, renal and coagulation systems, with hepatic dysfunction coming a belated last [10]. Reasons for this temporal sequence, for their relative weight in determining poor outcome, and for the variable combinations of organ dysfunction presenting in different individuals, remain uncertain.

Survivors and nonsurvivors can be distinguished early

Many specific scoring systems have been developed to quantitate MOF severity including Logistic Organ Dysfunction System (LODS) [15], Multiple Organ Dysfunction Score (MODS) [16] and Sequential Organ Function Assessment (SOFA) [17]. However, these are only valuable on a large population scale and cannot be used to predict the survival of an individual patient. Thus, patients with a predicted 50% chance of dying also have a 50% chance of survival, but into which category they will eventually fall is initially uncertain, at least from these scores. The trajectory of the score is more predictive as critically ill patients showing signs of improvement generally fare better than less sick patients who progressively deteriorate [10]. To provide a more individual tailored prediction, the integrative PIRO – 'prediction, outcome, response, organ dysfunction' – scoring system has been created and recently successfully tested (albeit retrospectively) in a large cohort [18•].

An exciting development that is likely to be routine clinical practice within the next decade is the use of biomarkers to accurately and promptly identify infection, sepsis, organ injury and outcome. For individual prognostication, a host of physiological and biological biomarkers [19,20] have been individually shown to be strongly predictive of subsequent outcome, even when taken on the first day of ICU admission. Often these have higher discriminating ability compared to clinical scores such as APACHE or SAPS. These biomarkers range from markers of inflammation including general inflammatory markers such as procalcitonin and cytokines, to markers of haemostasis activation (protein C, thrombomodulin), organ dysfunction (e.g. troponin, cystatin C), endocrine alterations (oestrogen, leptin, cortisol, and so on), the macrocirculation or microcirculation (e.g. oxygen consumption, lactate) and a range of miscellaneous markers including heart rate variability, plasma DNA and nucleated red blood cells.

An interesting corollary of these findings is that multiple markers across a wide range of disparate organ systems are perturbed yet are still able to predicate outcome. The implication is that outcome appears to be determined at an early stage of a patient's critical illness, even at the time of presentation to an emergency department [21•,22].

Why do people with multiorgan failure die?

The above biomarker studies suggest the magnitude of the systemic inflammatory response to infection (or other insult) is a major determinant of subsequent outcome. This is likely modulated through an increased 'hit' on downstream body organ systems. There does appear to be an individual genetic predisposition to mount an exaggerated response. Indeed, there are numerous studies on a host of polymorphisms and haplotypes showing either increased susceptibility to sepsis and organ failure, or an increased propensity to die, depending on the genetic variation being studied. Although the data in this area are inconsistent and sometimes directly contradictory, this does remain conceptually attractive [23•].

Multiorgan failure carries a fascinating paradox whereby the histology of failed organs taken from nonsurvivors looks remarkably normal, particularly if the organs were healthy preinsult. For example, 'acute tubular necrosis' is a misnomer in the vast majority of septic patients developing acute renal failure. Whereas many patients have significant morbidity that may compromise recovery, for example, end-stage chronic emphysematous respiratory failure, the pathological process is usually functional rather than attributable to gross structural damage. The capacity for organs to recover is thus likely to be present in most patients but, for whatever reason, the necessary recovery pathways are not switched on. The potential contribution of concurrent drug therapy in delaying recovery will be addressed later in this article.

Importantly, with advances in intensive care, nowadays only a minority of patients die in the acute phase from intractable hypotension and/or hypoxaemia. Most die after days to weeks of organ support. Death usually follows a treatment limitation/withdrawal decision based on either failure to recover or deterioration following a new insult, for example, a new bout of sepsis or a cerebrovascular event. Damas *et al.* [24•] demonstrated a strong correlation between severity of critical illness and the risk of secondary infection. Whereas this may relate to an increased length of stay and more invasive instrumentation in the sicker patient population, a state of profound immune suppression following the initial inflammatory burst will also predispose to new bouts of sepsis. So whereas immunoparalysis serves to blunt excessive deleterious inflammation, it can also be viewed

negatively in terms of susceptibility to new septic complications.

This generates an interesting and hitherto relatively unexplored question. The focus of most novel therapies for sepsis has been based on modulating the acute inflammatory process. Clearly, if given at the appropriate time this can reduce the degree of the proinflammatory response and, potentially, secondarily attenuate the magnitude of the subsequent anti-inflammatory response. However, as stated earlier, most patients now die 'late' as a consequence of a failure to recover adequate organ function; little effort has been directed towards pharmaceutically induced acceleration of recovery processes. Whether clinicians show equivalent levels of patience in young versus old patients, previously fit versus chronically ill, socially supported versus socially disadvantaged is a moot point. Practices vary across Europe [25]; however, if the rate of organ recovery is delayed, the patient is likely to be at higher risk of potentially premature withdrawal.

Considering multiorgan failure as an adaptive phenomenon

Although the body initially generates an inflammatory response in its attempts to fight invading pathogens or in response to trauma, this can only continue for a relatively limited period as it is injurious in its own right. A parallel can be drawn to prolonged physical or psychological stress when decompensation eventually occurs as a consequence of elevated catecholamines and other endogenous stressors. To illustrate this point, elevated endogenous catecholamines are directly associated with immunosuppression [26,27], thrombogenicity [28], myocardial damage and dysfunction [29], among others [30,31].

Therefore, it is imperative that a plausible hypothesis be developed that can reconcile all the disparate data described for critical illness into a feasible mechanistic process to which a logical therapeutic intervention strategy can be applied. This theory should be able to explain organ dysfunction despite a lack of major cell death or damage [32,33], preserved or even increased blood flow [34], a decrease in oxygen consumption with increasing severity [35] and the presence of adequate tissue oxygen in resuscitated sepsis [36], and the ability to recover relatively rapidly when the inflammatory situationresolves [37].

We have proposed that MOF could be considered as an adaptive state occurring in response to prolonged, severe stress [38]. This adaptation takes the form of a metabolic shutdown that may be primed directly or via a progressive decrease in energy supply from direct mitochondrial damage or inhibition, decreased hormonal stimulation (e.g. by thyroid hormone), or reduced mitochondrial protein turnover (biogenesis). As more than 90% of total body oxygen consumption is used by mitochondria, and mainly directed toward production of ATP through oxidative phosphorylation, any significant abnormality will necessarily compromise metabolic processes. Mitochondrial dysfunction has been widely reported by ourselves and others in both animal models [39,40] and humans [41,42]. This evidence includes morphological abnormalities, decreased transcript levels of genes encoding mitochondrial respiratory complex proteins, reductions in intermediate (NADH) and end-product (ATP) substrates, lower respiratory chain enzyme complex activities and decreased respiration.

A useful analogy may be made between this MOF hypothesis and similar processes occurring throughout biology including hibernation (cold), estivation (hot, arid conditions), prolonged deep water submersion (turtles) and dormancy (bacteria). Whereas survival is not guaranteed, this 'metabolic shutdown' strategy may enhance the chances of success. Clearly, many patients still succumb, so it should only be viewed as partially successful. Nevertheless, it should be considered in the context of our evolutionary response to severe infection or injury in which modern medicine has played no part. This is manifest by impressive survival figures reported from casualties of historical battles despite a lack of the paraphernalia we currently consider so crucial, such as fluid, blood, antibiotics, ventilatory and renal support.

Three confounders need to be considered in the context of current medical management. First, we cannot dismiss the potentially injurious effects of our treatments. If, as described above, endogenous catecholamines are injurious, does not the same apply to exogenously administered catecholamines [30,31]? Likewise, if recovery from MOF depends on restoration of functioning mitochondria, what is the possible impact of bacteriostatic antibiotics that are potent inhibitors of mitochondrial biogenesis [43,44]? Second, as described earlier, premature withdrawal of life-prolonging support may not enable sufficient time for the organs to potentially recover. Third, how can this hibernation strategy be reconciled with the ability to prognosticate early in patients developing critical illness? A possible answer may lie in the fact the old age can be considered teleologically unphysiological. Longevity has approximately doubled in the last 150 years, predominantly related to improvements in hygiene and food supply. There is a 13-fold risk of sepsis in the over-65 age bracket [45]; apart from having an increased risk of significant comorbidity, the elderly also generate a markedly different immune response [46]. Physiological responses to injury are thus dramatically altered.

Therapeutic implications

If MOF is indeed an adaptive attempt to cope with prolonged stress, then it behoves the clinician to work alongside these processes rather than counter to them. For example, giving an anti-inflammatory agent when the patient's immune status has already reached a negative inflammatory balance is unlikely to offer much benefit but may simply expose the patient to harm from side-effects such as new bouts of infection. The major advances in patient outcomes achieved over the last few years are virtually all related to reduced iatrogenic harm. Erickson *et al.* [47] recently reported a near 50% reduction in mortality from acute respiratory distress syndrome (ARDS) in a 10-year period (1996–2005) despite a lack of any new specific treatment. Lower tidal volumes, more appropriate attention to fluid balance, more regulated use of blood (including the introduction of leukodepleted blood) to reduce transfusion-related acute lung injury, reduced use of sedation and other such restrictive measures have all contributed to these better outcomes. Many other current, as yet relatively unchallenged, practices should also be placed under greater scrutiny. Attention is turning to excessive use of catecholamines and sedatives but what about covert effects of proton pump inhibitors, nutrition practices, antibiotic duration and so on [48]? All the above have immunomodulatory properties, at least *in vitro* if not *in vivo*, that may affect the response to sepsis.

We also need to better understand mechanisms such that modulation of one pathway does not negatively impact upon others. A classic example was the use of nonspecific nitric oxide synthase inhibition for elevating blood pressure in septic shock. Whereas this objective was obtained, a multicentre study was stopped prematurely because of increased harm [49]. Whether this was related to inhibition of known effects of nitric oxide such as cytotoxicity, inhibition of platelet aggregation, and stimulation of mitochondrial biogenesis, or to as yet unrecognized effects, is uncertain.

Furthermore, the pharmacokinetics of novel as well as established agents should be determined in a critically ill population rather than normal volunteers. Alterations in renal or liver function may affect metabolism and/or excretion, use of concurrent medication may interact with the drug, and protein binding will be vastly different, whereas production of mediators generated by the septic process, notably nitric oxide, may nitrosate proteins and affect the drug's activity. This is well demonstrated by recent enthusiasm for the use of statins as an adjunctive anti-inflammatory therapy for sepsis. Some caution, however, needs to be applied by virtue of the study by Kruger *et al.* [50•] who measured plasma levels of atorvastatin following a single dose given to different patient populations. Levels rose 8–10-fold in septic patients compared to healthy volunteers, and this doubled in the presence of a cytochrome P450-inhibiting drug such as erythromycin and fluconazole [50•]. Whether high doses are beneficial or increase the risk of complications such as myopathy need to be carefully evaluated.

Returning to the metabolic shutdown hypothesis, many current and putative therapies can affect metabolism. Clinical interventions that augment oxygen delivery and reverse tissue hypoxia may prove advantageous if given early [51], but ineffective or even harmful if delayed until MOF has become established [52,53]. Likewise, treatments that protect mitochondrial function, such as mitochondrially directed antioxidants, may be a useful adjunct in the early stages of sepsis [54•].

Strategies directly affecting metabolism may be considered though, again, timing and extent are likely to be crucial. A reduction in metabolism may benefit patients in whom ATP levels are subnormal (i.e. when the supply–demand balance is not being met) as this is associated with a poor outcome [42]. This could include therapeutic hypothermia [55,56], although clinical data are currently insufficient to extend its use outside survivors of cardiac arrest [57]. Another potential alternative is administration of hydrogen sulphide that, apart from its anti-inflammatory actions, will also inhibit cytochrome oxidase of the electron transport chain [58]. However, the minimal animal data obtained to date have not shown any benefit. Likewise, hormonal modulation of metabolism in MOF has proved disappointing with harmful results demonstrated with both growth hormone [59] and thyroxine administration [60]. There are also metabolic and anti-inflammatory effects related to insulin administration; whether doses are sufficient in the tight glycaemic control regimen to modulate metabolism is uncertain; if so, this may be one reason to explain the differences between the Van den Berghe and NICE-SUGAR results (mean insulin dose in the protocol groups being 71 and 50 units per day, respectively) [61,62]. Finally, treatments that stimulate mitochondrial biogenesis may be potentially beneficial as this may be linked to organ recovery after sepsis [63]; these include various hormones including oestrogen [64] and nitric oxide [65]. On the contrary, inhibiting biogenesis, for example, with prolonged courses of bacteriostatic antibiotics may impede recovery.

Conclusion

Converging data indicate that MOF, hitherto perceived as harmful, could be potentially viewed in a different, more positive light. It may represent an attempt by the body to adapt to prolonged stress by inducing a metabolic shutdown in a state akin to hibernation. Such organs have

the capability of making a full recovery, but the associated immune depression increases susceptibility to secondary infection. If this hypothesis is confirmed, it opens a new avenue for therapeutic intervention.

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