Metabolic Integrity of Specific Organ Systems

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This short review will address the potential uses for quantitative analyses of organ function in the critically ill patient. Multiple system failure is common in the critical-care unit, and the ability to measure reserves of organ function may enable earlier detection and treatment of this problem and provide a more accurate prognosis for such patients.

The critically ill patient, admitted to an intensive-care unit (ICU) for monitoring and supportive care, is at greatest risk when multiple organ systems are compromised by disease.1 The aim of this review is to briefly define the syndrome of multiple systems organ failure (MSOF); discuss its incidence/prevalence, demography, and etiology/pathogenesis in the ICU population; and then review and discuss recent approaches to quantitative assessment of function in four of the major organ systems affected. For expanded discussion, readers should consult recent notable reviews of this topic (1, 2). Here I will attempt to show how one might link decreased functional reserves in liver, kidney, lung, and brain to severity of MSOF and use quantitative assessments to predict outcome.

Survival analysis has been based on the following scheme: Survival depends on the system(s) involved by the primary disease process, the severity of dysfunction engendered, and the extent of encroachment on function in vital system(s)—in part determined by age and state of chronic health—all of which are balanced by the treatment prescribed: its appropriateness, effectiveness, and timeliness. Encroachment by a disease process into the functional reserves of vital system(s) can best be appreciated by quantitative assessment of system functions. Accuracy of prognosis at any given point in the natural history of a disease in an individual patient therefore depends on the accuracy of assessment of functional reserves, and on the ability of the therapy to prevent or reverse further encroachment by the disease on these reserves. Thus far, quantitative assessment of function has not been widely adopted in severity scoring systems, in part because of the complexity of such tests. However, the use of scoring systems such as the APACHE II system of Knaus et al. (3) or the Mortality Prediction Model developed by Teres et al. (4) indicates the possible utility of such approaches in the future.

Multiple Systems Organ Failure

Definition: Multiple systems organ failure is said to be present when more than one of the system dysfunctions detected by test values exceeding the threshold values shown in Table 1 are found (1). MSOF is a syndrome akin to the adult respiratory distress syndrome, i.e., in part a

<table>
<thead>
<tr>
<th>Table 1. Acute Organ System Dysfunction: Threshold Values</th>
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<tbody>
<tr>
<td><strong>Respiratory failure (presence of one or more):</strong></td>
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<tr>
<td>Respiratory frequency &lt;5, &gt;49 (&gt;two years of age)</td>
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<tr>
<td>Alveolar–arterial difference in O2 &lt;350 mmHg or Paco2/FIO2 &lt;200 (without congenital cardiac lesion)</td>
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<tr>
<td>Requires mechanical ventilatory support &gt;24 h</td>
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<tr>
<td>PacO2 &gt;50 mmHg and pH &lt;7.25</td>
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<tr>
<td><strong>Circulatory failure (presence of one or more):</strong></td>
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<tr>
<td>Heart rate &lt;50/min or episode of ventricular tachycardia/fibrillation</td>
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<tr>
<td>Mean systemic arterial pressure &lt;50 mmHg and (or) systolic systemic arterial pressure &lt;80 mmHg</td>
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<tr>
<td>Cardiac index &lt;2 L/min per sq. meter of body surface (acute onset) and (or) pH &lt;7.25, Paco2 &lt;35 without respiratory failure</td>
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<td><strong>Renal failure (presence of one or more):</strong></td>
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<tr>
<td>Urine volume 9.3 mL/kg body weight per hour for 8 h</td>
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<tr>
<td>Serum creatinine &gt;266 μmol/L</td>
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<tr>
<td>Urea nitrogen &gt;1.00 g/L or urea &gt;0.60 g/L</td>
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<tr>
<td>Hepatic failure (presence of both):</td>
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<tr>
<td>Bilirubin &gt;60 mg/L or a twofold increase in alkaline phosphatase in serum and</td>
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<tr>
<td>Prothrombin time &gt;4 s over upper limit of normal range or a twofold increase in aspartate aminotransferase in serum</td>
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<tr>
<td><strong>Hematologic failure (presence of one or more):</strong></td>
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<tr>
<td>Leukocytes &lt;1500/μL or &gt;40 000/μL</td>
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<tr>
<td>Platelets &lt;20 000/μL or evidence of ongoing disseminated intravascular coagulation</td>
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<tr>
<td><strong>Neurologic failure</strong></td>
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<tr>
<td>Glasgow Coma Scale &lt;6 (without sedation)</td>
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<td>Uncontrolled sepsis (presence of one or more):</td>
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<tr>
<td>Positive blood culture despite antibiotic therapy</td>
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<tr>
<td>Fever &gt;39.5 °C (rectal temp) for &gt;24 h or spikes on three successive days</td>
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</table>

product of our ability to prolong with supportive care the process of dying from critical illness, so that we are observing parts of the natural history of illness previously obscured by earlier death. Both these syndromes appear to be mediated and amplified by a malignant generalized inflammatory response, which may be initiated by a discrete focus of sepsis or necrosis. Although sepsis is a frequent component of the syndrome, documented and continuing infection is not an absolute requirement for initiation or perpetuation of the process (5–7).

Etiology/pathogenesis: The onset of MSOF, heralded by metabolic dysfunction, appears to be directly determined by mediators of inflammation, released as a result of the overexpression of immune mechanisms that originally evolved to protect the host (5). Many of the features of septic shock and of MSOF can be reproduced by administering the recombinant cytokines interleukin 1 and tumor necrosis factor or cachectin, singly or in combination (6). The process currently postulated to cause MSOF (Figure 1)

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1 Nonstandard abbreviations: ICU, intensive-care unit; MSOF, multiple systems organ failure; BSP, Bromsulphalein (sulfobromophthalain); and HBF, hepatic blood flow.

2 Received March 28, 1990; accepted May 1, 1990.

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primarily involves hematomatological elements produced by the marrow, the immune and reticular-endothelial systems, or the liver. The major target organs for early onset of secondary effects from these mediators appear to be the liver, the kidney, and the lung. Circulatory failure and cerebral dysfunction, stupor, or coma appear as later manifestations (7). Schemes such as the one shown (Figure 1) can be used to suggest possible therapeutic approaches; therefore, early detection of loss of metabolic integrity in the target organs for diagnosis and monitoring of disease progress and for estimation of prognosis is highly desirable.

Incidence/prevalence and demography: Using the threshold values for the static function tests shown in Table 1, or very similar values, several published series have examined the outcome from MSOF (8, 9). The incidence of MSOF in these studies varied with the patient population, but was about 15% of general ICU admissions in one large multi-institutional study in the U.S. (3). The other notable finding of these studies was the manner in which mortality increased as the number of involved dysfunctional systems increased and the surprising relative uniformity of these relationships.

Monitoring Metabolic Integrity

Because organ dysfunction is so closely tied to outcome for the critically ill patient, quantification of organ functions and early detection of threshold levels of dysfunction may be the most useful procedures for guiding therapy. One could define ideal test characteristics for these purposes by considering three sets of features: the general features—the test measures a variable continuously, and the variable is related quantitatively to organ structure/}

Fig. 1. Hypothetical mechanisms leading to multiple systems organ failure
PGs, prostaglandins; PAF, platelet-activating factor; PMNs, polymorphonuclear neutrophilic leukocytes; RE, reticuloendothelial; LPS, lipopolysaccharides; 2nd, secondary; TNF, tumor necrosis factor

function; the test discriminates well, i.e., shows small variability of measurement interindividually or can be easily normalized; and the test is noninvasive, cheap, robust, and reliable. The diagnostic features—the test shows adequate sensitivity, specificity, and positive predictive value for the chosen population sample, and the test has utility because diagnosis is needed for decision-making. The prognostic features—the test shows strong outcome validity in univariate logistic regression and in combination, e.g., with multivariate logistic regression and receiver-operating characteristic curve analyses; the test has strong construct and face validity, and experts agree intuitively; the test has good interrater reliability and can be simply combined to provide risk analysis with easy data retrieval (10).

In the following sections I will review approaches to dynamic assessment of organ function for the liver, kidney, and lung, which are in current use, and consider some approaches to monitoring the metabolic milieu for cerebral function, which are under development. Because these approaches have not been routinely applied in large series of patients with MSOF, one can only speculate on their utility in this setting. Perhaps some of these techniques may find a place in early detection and management of MSOF in the future.

Liver

Structure/Function

The liver accounts for 2.5% of body weight in adult humans and receives 25% of the cardiac output—80% via portal vein and 20% via the hepatic artery. It contains about 250 × 10^6 hepatocytes, which compose 70% of its mass, and 100 × 10^6 sinusoidal cells (endothelium, Kupffer, and fat storage cells), which compose 10% of its mass, the remaining 20% being blood elements. The largest gland in the body, the liver is a compound gland with many varied and diverse functions. The functions of each cellular type and of the subcellular elements of each cell type are to a considerable degree specialized. In addition, hepatocytes display a degree of heterogeneity of function. Thus liver-function tests may detect abnormalities of function that do not directly reflect the metabolic integrity of the hepatocyte or of the other cellular elements of the organ. Combination of static tests or use of quantitative tests may to some extent resolve this dilemma.

The acinar structure of the liver, as described by Rappaport in 1954, supports the use of a unifying concept of hepatic function, i.e., the regulation of solute concentrations in the blood delivered to the terminal hepatic venule through the sinusoids and in the bile from the secreting surface of the hepatocyte pairs bordering each canaliculus. Liver-function testing can thus be based on examination of the processes that determine the flux and concentrations of solutes added to and removed from the blood and excreted in the bile. Heterogeneity of function between hepatocytes located in zones 1 and 3 of the acinus can then be compared with regional patterns of damage induced by toxins, and the mechanisms perhaps better explained.

Quantitative Function Testing

Analogies can be drawn between each of the four organ systems reviewed here to help determine what aspects of the organ should be considered for measurement to arrive at a suitable overall assessment of metabolic integrity. Mass and structure must be assessed, blood flow and
composition must be assessable, and finally specific organ functions need to be assessed to determine their integrity. The degree of organ damage induced by disease and the induced dysfunction by altered neurohumoral control or by altered blood flow can then be separated, and more rational approaches to therapy perhaps designed and tailored to that particular patient's needs at that time.

**Mass**: Advances over the last 10 years in imaging techniques leave computerized tomography, described in 1981 (11), as the currently most useful and reliable method for noninvasively determining hepatic mass. Estimation of hepatic mass may be important to permit the fullest interpretation of quantitative function tests, in attempting to discriminate between loss of function from decreased hepatocyte numbers or sick hepatocytes. Future advances in imaging techniques may allow estimation of the gross composition of the organ for fat content (e.g.) or even the ratio of a molecular species and total content, as with use of 31P in nuclear magnetic resonance techniques (11). At present, these techniques remain experimental.

**Blood flow**: Qualitative impressions of patterns of blood flow in the portal vein and the hepatic artery are again best obtained by using imaging techniques, with ultrasound studies being preeminent in this regard. However, for quantitative estimation of blood flow in the human liver, one must rely on older indicator infusion techniques, because the use of directly implanted electromagnetic flow probes, the "gold standard," is contraindicated (12).

The use of indicator infusion for measuring hepatic blood flow depends on the indicator's having a very high intrinsic clearance rate by the liver. If the intrinsic efficiency of the elimination of the indicator from blood by the liver is reduced, then inaccurate values will be obtained for derived hepatic blood flow. Substances with high intrinsic clearance rates include propranolol, lidocaine, indocyanine green, Bromsulphalein (BSP, sodium sulfbromophthalain), and colloidal particles of 131I-labeled albumin coated onto heat-treated microspheres. These substances show flow-limited clearance and therefore obey essentially first-order kinetics when used in modeling.

Bradley used BSP and a continuous infusion when he originally described the technique in 1945. His model assumes that the indicator is removed only by the liver and not by other tissues, requires blood to be sampled from one hepatic vein directly on the assumption that the sample represents mixed hepatic venous blood, assumes that the clearance of indicator by liver is not spontaneously variable, and finally assumes that the delivered concentrations of indicator are the same in the portal venous and hepatic arterial blood. Separate contributions from these two sources cannot be estimated by this method. However, BSP has several features that violate the assumptions of the method. Some (5–7%) BSP is cleared by nonhepatic tissues; also BSP undergoes enterohepatic recirculation after conjugation with glucuronide and excretion in bile. Indocyanine green has neither of these drawbacks and its use has therefore supplanted BSP in this test. By Fick's principle, hepatic blood flow (HBF) can be calculated as follows:

\[
HBF = \frac{\text{BSP (removed}=\text{infused)}}{C_{\text{in}} - C_{\text{out}}}
\]  

where BSP infused is the infusion rate, \(C_{\text{in}}\) is the concentration of indicator in systemic blood, and \(C_{\text{out}}\) is the indicator concentration in hepatic venous blood.

One can use a single-injection method for this sort of estimation, in which case the estimation of blood flow is based on Lewis's analysis, as follows:

\[
HBF = \frac{k \cdot \text{blood vol.}}{\text{hepatic extraction ratio}}
\]  

where \(k\) is the fractional clearance of the indicator, or 0.693/half-life of the indicator in the peripheral venous blood; blood volume is obtained by extrapolating the initial measured concentration to zero time and dividing that value into the exact quantity of indicator injected; and the hepatic extraction ratio is the difference between indicator concentrations in peripheral blood and in the hepatic vein, divided by that in peripheral blood: [peripheral blood – hepatic vein]/peripheral blood.

For logistic reasons, no method for routine use in measuring hepatic blood flow can be based on sampling hepatic venous blood; thus systemic clearance of test compounds such as indocyanine green and also galactose at low concentration has been used. One extrapolates the clearance obtained to organ blood flow by assuming an extraction ratio value, and substituting this in equation 2. Obviously, any extrahepatic removal of indicator in these studies will lead to overestimation of HBF.

**Specific function**: To assess specific function of the liver, investigators have primarily used capacity- rather than flow-limited processes. Galactose elimination capacity, antipyrene clearance, the aminopyrine and caffeine breath or saliva tests, lidocaine clearance and metabolism, and tolerance to ammonia, tyrosine, and phenylalanine have all been advocated as dynamic tests of hepatic function.

Galactose elimination capacity is estimated by saturating the hepatic uptake mechanism, i.e., converting the flow-limited, first-order kinetics seen at plasma concentrations of galactose <0.3 g/L (1.7 mmol/L) to capacity-limited, zero-order kinetics seen at plasma concentrations >0.4 g/L (2.2 mmol/L). This is achieved by giving the subject an intravenous bolus of galactose, 0.5 g/kg body weight, and monitoring the decline in galactose concentration in plasma for 1–2 h. The kinetics of galactose removal from blood were first studied by Tygstrup and others in 1954, but more recently it has been used to estimate both hepatic blood flow and hepatocyte function (13). Giving galactose by continuous infusion to maintain a concentration in blood of 0.1 g/L (0.6 mmol/L) appears to provide adequate estimations of flow. For measuring hepatocyte function, one must remember that extrahepatic galactose removal also occurs: at zero liver function, galactose removal rates of 1.5–3.0 mg/min per kilogram of body weight may well be seen. Galactokinase is probably the rate-limiting enzyme for hepatocyte uptake in most circumstances, but enzymes active later in the path may be affected by disease and drugs, notably ethanol, and their impairment may then become rate-limiting for galactose elimination.

Xenobiotic clearance tests depend on the function of microsomal enzyme systems, with cytochrome P450-dependent processes predominating. These are capacity-limited processes and the xenobiotics chosen have low extraction and low protein binding in plasma (14). Administration of 14C- or 13C-labeled aminopyrine followed by the measurement of radiolabeled exhaled CO2 is the most frequently used of these tests at present. The appearance of labeled
CO\textsubscript{2} in the exhaled breath correlates directly with the decline in the concentrations of aminopyrine in plasma. The appearance of lidocaine metabolites in plasma has been recently introduced as a quantitative liver-function test in patients admitted for liver transplant and may be of equal value. The enzymes that depend on cytochrome P450 as a cofactor are inducible by exposure to ethanol, cigarette smoke, and various drugs and xenobiotics.

The synthetic functions of liver have been indirectly followed by estimating static values of serum albumin and other more rapidly metabolized protein products from the liver, such as prealbumin, retinol-binding protein, and clotting factors measured by performing prothrombin time estimation or other clotting studies. These tests, in combination with other features of liver disease, form the basis for Pugh's modification of the Child–Turcotte's classification of liver failure and have also been used to form prognoses for various liver diseases (15–17). More-direct estimations of the liver's synthetic function may be provided by investigating its handling of amino acids and NH\textsubscript{4}\textsuperscript{+} ions. Altered patterns of amino acids in plasma are well known in liver disease, but the sequence of possible events leading to alterations of these patterns does not necessarily mean that these changes directly correlate with loss of the metabolic integrity of hepatocytes. Instead, these patterns of change may reflect secondary changes in muscle metabolism under the influence of altered hormonal control induced by the liver dysfunction. However, the clearance of amino acids from plasma and the changes in NH\textsubscript{4}\textsuperscript{+} concentration after a 40-g protein meal have been advocated as means of assessing these pathways. Acute changes in amino acid concentrations in plasma of experimental animals reveal that acute liver damage induced by thioacetamide is characterized by greater increases of aromatic than of branched-chain amino acids, consistent with the ability of muscle to utilize the branched-chain acids for energy metabolism, and by a marked decrease in the concentration of arginine, an unchanged concentration of citrulline, and a very marked increase in ornithine in plasma, changes consistent with a decrease in urea synthesis (18). These changes have been noted by others. The complexity of this area calls for much additional work.

**Kidney and Lung**

**Structure/Function**

Techniques for the quantitative assessment of the excretory capacity of the kidney and of the gas-exchanging ability of the lungs have been more widely applied in clinical studies than have the quantitative tests of liver function. The advent of liver transplantation has altered the direction of liver assessment to some extent, so that these quantitative tests of liver capacities are becoming more widely considered. Structure–function correlations in disease states of the kidney and lung have been described for a large number of disease processes.

**Quantitative Function Testing**

Although the classic tests of function of these organ systems establish a baseline from which variations will indicate grossly altered metabolic integrity of the organ (19), recent studies of detailed mechanisms in the kidney responsible for renal tubular function and pressure-related natriuresis (20) and studies of the pulmonary endothelial capacity for metabolic interactions with blood (21) suggest the possibility of earlier detection of altered cellular integrity. The utility of this earlier detection in the critically ill patient remains to be established, and currently the clinician still relies on the classic tests.

**Kidney**

*Mass*: Plain abdominal films fairly reliably allow assessment of kidney size and are useful to indicate any shrinkage as a result of chronic disease. Computerized tomograms are also used for this purpose.

*Blood flow*: Renal plasma flow can be assessed from indicator perfusion and removal studies analogous to those used for hepatic flow. Experimentally p-aminohippuric acid is used for total flow, inulin for glomerular filtration rate assessment, and other indicators for tubular function. Clinically we rely heavily on creatinine clearance estimations.

*Specific function*: Urinalysis and the estimation of specific gravity, urine osmolality, urine-to-plasma osmolality ratios, urine sodium, fractional excretion of sodium, and the urine/plasma urea and creatinine ratios are useful indices of prerenal vs renal causes for decreased urine volume. Clinically these tests serve as sufficient warning of impending dysfunction for therapy to be applied in most instances, or for inciting removal of toxins responsible for nephropathy. Estimating creatinine clearance (Ccr) from analyses of plasma and collected urine can be circumvented by using the following formula, proposed by Cockroft and Gault (Nephron 1976;16:31): Ccr = (140 – age, years) \cdot weight, kg \cdot (0.85 if female)/7.2 \cdot Pcr, where Pcr is plasma creatinine in mg/L.

**Lung**

*Mass*: Plain chest roentgenography and gas-dilution estimations of lung volume are used to assess lung size. Chest expansion and the rate of gas flow are assessed by using spirometry.

*Blood flow*: Blood flow through the lungs is assessed from the invasive measurement of cardiac output and thermodilution or indicator dilution, or by noninvasive echo-Doppler tests.

*Specific function*: Blood gas analysis underlies most of the specific testing of lung function. The metabolic function of the lung has not been approached clinically from a quantitative viewpoint at this time and tests of these functions remain experimental.

**Brain**

**Structure/Function**

The integrity of the very complex mechanisms involved in cerebral function is still best established clinically in conscious subjects by physical examination and assessment of functional state. As coma is approached, through mechanisms of either toxic cerebral depression or through increases in intracranial pressure, the higher brain functions are lost. The Glasgow Coma Scale is an attempt to quantify the onset of coma, but is a relatively crude means of doing so. Also it provides no really secure estimation of the integrity of brain structures, because deep metabolic coma, which is completely reversible with treatment of the metabolic abnormality, cannot be distinguished from structural or ischemic causes for coma.

The unconscious patient must be assessed by other means than clinical examination. In this situation one needs to be assured of neuronal integrity, which can be done by assessing electrical brain activity (through an electroencephalogram or evoked potentials) and (or) by
monitoring cerebral blood flow and oxygenation.

Quantitative Function Testing

Again, and by analogy with the other systems we are reviewing, one first wishes to be assured of the structural integrity of the organ mass, e.g., through use of imaging techniques. After next evaluating blood flow and oxygenation, finally one approaches specific function. Regarding blood flow, direct estimates and indirect estimates may involve the use of tests to assess the state of high-energy bonds in the tissue cells (31P by NMR), blood flow, oxygen saturation, and cytochrome a,a3 ratios by near infrared spectroscopy [Somanetics™ (22)], or measures of cerebral perfusion pressure. In the past, measurement of intracranial pressure and estimates of cortical flow by use of 133Xe have been necessary to assess blood flow in the brain. Near-infrared spectroscopy and 31P NMR are the tests of the future; near-infrared spectroscopy, involving a technique similar to pulse oximetry, may be the methodology most likely to develop into widespread use because of the noninvasive nature of the estimation and the amount of information potentially acquired. Further validation of this technique is needed.

Conclusion

If we define multiple systems dysfunction on the basis of the rather crude indices of organ failure shown in Table 1, correlations have been shown between the number of systems failing and outcome. The opportunity to better define system reserves by using quantitative tests of organ function may provide more nearly accurate estimations of outcome through use of the approach utilized by Knaus et al. (3), who developed a severity score based on combined assessments of dysfunction in organ systems. Quantitative assessment of organ function may also offer potentially earlier detection of a system's loss of function. When this correlates with the onset of a disease state in that organ, there may be an opportunity for earlier application of specific or non specific therapy for prophylaxis or treatment.

Because MSOF may originate with liver dysfunction, and certainly involves endothelial cells in various tissues, observation of quantitative function in the early phases of the syndrome in samples from a wide range of patients may be of great interest.

References