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Cardiac Support and Multiorgan Dysfunction Syndrome

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1. Introduction

Approximately 5 million Americans suffer from heart failure (HF), the burden of which will grow exponentially over the next 50 years. HF currently results in 3.5 million hospitalizations and 20% of all hospital admissions among individuals >65 years of age. Surgical interventions for HF include cardiac repair (coronary artery bypass grafting, valve repair or replacement), cardiac support (mechanical circulatory support devices) and cardiac replacement (heart transplantation). These modern interventions of cardiac surgery and critical care medicine dramatically improved outcomes. They are offered to patients with increasingly high-risk clinical profiles and a higher likelihood of complications.

The development of vital-organ support therapies (respirator, dialysis, transfusion, etc) in the intensive care units (ICUs) increased the survival of critically ill patients. However, despite these organ-saving therapies, up to 15% of these patients have an unfavourable perioperative course. Frequently, more than one organ system becomes dysfunctional, leading to progressive multiorgan dysfunction (MOD) (**Lietz et al., 2007**). The hallmark of MOD is the development of progressive physiologic dysfunction in two or more organ systems after an acute threat to systemic homeostasis. MOD is the leading cause of morbidity and mortality in the ICUs and after mechanical circulatory support device (MCSD) implantation (**Deng et al., 2005**).

2. Epidemiology

According to a multiyear survey conducted in surgical ICU patients, more than 50% patients develop some degree of MOD during their ICU stay (**Barie et al., 2000**) and currently MOD is the major cause of mortality in surgical ICUs (**Barie et al., 1996**). The recent data from the ICUs around the country show that the severity of MOD correlates significantly with the mortality, the observed incidence of dysfunction of 1, 2, 3, and ≥4 organ systems was 73.6%, 20.7%, 4.7%, and 1% respectively with corresponding mortality rates of 21.2%, 44.3%, 64.5%, and 76.2% (**Angus et al., 2001**).

3. Evolution of mechanical cardiac support

Early descriptions of mechanical support of the human circulation are documented at least back to the early 19th century. The experimental application of mechanical support in animal models was reported in the 1930's. Major interest in mechanical support of the human circulation was generated by the advent of open–heart surgery in the 1950's (**Kirklin et al., 2006**). Basic pump design has remained same over this development period, but power delivery and control has moved from large bedside consoles to wearable components, enabling patient autonomy in an outpatient setting (**Schmid et al., 1999**). This has brought about substantial improvements in patient quality of life (**Dew et al., 1999**) and a reduction in resource use (**Gelijns 1997**). Smaller, inexpensive and less obtrusive blood pumps are undergoing development and some are being tested in clinical trials (**Katsuma 1998, Wieselthaler 2000, Goldstein 2005**). However, while the potential benefits are encouraging, these designs still have to prove their durability, reliability and physiological suitability for chronic applications.

Following the initiative by the US National Heart Lung and Blood Institute in the 1970's to develop long-term artificial heart devices (The Artificial Heart Program 1991), two electrically powered pumps emerged from this initiative and have recently completed trials sponsored by the Food and Drug Administration for evaluating safety and efficacy and have received certification for commercial application in 1998, the HeartMate® 1205 VE (ThermoCardio Systems, Woburn, MA) (**Poirier 1999**), the Novacor® N100 PC (World Heart Corporation, Oakland, CA) (**Portner 1989, Robbins 1999**), and the ABIOCOR total artificial heart (Abiomed, Inc., Danvers, MA), the last under the Humanitarian Device Exemption (HDE) program of the FDA in September 2005. Recently with the introduction of continuous flow devices e.g. HeartMate-II (Thoratec, Inc.) there is increased use of mechanical support in patients with advanced HF.

4. INTERMACS based definition of different forms of organ dysfunction

4.1 Neurological Dysfunction

The INTERMACS database (**Kirklin et al., 2008**) defines neurological dysfunction as any new, temporary or permanent, focal or global neurological deficit ascertained by a standard neurological examination (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note).

4.2 Coagulation dysfunction

According to the INTERMACS database coagulation dysfunction is divided into bleeding and hemolysis. Bleeding as any episode of internal or external bleeding that results in death, the need for re-operation or hospitalization; or necessity of transfusion of red blood cells that is equal or greater than 4 packed units within any 24 hour period during the first 7 days post implant or than 2 packed units within any 24 hour period after 7 days following implant. In patients that are less than 50 kg it is considered 20 cc/kg or 10 cc/kg respectively.

Hemolysis as a plasma free-hemoglobin value that is greater than 40 mg/dl, in association with clinical signs associated with hemolysis (e.g., anaemia, low hematocrit, hyperbilirubinemia) occurring after the first 72 hours post-implant. Hemolysis related to documented non-device-related causes (e.g. transfusion or drug) is excluded from this definition.

4.3 Renal dysfunction

The INTERMACS database distinguishes between two situations of renal dysfunction: Acute renal dysfunction is defined as abnormal kidney function requiring dialysis including hemofiltration) in patients who did not require this procedure prior to implant, or a rise in serum creatinine of greater than 3 times baselines or greater than 5 mg/dl (in children, creatinine greater than 3 times upper limit of normal for age) sustained for over 48 hours. Chronic renal dysfunction is defined as an increase in serum creatinine of 2 mg/dl or greater above baseline, or requirement for hemodialysis sustained for at least 90 days.

4.4 Pulmonary dysfunction

Respiratory dysfunction is defined as impairment of respiratory function requiring reintubation, tracheostomy or (for patients older than age 5 years) the inability to discontinue ventilatory support within 6 days (144hours) post-VAD implant. This excludes intubation for re-operation or temporary intubation for diagnostic or therapeutic procedures.

4.5 Liver dysfunction

The INTERMACS database defines hepatic dysfunction as any increase in any two of the following hepatic laboratory values (total bilirubin, aspartate aminotransferase / AST and alanine aminotransferase/ALT) to a level greater than three times the upper limit of normal for the hospital, beyond 14 days post-implant (or if hepatic dysfunction is the primary cause of death).

5. Clinical scoring systems

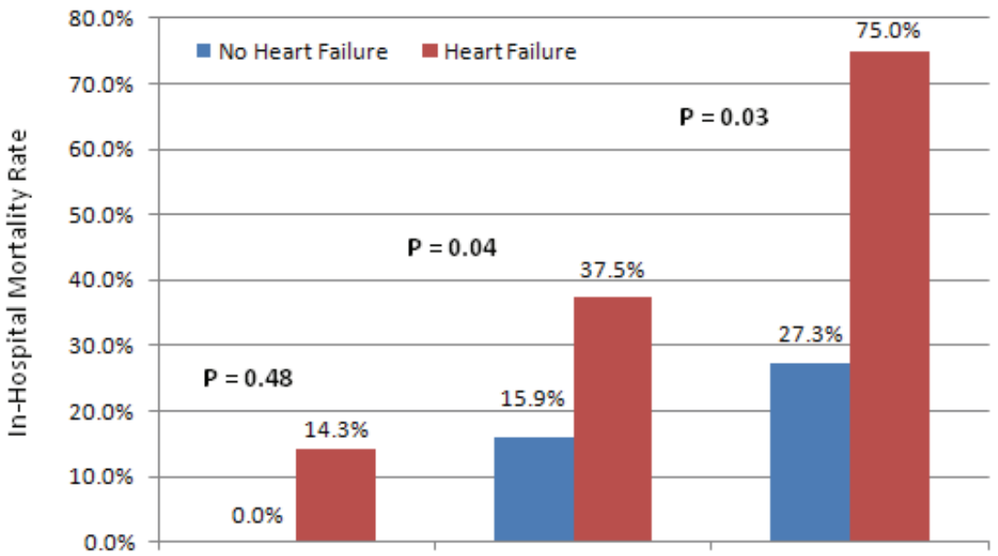
Prognostic scoring systems are integral to critical care practice. Composite outcome scales permit the quantification of complex clinical phenomena that cannot be adequately described by a single clinical or biochemical measure. Such scales are used for assessment of clinical status, changes in clinical status, evaluation of therapy, outcome prediction, and resource allocation. Currently, different clinical scoring systems are available to predict outcomes after trauma or injury including the APACHE II, III and IV scores (**Zimmerman et al., 2006**), ISS, MOD-score, EURO-score, and SOFA-score (**Marshall et al., 1995; Vincent et al., 1996; Vincent et al., 1998; Nashef et al., 1999; Minne et al., 2008**). These scoring systems are important in ICU-based research. They allow for MOD-phenotype definition and patient stratification based on objective evaluation of illness severity. While all of these scores have been validated and are in clinical use, they have shortcomings. The EURO-score solely uses pre- and intraoperative risk factors to assess postoperative risk. The APACHE scoring system uses day-1 post-ICU admission data for outcome prediction. In addition, while the APACHE-IV score was developed from APACHE-III to restore discrimination performance, the highest discrimination inaccuracy was seen in the decile of patients at highest risk for death (**Zimmerman et al., 2006**).

The SOFA-score, in contrast to APACHE and other ICU-outcome prediction models based on measurements at one individual time point, has the strength of modelling changes in the patient's status. The SOFA-score is a six-organ dysfunction/failure score measuring MOD daily. Each organ is graded from 0 (normal) to 4 (the most abnormal), providing a daily score between 0 and 24. Shortcomings of the SOFA-score, the best dynamic score currently

available, include 1) the treatment-dependent definition of the cardiovascular parameter (positive inotrope medication type and dose) which may reflect variation of practice and not of disease severity, and 2) absence of an immune system parameter.

6. Scoring systems and heart failure

In a pilot study designed to understand the utility of current clinical MOD-scoring systems, we hypothesized that a preoperative diagnosis of HF is associated with an increased risk of postoperative in-hospital mortality independent of the SOFA score. Thus, we analyzed 145 patients requiring a ≥7d postoperative ICU stay and obtained complete maximum postoperative SOFA-score data (5.2% of all 2768 CUMC cardiac surgery cases from January 01 2007 to June 30 2009). Patients were separated into Group-HF (pre-existing HF diagnosis) and Group-NoHF (no known diagnosis of HF). Patients were stratified by a maximum SOFA score of <10, 10-14 and ≥15. In-hospital mortality rates were compared among groups using the Chi-square test. Group-HF (n=66, 46%) had a higher in-hospital mortality rate than Group-NoHF (n=79, 54%) (35% vs. 13 %, p=0.003). Although mortality rates, when the SOFA was <10 and 10-14, were not different in Group-HF and Group-NoHF, patients with SOFA≥15 in Group-HF had a very high mortality rate (71%) (**Figure 1**). Thus, both the SOFA score and pre-existing HF appear to be important risk factors for in-hospital mortality in cardiac surgery patients; in-hospital mortality is exceptionally high in patients with both risk factors. Novel tools are needed to improve our understanding of the interaction between HF and SOFA score, improve outcome prediction and improve management in this emerging cohort.



TN	2	7		44	40		11	20	
DN	0	1		7	15		3	15	

Fig. 1.

An ideal descriptor should be simple, routinely and reproducibly measured, and readily evaluable in heterogeneous groups of critically ill patients. It should be derived from independent clinical and/or laboratory data, rather than through subjective clinical evaluation, and should measure physiologic dysfunction directly, rather than the therapeutic intervention employed to support organ function. The descriptor should provide a comprehensive reflection of the physiologic function in the system of interest, and should be specific for the function of that system. Consistent with a definition of MOD as an acute and potentially reversible process, the ideal descriptor should be capable of differentiating the sequelae of an acute homeostatic insult from the chronic effects of primary disease in the organ system of interest. Moreover, the ideal descriptor should be relatively unaffected by transient abnormalities associated with resuscitation or acute reversible complications of therapy, and should be maximally abnormal after resuscitation and well before the time of death. The quantitative value of the descriptor should be minimally affected by therapeutic intervention in the absence of objective functional improvement. Finally, the descriptor should be continuous, rather than dichotomous, and abnormal in one direction only (**Marshall et al., 1995**).

7. Leukocyte gene expression signatures

7.1 Leukocyte gene expression profiling after cardiac surgery

In a pilot project using a transcriptome-wide peripheral blood mononuclear cell (PBMCs) profiling approach we analyzed expression patterns before and after MCSD-implantation in 11 patients with an uncomplicated course (i.e. day -1, day1 and day 7 after surgery). Agilent-44K whole genome microarray analysis was performed on the PBMCs. Data was analyzed using Significance Analysis of Microarrays (SAM) and High-Throughput GoMiner in comparison to baseline. Day 1 profiles included differential expression of 821 genes (SAM, FDR<0.1, fold change >1.5), enriching >60 Gene Ontology (GO) categories. Grouping by component genes revealed GO-clusters including "IL-1 related" (primarily-up-regulated), "T-cell related" (primarily-down-regulated), and "apoptosis related" (up- and down-regulated genes). Day 7 profiles included GO-categories related to repair processes. In conclusion, transcriptome-wide expression profiling of PBMCs suggests a response pattern to MCSD-implantation with pro-inflammatory activation and simultaneous T-cell suppression (**Sinha et al., 2010**).

7.2 Leukocyte gene expression profiling of MOD

As a pilot study on differential leukocyte GEP in MOD, we analyzed the mixed peripheral blood leukocyte GEP in 9 patients after cardiac surgery in comparison to three age-matched healthy control persons. We enrolled 3 healthy controls and 9 consecutive HF patients who underwent MCSD implantation. MOD was defined using sequential organ failure assessment (SOFA) score. Patients were divided into low (≤4), intermediate (5-11), and high (≥12) SOFA-score groups. The blood samples were collected and processed for peripheral blood mononuclear cell separation. Total RNA was purified, amplified and hybridized on Illumina Whole Genome Expression Chips. The expression data was extracted and analyzed using GeneSpring GX 11.0.1. Biological interpretation of the differential signatures was performed using High-Throughput GoMiner. The mean age of the patients was 51±7 years. Using Kruskal-Wallis testing, 1438 unique transcripts were differentially expressed across groups (false discovery rate (FDR) ≤0.02, fold change≥1.5). Based on these genes,

hierarchical clustering using Pearson distance metrics separated the high-SOFA groups from all other groups. Gene Ontology analysis (FDR≤0.02) revealed enrichment of 80 categories including "immune response", "defence response", "lymphocyte activation", and "regulation of cell death". AHF patients undergoing MCSD surgery who develop postoperative MOD have unique leukocyte gene expression signatures. Comparing blood samples drawn with CPT and whole blood PAXgene tubes, we found a comparable differentiation using the PAX-samples (**Shahzad et al., 2010**).

7.3 Leukocyte gene network reverse engineering

In a feasibility study for the reverse engineering Aim 2.2, based on 285 microarrays (7370 genes) from 98 heart transplant patients enrolled in the "Cardiac Allograft Rejection Gene Expression" (CARGO) study (**Deng et al., 2006**), we used the information-theoretic, reverse-engineering algorithm called ARACNe (Algorithm for the Reconstruction of Accurate Cellular Networks) and chromatin Immunoprecipitation assay to reconstruct and validate a putative gene PBMC interaction network. We focused our analysis on transcription factor (TF) genes and developed a priority score to incorporate aspects of network dynamics and information from published literature to supervise gene discovery. ARACNe generated a cellular network and predicted interactions for each TF during rejection and quiescence. Genes that were ranked highest by priority score included those related to apoptosis, humoral and cellular immune response such as GABP, NFKB, FADD and CREB. We used the transcription factor CREB to validate our network. ARACNe predicted 29 putative first neighbour genes of CREB. Eleven of these (37%) were previously reported. Out of the 18 unknown predicted interactions, 14 primers were identified and 11 could be immunoprecipitated (78.6%). Overall, 75% (n = 22) inferred CREB targets were validated, a significantly higher fraction than randomly expected ($p<0.001$, Fisher's exact test). We concluded that our results confirm the accuracy of ARACNe to reconstruct the PBMC transcriptional network and show the utility of systems biological approaches to identify possible molecular targets and biomarkers (**Cadeiras et al., 2010**).

8. Future research

Circulating peripheral blood leukocyte populations monitor tissues and blood for agents that pose a danger to the organism (**Matzinger, 2007**). They sense the functional state of all organs in a coordinated way and provide diagnostic information. They constitute a "systemic" organ that can be easily monitored to assess the state of various tissues and the blood. Serial leukocyte GEP can characterize the systemic inflammatory response following intravenous endotoxin administration in healthy individuals (**Calvano et al., 2005**), in heart transplant rejection Deng 2006, and in MOD following trauma (**Laudanski et al., 2006**). Therefore, the information about gene activity in a patient's mixed peripheral leukocyte pool can be used to improve our understanding of organ dysfunction. In particular, knowing the pattern of leukocyte gene expression of a patient at the same time when the patient's organ function status is known can clarify the relationship between these two system levels and may provide a better scoring tool for evaluating MOD.

The integration of a validated leukocyte transcriptome classifier into a clinical MOD scoring system is a novel systems biology strategy that has the potential to improve the prediction, management and outcome of MOD. Developing an immune system GEP parameter needs

to proceed in well-defined succinct stages. Establishing a quantitative phenome-transcriptome relationship is an important step in developing a leukocyte GEP-classifier (**Shahzad et al., 2009**). Although this relationship is not necessarily of causal nature, it is critical to identify genes and/or pathways that relate to the biology of the MOD phenotype. The development and independent validation of a GEP-classifier in comparison to a quantifiable clinical phenotype is the critical step in the development of the new GEP parameter. The integration of this GEP-classifier into the clinical MOD-scoring system is an important step towards improving patient outcome and ICU resource use.

The goal is to investigate the interaction between peripheral blood leukocytes and the multi-organ dysfunction syndrome (MOD) in heart failure patients undergoing cardiac support surgery. Specifically, we plan to measure changes in leukocyte gene expression profiles (GEP) in patients developing this postoperative complication in comparison to matched patients who do not develop MOD. From this, we plan to develop and validate a leukocyte GEP test, integrate it into current clinical MOD-scoring systems and demonstrate improved patient outcome prediction. We hope that this will 1) lead to an improved understanding of the mechanisms leading to death in MOD-patients, 2) help identify those patients before cardiac surgery who have a higher probability of MOD, and, after cardiac surgery, to identify 3) those patients who are entering the subclinical phase of MOD, and 4) those patients who are in an advanced state of MOD with very little probability of recovery.

9. Importance & significance

In the United States, MOD develops during 15% of all ICU admissions, causes up to 80% of all ICU deaths, and results in ICU costs of >$100,000 per patient or ~$500,000 per survivor (**ACCP, 1992; Barie et al., 1996; Barie et al., 2000**).

Heart failure related MOD represents a significant healthcare resource challenge (**Ong et al., 2009**). A great amount of resources are spent in the last 6-month period of life of HF patients with a complicated course. The cost of Mechanical Circulatory Support Device therapy with a complicated course, in comparison to an uncomplicated course, is >$100,000 higher (**DiGiorgi 2005**). Overall, HF costs $20-56 billion per year. However, more resource consumption does not necessarily yield better outcomes (**Orszag, 2008**) although higher resource spending increases the likelihood of favourable outcomes (**Ong et al., 2009**). Therefore, the major challenge is to identify 1) before cardiac surgery, those patients who have a higher probability of MOD, 2) after cardiac surgery, those patients who are entering the subclinical phase of MOD, and 3) those patients who are in an advanced state of MOD with very little probability of recovery.

10. Conclusion

With the increased incidence of HF and advances in critical care medicine more patients are undergoing cardiac support surgeries with high-risk clinical profiles. This puts HF patients at increased risk of developing MOD, which is the leading cause of morbidity and mortality in the ICUs. Currently available clinical scoring systems are limited to accurately predict the risk of MOD. The integration of a validated leukocyte transcriptome classifier into a clinical MOD scoring system represents a novel systems biological strategy that has the potential to 1) improve the prediction, management and outcome of MOD and 2) optimize health resource utilization in the ICU.

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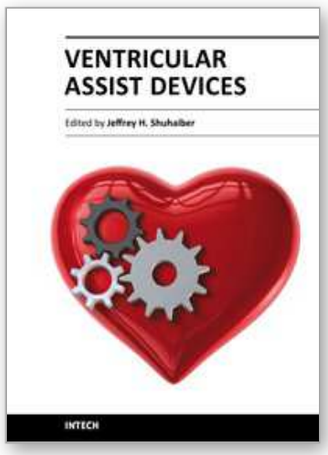
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Ventricular Assist Devices

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The assist devices will continue adding a large number of years of life to humans globally and empower the medical society to optimize heart failure therapy. While expensive and cumbersome task, the foundation provided in this book reflects a contemporary product of original research from a multitude of different experts in the field. We hope this cumulative international effort provides the necessary tools for both the novice as well as the active practitioner aiming to change the outcome of these complex patients.

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