Ceramides: A Class of Lipids with Links to Heart Disease

Introduction
Low-density lipoprotein (LDL) cholesterol is the primary measure of atherosclerotic risk and thus a therapeutic target in clinical practice. The focus on LDL cholesterol and its control by diet, lifestyle, and pharmaceuticals has contributed to a significant and sustained reduction in blood concentrations of total and LDL cholesterol among U.S. adults since 1988. Despite population-wide improvements in lipid levels, heart disease remains the number one cause of death both within the U.S. and globally. Consequently, there is an ongoing search for risk factors to help identify and treat patients prior to the development of symptomatic heart disease.

Traditional risk factors for atherosclerosis include elevated body mass index, hypertension, smoking, and increased blood cholesterol. Current guidelines endorse focusing on circulating cholesterol and non-specific inflammatory markers as biomarkers for atherosclerosis. However, the pathophysiology of atherosclerosis is a complex intersection of dyslipidemia, inflammation, endothelial dysfunction, and platelet activation. Recent data supports causal associations between each of these pathways and plasma ceramides (Figure 1).

Plasma Ceramides: A Multifaceted Risk Marker
“Ceramides are complex lipids that play a central role in cell membrane integrity, cellular stress response, inflammatory signaling, and apoptosis,” says Jeffrey W. Meeusen, PhD, Co-Director of Cardiovascular Laboratory Medicine in the Department of Laboratory Medicine and Pathology at Mayo Clinic in Rochester, Minnesota. Synthesis of ceramides

Figure 1. Atherosclerosis begins when lipoproteins infiltrate the vascular intima, drawing monocytes across the endothelium. Phagocytosis of lipoproteins by monocytes creates lipid-bloated foam cells, which release cytokines and effector molecules that promote myocyte migration while upregulating endothelial cell adhesion and platelet activation proteins and disrupting vasodilation mechanisms. Ceramides A) increase LDL infiltration and promote LDL aggregation; B) are upregulated in response to inflammatory cytokines; C) are enriched in atherosclerotic plaque; and D) increase platelet activation while disrupting endothelial function.
from saturated fats and sphingosine occurs in all tissues. During dyslipidemia and caloric excess, ceramides are synthesized de novo and accumulate in tissues not suited for fat storage (Figure 2).

Low-density lipoprotein (LDL), infamous as the carrier of “bad” cholesterol, also transports ceramides in the blood (Figure 1). Ceramides promote LDL infiltration into the vessel wall and enrich LDL 50-fold within arterial plaque. The inflammatory cytokines interferon-γ, tumor necrosis factor-α (TNFα), and interleukin-1β all stimulate ceramide synthesis. And, ceramides are implicated in platelet activation and endothelial dysfunction via uncoupling of nitric oxide signaling pathways.

In addition to the biochemical role in atherosclerosis progression, plasma concentrations of ceramides are elevated in several heart-disease-related conditions. Plasma ceramides are significantly elevated among patients with stage 3 hypertension. Plasma ceramide concentrations correlate with an increased New York Heart Association functional class in a study of 423 patients hospitalized for heart failure. Patients with type 2 diabetes mellitus have significantly elevated plasma ceramide concentrations. Furthermore, elevated ceramides correlate positively with insulin resistance.

Ceramides Predict Clinical Outcomes

Un targeted metabolomic analysis identified three plasma ceramides as significantly linked to cardiovascular mortality in a cohort with coronary artery stenosis confirmed by angiography. A total of 258 patients suffered a fatal myocardial infarct within three years. The ceramides linked with cardiovascular mortality were N-palmitoyl-sphingosine [Ceramide (16:0)], N-stearoyl-sphingosine [Ceramide (18:0)], and N nervonoyl-sphingosine [Ceramide (24:1)]. The association was independent of age, body-mass index, smoking status, statin use, triglycerides, LDL and total cholesterol. Additional predictive value was found when ceramides were normalized to N-lignoceroyl-sphingosine [Ceramide (24:0)], a highly abundant plasma ceramide not influenced by disease (Figure 2).

Independent studies performed at Mayo Clinic verified that targeted measurement of these ceramides could be performed with accuracy and precision suitable for clinical application. The clinical utility of these ceramides for predicting risk of cardiovascular disease was confirmed in a follow-up study of patients referred for coronary angiography. Cardiologists at Mayo Clinic have begun using plasma ceramides in clinic and are continuing to investigate additional applications.

Multiple published studies have repeatedly confirmed the strong predictive value of ceramides (Table 1). Risk conferred by plasma ceramides is independent of traditional risk factors including age, sex, body-mass index, smoking status, and blood cholesterol. Additionally, the predictive value remains significant after adjusting for other markers such as C-reactive protein (CRP), apolipoprotein B (ApoB), and lipoprotein associated phospholipase A2 (Lp-PLA2).

Interpreting Elevated Ceramides

New risk factors for heart disease are proposed regularly. When evaluating the potential of a new risk factor, several aspects must be considered. The first is whether the new risk marker provides new information independent of established risk factors. Plasma ceramides are able to stratify risk among patients even after adjustment for multiple traditional and contemporary risk factors.

A second consideration for new biomarkers is their practical application in the clinic. Three plasma ceramides and each of their ratios to a fourth ceramide are all independently linked to increased hazard ratios. Thus, there are a total of six results all predictive of cardiovascular disease. While this may be intriguing on an academic level, it allows for the potential of confusion regarding risk in clinical practice. This prompted development of a ceramide risk score.

“The ceramide risk score incorporates the values from all six ceramide results into a clearly defined risk category,”

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**Figure 2.** Ceramide synthesis is facilitated de novo from fatty acids or by rapid interconversion with sphingomyelin. Multiple different ceramide synthase (CerS) enzymes are known, each with a unique tissue distribution and fatty acid selectivity. Ceramides shown are measured for atherosclerotic cardiovascular disease risk assessment.
says Dr. Meeusen. One or two points are added to the score for each result above the median or the third quartile, respectively. Thus, the potential risk attributable to ceramides is summarized on a twelve-point scale. Applying the ceramide risk score to two large observational studies (>1,500 each) revealed that patients with a score of 10-12 had a four- to six-fold increase in the rate of events compared to patients with a score ≤ 2 points (Table 2).

Caveats Associated with Novel Testing
Some data suggest that ceramides can be elevated in response to inflammation. Therefore, it is conceivable that individuals with infections or other inflammatory diseases may have elevations for that reason which may or may not be indicative of unstable coronary artery disease. Thus, if the inflammatory state is transient, a repeat ceramide measure after resolution may be prudent. The link between inflammatory diseases and atherosclerosis is currently being investigated, and ceramides are no exception. We will update this recommendation when more data are available.

“'We have corrected our local data for a large number of other variables and biomarkers, and the increased risk conferred by ceramides is maintained,' says Dr. Meeusen. ‘There is more still to do and we will continue to add covariates and interrogate different populations. We are optimistic based on unpublished data being gathered that the independent predictive utility of ceramides will be maintained.”

<table>
<thead>
<tr>
<th>Study</th>
<th>Population / Study Design</th>
<th>Endpoint / Events / Follow-up</th>
<th>Baseline LDL-C Median (IQR)</th>
<th>Baseline Statin Therapy n (%)</th>
<th>Adjusted HR* Cer(16:0) Cer(18:0) Cer(24:1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LURIC</td>
<td>CAD / Case-control (n=445)</td>
<td>CV Mortality; (n=258) &lt;3 years</td>
<td>115 mg/dL (112 – 117)</td>
<td>227 (51%)</td>
<td>1.62 (1.28 – 2.06) 1.50 (1.18 – 1.90) 1.54 (1.20 – 2.00)</td>
</tr>
<tr>
<td>Athero-Remo</td>
<td>Elective angiography / Observational (n=581)</td>
<td>ACS admit or CV-death (n=56) &lt;1 year</td>
<td>105 mg/dL (82 – 137)</td>
<td>357 (62%)</td>
<td>1.56 (1.13 – 2.14) 1.54 (1.06 – 2.24) 1.84 (1.24 – 2.72)</td>
</tr>
<tr>
<td>Corogene</td>
<td>Elective Angiography / Case-control (n=160)</td>
<td>CV Mortality (n=80) &lt;2.5 years</td>
<td>72 mg/dL (55 – 92)</td>
<td>122 (76%)</td>
<td>4.49 (2.24 – 8.99) 2.95 (1.56 – 5.55) 2.98 (1.79 – 4.97)</td>
</tr>
<tr>
<td>BECAC</td>
<td>Elective angiography / Observational (n=1,587)</td>
<td>CV Mortality (n=81) &lt;5 years</td>
<td>116 mg/dL (89 - 147)</td>
<td>994 (62%)</td>
<td>1.52 (1.21 – 1.92) 1.29 (1.01 – 1.65) 1.31 (1.03 – 1.66)</td>
</tr>
<tr>
<td>SPUM-ACS ACS</td>
<td>Hospitalization / Observational (n=1,637)</td>
<td>CV Mortality (n=51) &lt;1 year</td>
<td>121 mg/dL (81 - 150)</td>
<td>446 (27%)</td>
<td>1.69 (1.39 – 2.06) 1.48 (1.24 – 1.76) 1.64 (1.32 – 2.03)</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>Elective angiography / Observational (n=504)</td>
<td>MACE; (n=61) &lt;5 years</td>
<td>121 mg/dL (100 – 147)</td>
<td>142 (28%)</td>
<td>1.44 (1.11 - 1.86) 1.65 (1.04 - 2.62) 1.79 (1.20 - 2.68)</td>
</tr>
</tbody>
</table>

Table 2. The ceramide risk score provides a readily interpretable guide for atherosclerotic cardiovascular disease risk by combining information from all measures into a 12-point scale. Individuals with increased ceramide risk score have 4 to 6-fold increased rates of events.

Ceramides are Modifiable
Finally, a biomarker is only useful in the clinic when it is able to guide effective interventions. Randomized clinical trials based on ceramide measures have not been reported. However, several reports have found that ceramide concentrations are significantly decreased by caloric restriction, gastric bypass, aerobic exercise and statin therapy. A significant decrease in plasma ceramides was observed among subjects taking simvastatin (alone or in combination with ezetimibe) and rosuvastatin. Despite the paucity of outcome studies, these data are promising in that therapies already known to be effective at reducing risk of heart disease are also able to modify plasma ceramide concentrations.

In conclusion, plasma ceramides are a promising new clinical diagnostic for the identification of patients at risk of adverse cardiovascular events. Testing for plasma ceramides is available to Mayo Clinic patients and health care providers worldwide through Mayo Medical Laboratories, the reference laboratory of Mayo Clinic. The lab offers advanced laboratory testing and pathology services to more than 5,000 health care organizations in more than 60 countries. For more information, contact Dr. Meeusen at 507-284-9939.
Pediatric Cardiogenic Shock: What is the Role of Medical and Mechanical Circulatory Support?

Introduction

Cardiogenic shock, defined as cardiac pump impairment that results in insufficient delivery of blood flow to tissues to meet resting metabolic demands, is considered the most severe expression of left ventricular failure. This clinical syndrome of low cardiac output state with resultant end-organ dysfunction can mimic other forms of severe shock, thus making it challenging from both a diagnostic and management standpoint. Despite these challenges, the prompt evaluation and timely medical and/or mechanical management of cardiogenic shock is associated with improved outcomes and increasing survival in pediatric patients presenting with cardiogenic shock.

Cardiogenic shock is a relatively uncommon form of shock occurring in 5-13% of pediatric emergencies, but in up to 20% of shock patients admitted to the pediatric intensive care unit. It can represent a fulminant form of myocarditis preceded by a short prodrome of viral symptoms or, more commonly, an acute exacerbation of chronic heart failure as seen in various forms of cardiomyopathy. Common causes of cardiogenic shock in this population include cardiomyopathy, myocarditis, congenital heart disease and arrhythmia (Table 1). “Acute heart failure and cardiogenic shock is associated with need for prolonged hospitalization, with a typical hospitalization lasting two to three weeks,” says Charlotte S. Van Dorn, MD, pediatric cardiologist and intensivist at Mayo Clinic in Rochester, Minnesota. “Approximately a third of these children either die or undergo heart transplantation within one year of presentation.”

The evaluation and subsequent diagnosis of cardiogenic shock can be challenging for the clinician first encountering a child in shock. Immediate attention must be given to the child presenting with acute-onset respiratory distress, poor perfusion and altered mental status not responsive to usual therapies of fever abatement, volume administration and oxygen supplementation. Persistently altered vital signs, including tachycardia and hypotension, as well as, specific physical ex-

Table 1: Etiologies of decompensated heart failure and cardiogenic shock in children

<table>
<thead>
<tr>
<th>Category</th>
<th>Common Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary myocardial failure</td>
<td>Congenital heart disease, dilated cardiomyopathy,</td>
</tr>
<tr>
<td></td>
<td>fulminant viral myocarditis, rejection post heart</td>
</tr>
<tr>
<td></td>
<td>transplant</td>
</tr>
<tr>
<td>Ischemia</td>
<td>Post-cardiopulmonary bypass, cardiac arrest</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>Tachyarrhythmia, bradyarrhythmia, heart block</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>Post-operative bleeding, post-pericardiotoxicity</td>
</tr>
<tr>
<td></td>
<td>syndrome, pericarditis</td>
</tr>
<tr>
<td>Acute valvular dysfunction</td>
<td>Endocarditis, papillary muscle rupture, post-</td>
</tr>
<tr>
<td></td>
<td>catheterization or post-surgical</td>
</tr>
<tr>
<td>Coronary insufficiency</td>
<td>ALCAPA, coronary ostial stenosis/atesia, coronary</td>
</tr>
<tr>
<td></td>
<td>thromboembolism, coronary vasospasm</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>Long-chain fatty acid oxidation disorders</td>
</tr>
<tr>
<td>Toxic states</td>
<td>Thyrotoxicosis, drug ingestion/inhalation</td>
</tr>
</tbody>
</table>

Table 2: Clinical symptoms and signs of pediatric cardiogenic shock

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Poor appetite, increased work of breathing, exercise intolerance, fatigue, lethargy, altered mental status, poor urine output, recent viral prodrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital Signs</td>
<td>Tachycardia, arrhythmia, heart block, tachypnea, hypotension</td>
</tr>
<tr>
<td>Clinical Signs</td>
<td>Murmur, gallop, irregular rhythm, diminished peripheral pulses, jugular venous distention, hepatomegaly, abdominal distention, edema, respiratory distress, crackles</td>
</tr>
</tbody>
</table>

Charlotte S. Van Dorn, MD
amination findings such as hepatomegaly, jugular venous distension, and gallop, may be indicative of impending cardiac failure in the previously well pediatric patient (Table 2). A targeted outpatient or emergency department evaluation, to include an electrocardiogram, chest x-ray, laboratory testing, focused critical care cardiac ultrasounds and formal echocardiogram, if available, may result in a timely diagnosis and expedite treatment measures. Specific laboratory markers that may be helpful in differentiating cardiogenic shock from other forms of pediatric shock may include a relatively normal complete blood count and C-reactive protein, elevated renal and liver function tests, serum lactate, as well as high levels of brain natriuretic peptide, a peptide secreted by the ventricles in response to stretch. Subsequent electrocardiogram findings may demonstrate a primary arrhythmia, acute or chronic ischemia, or ventricular hypertrophy with strain pattern. A chest x-ray prior to and after volume administration may reveal cardiomegaly with and without associated pulmonary edema (Figure 1). Finally, an echocardiogram may demonstrate previously undiagnosed congenital heart disease, cardiomyopathy with diminished function, or pericardial effusion with tamponade physiology. While the echocardiogram may be helpful in diagnosing cardiogenic shock, further patient stabilization within the emergency department or intensive care unit should not be delayed to obtain this study.

Management Options
Initial management of the pediatric patient presenting with suspected cardiogenic shock should first include the rapid identification of their pathophysiological state (Figure 2). A cold and dry state represents reduced myocardial contractility but normal ventricular end-diastolic pressures as seen in systolic dysfunction. In contrast, the warm and wet state describes the patient presenting with intact myocardial contractility but high left ventricular end-diastolic pressures indicative of diastolic dysfunction. “The most ominous state is that of the cold and wet patient that has both reduced myocardial contractility and increased left ventricular end-diastolic pressures characteristic of simultaneous systolic and diastolic dysfunction,” says Dr. Van Dorn. Once identified, targeted medical management can be pursued to alleviate symptoms, support end-organ perfusion, and improve cardiac dysfunction.

Medical Interventions
Primary goals for the medical management of cardiogenic shock must include optimization of preload and afterload while limiting myocardial demand and augmenting systolic and/or diastolic function. For the pediatric patient present-
mia and frequently increase myocardial oxygen demand in the already poorly contractile heart. If a child in cardiogenic shock has signs of high afterload, vasodilator therapy such as nitroprusside or nicardipine may be necessary to decrease the work performed by the failing left ventricle. In addition to vasodilators, inotodilators, such as milrinone or dobutamine, are almost always used in systolic and diastolic failure due to their ability to provide inotropy and luscitropy as well as vasodilatation. The use of beta blockers, while excellent for reducing afterload in chronic heart failure, should be avoided in acute decompensated heart failure and cardiogenic shock as this may potentiate myocardial dysfunction due to downregulation of beta receptors. During the acute setting, intravenous medications such as inotropes, vasodilators and diuretics are the mainstay of therapy. However, depending on disease progression and response to therapy, certain patients may ultimately tolerate transition to an oral heart failure regimen including angiotensin-converting enzyme inhibitors and beta blockers, as well as oral diuretics.

Mechanical Circulatory Support

Unfortunately, for certain pediatric heart failure populations, medical management alone is not enough to support the failing myocardium. In those patients with ongoing hypotension, persistent acidosis, low urinary output and/or clinical evidence of poor perfusion despite escalation in inotropic therapy, the use of mechanical circulatory support may be needed. Fortunately, options for mechanical support in pediatric cardiogenic shock have grown exponentially in the last two decades.

At this time, two primary forms of mechanical circulatory support are available for medically refractory cardiac failure: extra-corporeal membrane oxygenation (ECMO) and ventricular assist devices (VADs). ECMO cannulation can be achieved from a neck, femoral or open sternotomy approach and is most often used for urgent and short-term mechanical circulatory support. “Despite its invasive nature, the timely initiation of ECMO has been associated with decreasing morbidity and improved survivability to decannulation, VAD support, and subsequent heart transplantation,” says Dr. Van Dorn. If cardiac function does not immediately recover on ECMO, the decision may be made to transition to a longer-term form of mechanical support, a VAD. Options currently available include the Berlin Heart EXCOR in very small children and the HeartWare HVAD or Thoratec HeartMate II in older children and young adults. VAD use, as compared to ECMO support, is gaining favorability as more pediatric patients are able to tolerate extubation, ambulation, cardiac rehabilitation and, in some populations, hospital discharge. In addition to allowing for improved functional status, the transition to VAD support has also been associated with improved survival up to and following heart transplantation.

Outcomes

The prompt identification, evaluation and treatment of cardiogenic shock can improve outcomes and decrease mortality in critically ill pediatric heart failure patients. However, despite improvements in both medical and mechanical management, morbidity and mortality remain high as compared to other forms of pediatric shock. The current estimated mortality rate is as high as 5 to 10 percent, but increases up to five-fold in the presence of comorbidities such as acute kidney or liver failure and sepsis. Early myocardial support, both with medical or mechanical support, can improve end-organ function and perfusion, and thus reduce morbidity and mortality in this patient population.

Conclusions

Pediatric cardiogenic shock, although not common, is a non-specific and challenging clinical scenario of decompensated heart failure and impending cardiovascular collapse. The presence of persistent signs and symptoms of myocardial distress and end-organ hypoperfusion should prompt clinicians to broaden their evaluation and initiate timely interventions. While medical management can improve preload, afterload and myocardial contractility, ultimately mechanical support may be required in medically refractory shock. While ECMO and VADs are both excellent options for mechanical support, VAD therapy has been associated with improved functional status and survival to heart transplantation. Outcomes in cardiogenic shock continue to improve; however, mortality remains high, especially in those patients with comorbidities.
Margaret M. Redfield, MD, received the 2016 Distinguished Mayo Clinic Investigator Award. This award honors individuals whose research career demonstrates evidence of great distinction, high scholarship, creative achievement, and evidence of excellence in education and administrative responsibilities. Dr. Redfield is the Walter and Leonore Annenberg Professor of Cardiology and Critical Care Medicine. She is director of the Mayo Clinic Program in Circulatory Failure, and she is a co-director of the Cardiorenal Research Laboratory and the NIH Cardiovascular Training Grant at Mayo Clinic. Dr. Redfield is internationally recognized for her contributions to heart failure research and, particularly, the epidemiology, pathophysiology, and therapeutics of diastolic heart failure.

Richard C. Daly, MD, cardiovascular surgeon at Mayo Clinic in Rochester, Minnesota, received the Mayo Clinic 2016 Distinguished Clinician Award. This prestigious award is presented by the Mayo Clinic Officers and Councilors to annually recognize individuals who make outstanding contributions in patient care and embody Mayo’s primary value: The needs of the patient come first. Dr. Daly is the surgical director of both the Heart Transplant Program and the Lung Transplant Program at Mayo Clinic in Rochester.

Paul R. Julsrud, MD, radiologist at Mayo Clinic in Rochester, Minnesota, has received the Gold Medal from the North American Society for Cardiovascular Imaging. This award is presented annually to the individual who has best exemplified the stated goals of the society: to promote study, research, and teaching of cardiovascular imaging. The Gold Medal is the highest lifetime achievement award bestowed by the society. The recipient is selected by peers as one who has consistently demonstrated excellence in advancing the science of cardiovascular imaging, and has become a recognized expert in the field. In addition, the award acknowledged Dr. Julsrud’s service in various leadership positions in the profession, including serving as president of the society.

Brian P. Shapiro, MD, cardiologist at Mayo Clinic in Jacksonville, Florida, has been named the 2017 Florida Heart Researcher of the Year by the Florida Chapter of the American College of Cardiology. Each year, the Florida Heart Research Foundation in collaboration with the Florida Chapter of the American College of Cardiology recognizes an individual within the state of Florida whose research is felt to have had the broadest impact on the advancement of knowledge in the diagnosis, treatment, and prevention of cardiovascular disease.

Jonathan N. Johnson, MD, has been named chair of the division of pediatric cardiology at Mayo Clinic in Rochester, Minnesota. Dr. Johnson received his BS in biochemistry from the University of Wisconsin in Madison, and his medical degree from Wayne State University of Medicine in Detroit. He did his residency in pediatrics and his fellowship in pediatric cardiology at Mayo Clinic in Rochester. As a fellow, he received the Mayo Brothers Distinguished Fellowship Award, the C. Anderson Aldrich Research Award, and the Donald C. Balfour Mayo Clinic Alumni Association Research Award. He serves as the medical director of the Pediatric Heart Transplant Program at Mayo Clinic in Rochester. Dr. Johnson succeeds Frank Cetta Jr., MD, as chair.
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