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The Surgically Induced Stress Response

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Abstract

The stress response to surgery, critical illness, trauma, and burns encompasses derangements of metabolic and physiological processes that induce perturbations in the inflammatory, acute phase, hormonal, and genomic responses. Hypermetabolism and hypercatabolism result, leading to muscle wasting, impaired immune function and wound healing, organ failure, and death. The surgery-induced stress response is largely similar to that triggered by traumatic injuries; the duration of the stress response, however, varies according to the severity of injury (surgical or traumatic). This spectrum of injuries and insults ranges from small lacerations to severe insults such as large poly-traumatic and burn injuries. Burn injuries provide an extreme model of trauma induced stress responses that can be used to study the long-term effects of a prolonged stress response. Although the stress response to acute trauma evolved to confer improved chances of survival following injury, in modern surgical practice the stress response can be detrimental. (*JPEN J Parenter Enteral Nutr.* 2013;37:21S-29S)

Keywords

surgical stress; stress metabolism; response to injury; burns; nutrition therapy

Following surgical or accidental trauma, the nervous system activates the stress response by sending impulses from the injured site to the hypothalamus. The hypothalamus either removes its inhibitory tone on the pituitary or releases hormones which stimulate the production and/or release of pituitary hormones. Pituitary hormones act on their respective target organ causing the release of hormones such as the stress hormone, cortisol. Elevations of cortisol, glucagon, catecholamines, and a host of inflammatory cytokines, also exacerbate the stress response to surgery.

Afferent nerve signals from the injured site and proinflammatory cytokines have the net effect of increasing the secretion of hormones from the pituitary gland. Increased secretion of the anterior pituitary hormones corticotrophin (ACTH) and growth hormone (GH) have particularly significant metabolic consequences. Other anterior pituitary hormones such as thyrotrophin (TSH) and the gonadotropins (follicle stimulating hormone [FSH] and luteinizing hormone [LH]) are not as significantly affected.

Agents Generating the Stress Response to Surgery

Cortisol

Corticotrophin-releasing hormone (CRH), released by the hypothalamus, stimulates the anterior pituitary release of ACTH into the bloodstream. ACTH is a by-product of the breakdown of pro-opiomelanocortin. To complete the hypothalamic-pituitary (HPA) axis, cortisol (the stress hormone) is produced by the adrenal glands following ACTH stimulation.

The HPA axis is regulated by a negative feedback mechanism in which cortisol suppresses the release of both CRH and ACTH. Cortisol is a catabolic glucocorticoid hormone that mobilizes energy stores to prepare the body for the fight or flight response to stressors. It promotes gluconeogenesis in the liver, leading to raised blood glucose levels. Hyperglycemia reduces the rate of wound healing and is associated with an increase in infections and other comorbidities including ischemia, sepsis, and death.

During and after surgery the negative feedback mechanisms fail and high levels of both ACTH and cortisol persist in the blood. In the presence of raised cortisol levels in a severe stress

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response, the rate of protein breakdown exceeds that of protein synthesis,¹ resulting in the net catabolism of muscle proteins to provide substrates for gluconeogenesis. Further substrates for gluconeogenesis are provided through the breakdown of fat. Triglycerides are catabolized into fatty acids and glycerol, a gluconeogenic substrate.

GH

Growth hormone-releasing hormone (GHRH) from the hypothalamus stimulates the anterior pituitary to release GH. Propagation of the GH initiated signal occurs via the insulin-like growth factors which regulate growth. Signaling via these effectors regulates catabolism by increasing protein synthesis, reducing protein catabolism, and promoting lipolysis. Like cortisol, GH increases blood glucose levels by stimulating glycogenolysis. The hyperglycemic effect is also increased due to the anti-insulin effects of GH. However, the increased secretion of GH after surgery is not thought to be important in the perioperative period.²

Vasopressin

Vasopressin is a major antidiuretic hormone which released from the neurohypophysis. After surgery, it acts on arginine vasopressin (V_2) receptors in the kidneys, leading to the insertion of aquaporins into the renal wall. Aquaporins allow the movement of water from the renal tubule back into the systemic circulation. Vasopressin concentrations can be raised after surgery by pain alone.

Burn Injury Induces a Genomic and Hormonal Response Analogous to Trauma

Patients inflicted with burn injury undergo an elaborate hypermetabolic and hyperinflammatory response that persists for several years postburn.³⁻⁵ This effect has been proven amongst clinical parameters and at the cellular level. A large, prospective study in 977 severely burned children was conducted to document the hypermetabolic response.⁵ Interesting enough, the results depicted a sustained response, many throughout the 3-year study period. Predicted resting energy expenditure remained increased in burn patients ($P < .05$). Bone mineral content, lean body mass, and fat content decreased in burn patients when compared with nonburned controls ($P < .05$). Urinary epinephrine, norepinephrine, and cortisol increased several-fold in burn patients for 2, 18, and 36 months postburn respectively ($P < .05$). Up to a 2,000-fold increase in cytokines IL-6, IL-8, G-CSF, and MCP-1 was seen immediately postburn and remained significantly elevated for 3 years compared with controls. Similarly, GM-CSF, INF- γ , TNF- α , IL-1 β , IL-2, IL-5, IL-7, IL-10, and IL-17 showed significant elevations in the serum of burned children ($P < .05$). Serum proteins also showed drastic alterations in burn patients. Before increasing

to levels in nonburned controls, α_2 -macroglobulin remained decreased for 60 days postburn. Similarly, retinol-binding protein, prealbumin, transferrin, and apolipoprotein A₁ underwent marked decreases compared with controls and remained low for up to 90 days postburn. Conversely, haptoglobin, α_1 -acidglycoprotein, and C-reactive protein significantly increased in response to burn. Serum glucose levels in burn patients took 6 months to return back to normal while insulin levels remained elevated throughout the study period ($P < .05$). The results of this study depicted the extent of involvement of multiple organ systems for up to 3 years postburn.

The extent and magnitude of severe burn injury was similarly depicted when catecholamine levels were investigated in 413 burn patients and compared with those of 12 normal, healthy controls.⁶ Catecholamine levels were found to be directly proportional to extent of burn injury, but, in addition, an interesting trend in catecholamine levels were noted as well. Although epinephrine levels vary over time, they remained elevated for up to 60 days postburn ($P < .05$). On the other hand, norepinephrine remained significantly elevated for 2 years in the same burn patients when compared with nonburned controls ($P < .05$). These supraphysiologic elevations in urinary catecholamines foster the notion of a hypermetabolic response in burned patients.

These persistent perturbations of hormonal, acute phase, stress, and inflammatory proteins contribute to the clinical presentation of the burn stress response. Due to high levels of catecholamines, the patients are in a tachycardic, nervous, hypermetabolic state, which increases the stress on the heart. Continuing elevations of cytokines indicates prolonged immune-inflammatory dysfunction, which is confirmed by the long-term immunosuppression reported in these patients. Recent investigations have linked the elevations of particular cytokines IL-6 and MCP-1 to insulin resistance. Severely burned patients remain insulin resistant for at least 3 years postinjury. The duration of these responses has led to the interrogation of the transcriptomes of particular tissues—peripheral blood leukocytes, skin, muscle, and fat. These studies have shown that signaling related to insulin resistance and protein catabolism is altered in tissue from burned patients for at least a year postinjury.^{7,8}

Comparison of transcriptome changes in peripheral blood leukocytes from humans exposed to experimental endotoxemia, blunt trauma, and severe burn injury showed that many of the same genes are involved in the response to each insult, however, the duration and magnitude of the response to burn injury is greatest. This confirmed that a burn injury is in fact an extreme model of critical illness and trauma. Similarly, burn injury evokes hormonal changes in line with those seen in patients postoperatively. Increased and sustained levels of catecholamines, glucagon, and glucocorticoid have been reported in burn patients.⁹⁻¹¹ Surgically induced stress most certainly invokes a large, controlled response akin to burn injury.

Clinical Consequences of the Injury-Induced Metabolic Stress Response

Since Sneve's early description of the catabolic response in burn patients,¹² efforts to define and modulate the metabolic responses to injury and stress have continued. The characterization of a 2-phase hypermetabolic response to injury by Cuthbertson, divided the response to injury into quantifiable events.¹³ The initial ebb phase, occurring within several hours of the injury and lasting for 2-3 days, consists of reductions in cardiac output, oxygen consumption (VO_2), the basal metabolic rate, and glucose tolerance. The second flow phase, beginning after the ebb phase and lasting for days to weeks depending on injury severity, is characterized by increases in cardiac output, respiratory rate, VO_2 , hyperglycemia, skeletal muscle catabolism, and a negative nitrogen balance. Although the ebb and flow phase model is very simple, and may not adequately describe the metabolic responses induced following severe or multiple insults, the correlations established between injury and hypermetabolism continue to guide advancements in surgical care.

Postburn muscle catabolism occurs in conjunction with an increase in metabolic rates.¹⁴ Soon after this link was made, Moore¹⁵ suggested that following a traumatic injury, proteolysis and muscle catabolism could be reduced by feeding the patient continuously. Reversal of preexisting protein deficiencies with long-term parenteral nutrition (PN) was explored to achieve a reduction of the risk of postsurgical complications.¹⁶

The postburn hypermetabolic response is induced by increased serum catecholamine concentrations and maintenance of ambient temperature or administration of pharmacotherapeutic agents. Both burn and severe traumatic injuries induce a hypercatabolic response that, along with a heightened inflammatory response, leads to organ failure.³ The attenuation of the hypermetabolic response through nutrition and pharmacologic interventions results in improved patient outcomes.

Traumatic injury induces inflammatory and hormonal responses that alter metabolic processes, thereby changing nutrition requirements. The stress response to injury evolves temporally as the patient moves through the ebb and flow phases and eventually into the rehabilitative period. During each of the periods, nutrition requirements and nutrient intake, absorption and substrate utilization are different.

Major surgery, critical illness and sepsis, and traumatic and burn injuries induce elevations in the metabolic rate in an attempt to restore homeostasis. Although initially beneficial, the exaggerated and prolonged inflammatory, metabolic, and catabolic responses induce clinical complications, delay recovery, and increase mortality.

Significant basal metabolic rate (BMR) elevations occur in patients with burns over 30% or more of total body surface area. Inflammatory, hormonal, and stress signaling mechanisms drive the hypermetabolic response including elevations

of circulating catecholamines, glucocorticoids, and glucagon, with subsequent increases in gluconeogenesis, glycogenolysis, and protein catabolism. Insulin resistance and peripheral lipolysis develop as well.

Nutrition and Resuscitative Interventions

Surgical stress may impair metabolism, thereby negatively affecting the body's ability to grow, heal, maintain homeostasis, or adapt to the patient's surroundings. This may also affect the metabolic pathways through which absorption of nutrients and subsequent break down leads to generation of energy. Nutrition supplementation is needed to counteract dietary deficiencies, to augment the reduced function of the alimentary tract, and to support healing and recovery. Improved understanding of the pathophysiological response to injury has enabled the development of nutrition supplementation protocols that support recovery while reducing the effects of muscle catabolism, the major contributor to postsurgery or trauma adverse outcomes.

To heal following surgery and injury, increased availability of glucose, amino acids, and other nutrients is needed. Muscle proteolysis facilitates the release of glutamine and alanine following neuroendocrine and inflammatory signaling. These amino acids are required for protein synthesis and also serve as the building blocks fueling hepatic gluconeogenesis. Alanine and ammonia are derived from glutamine in the gut; these compounds are either used or converted to urea. To limit protein catabolism for the release of these amino acids, adequate nutrition supplementation is required.

Severely burned patients require fluid resuscitation to prevent hypovolemic shock. Resuscitation fluid is administered in accordance to the percentage of body surface area burned and body weight. The best indication of volume status is urinary output. Minimum target values are 0.5ml/kg/hr for adults and 1ml/kg/hr for children. Pulmonary edema and cardiac dysfunction can result from over resuscitation and subsequent hypervolemia. Following severe burn injury, early resuscitation is paramount. When immediate medical care is not available, oral rehydration with basic electrolyte replacement should be provided. Due to the increased caloric and protein requirements, early initiation of nutrition support is also necessary. The severely burned patient may not be able to ingest sufficient nutrition intake orally, especially with larger burns. Therefore, enteral nutrition delivery is initiated to enable achievement of requisite nutrition targets. Feeding tubes are recommended in all patients with burns > 20%. Enteral nutrition should be started and increased to goal as soon as resuscitation is complete. Adequate carbohydrates are needed to prevent loss of lean body mass,¹⁷ and sufficient fat to prevent a free fatty deficiency.¹⁸ Formulas supplemented with the anti-inflammatory and immunomodulating omega-3 fatty acids may contribute to better outcomes after burn injury.¹⁹ In general, a high carbohydrate, high protein, low fat enteral diet supplemented with

glutamine and antioxidants has recently been suggested as the optimal combination.²⁰ Preservation of gut mucosa integrity relies on early resuscitation and enteral feeding. Without these steps, splanchnic blood flow is diminished, leading to mucosal atrophy, bacterial overproliferation and translocation, and subsequent development of sepsis. Because nutrition supplementation alone is inadequate for the prevention of muscle catabolism, pharmacologic, surgical, or environmental interventions may be needed as well.

Postburn outcomes can be significantly improved by early excision and wound closure, prevention of excessive heat loss by elevating ambient temperatures, and early implementation of nutrition supplementation. Taking these outlined steps results in attenuation of the postburn hormonal and inflammatory responses, reduced hypermetabolism, decreased catabolism, and enhanced wound healing resulting in improved morbidity and decreased mortality.

Interventions to Specifically Modulate the Hypermetabolic Response

Insulin

Insulin is secreted by the β -cells of the pancreas in response to food or raised blood glucose or protein levels. The net effects of insulin are anabolic: hence it promotes glycogenesis and the uptake of glucose into muscles and fat. However, during the surgical stress response the amount of insulin secreted does not adequately meet the body's increased needs and cells become resistant to the reduced amount of insulin secreted. The degree of insulin secretion suppression and resistance is proportional to the scale of the operation.²¹ This contributes to a net catabolic state with an uncorrected hyperglycemia. Clinically, this is important as it has been shown in some studies that patients in whom insulin sensitivity is reduced by 50% after surgery suffer major complications and severe infections 6- and more than 10-fold, respectively, compared with controls.²²

Large operations and large burn wounds have similar effects on insulin homeostasis. Therefore, important lessons can be learned from studies in burn patients. Recently, a study investigating hyperglycemia and insulin resistance in 20 pediatric burn patients was performed.⁸ Fasting serum glucose levels persistently remained elevated throughout the duration of the study period (466 days) in burn patients compared with non-burned controls ($P < .05$). In addition, increased fasting insulin levels were observed in burn patients with peak levels of insulin at around 40-60 days postburn ($P < .05$). Thereafter, insulin trials have been proposed in burn patients. One randomized clinical study found that intensive insulin therapy significantly decreased the incidence of infections and sepsis, improved organ function, remedied insulin resistance, and reversed the posttraumatic catabolic state.²³ Increased fractional synthesis rate of donor site wound protein has also been seen in burn patients on intensive insulin treatment.²⁴ Furthermore, muscle

protein breakdown and sustained lean body mass were found in burn patients on continuous insulin infusions. Undoubtedly, euglycemia within a reasonable range decreases morbidity and healing time in the postoperative patient.

Propranolol

The nonselective β -blocker propranolol has long been used in the trauma setting for the control of tachycardia. Its use in pediatric burn patients has been studied extensively.²⁵⁻³⁰ In a randomized controlled trial, 90 burn patients were given propranolol daily at a dose of 4 mg/kg/day for a duration of 1 year.³¹ When compared with control burn patients, a significant reduction in predicted resting energy expenditure, and predicted heart rate were found. In addition, decreased central fat and central mass as measured by dual image x-ray analysis (DEXA) studies were found on patients receiving propranolol treatment. Another study investigated the effects of propranolol given to 171 pediatric burn patients on cardiac work.²⁷ Decreased heart rate was sustained in patients receiving propranolol after the second day and persisted throughout the treatment period ($P < .001$). Propranolol was initiated at a dose of 1 mg/kg/d in these patients but increased to 4mg/kg/day to maintain this response. It is evident from these investigations that propranolol ameliorates the hyperdynamic and hypercatabolic response seen in burn patients.

Oxandrolone

Oxandrolone is an analogue of testosterone. However, oxandrolone contains only 5% of its virilizing androgenic effects.³² Oxandrolone has been shown to improve lean body mass in conditions in which muscle wasting is evident. Burn victims are a subset of this population as they exhibit peripheral lipolysis and marked extremity muscle wasting. A study analyzing the effects of oxandrolone with and without exercise in pediatric burn patients was published in 2007.³³ A significant increase in lean body mass and body weight was found in patients receiving oxandrolone and on exercise therapy compared with treated with placebo and exercise ($P < .05$). Another study found that burned children treated with oxandrolone had a significantly decreased length of intensive care unit stay (0.48 ± 0.02 days/%burn) when compared with burned children receiving the standard burn care (0.56 ± 0.02 days/%burn).³² The same study showed preserved lean body mass and increased prealbumin and total protein levels in patients on oxandrolone treatment compared with controls ($P < .05$). Five-year outcomes to determine safety and efficacy profiles in burned children treated with oxandrolone examined 70 children on a dose of oxandrolone 0.1 mg/kg/d, twice daily. The results of this trial indicated long-term safety with minimum side effects. Improvements in muscle strength, cardiac work, and height were observed. The additional outcome of increased bone mineral content in these burn patients was postulated to occur via an insulin-like growth factor-1 mediator.³⁴

Exercise

Early ambulation and rehabilitation has remained on the forefront for patients undergoing all types of surgery. Even patients undergoing cardiac procedures have been recommended some form of controlled cardiac rehabilitation program. Recently, a 10-year study investigated the incidence of cardiovascular events in 975 patients post-cardiovascular surgery while exercising during cardiac rehabilitation.³⁵ These patients underwent various procedures including percutaneous transluminal coronary angioplasty (PTCA; 75%), post-cardiac surgery (coronary bypass graft, 13.2%), valvular surgery and other cardiac surgery (4.2%), and others (7.6%). During the 13,934 patient-hours of cardiac monitoring during exercise, no deaths, acute myocardial infarctions, or cardiac arrests were observed. Exercise rehabilitation programs can be safely implemented in patients postsurgery safely, provided pre-exercise evaluation and close monitoring during exercise, at least in the trial period, are mandated. The effects of exercise on lean body mass, resting energy expenditure, muscle strength, range of motion, thermoregulation, and quality of life in pediatric burn patients has extensively been studied.^{33,34,36-40} Many of these studies initiated an exercise program approximately 6 months postburn. One such study found increased peak torque in patients in the exercise arm (EX) vs those treated with the standard of care (SOC; EX, $54.31 \pm 44.25\%$ vs SOC, $12.29 \pm 16.49\%$; $P = .02$). An increase in lean body mass was also found in the EX when compared with patients treated with SOC (EX, $8.75 \pm 5.65\%$ vs SOC, $2.06 \pm 3.17\%$; $P = .004$).³⁷ Exercise in pediatric burn patients improves not only musculoskeletal composition but also pulmonary function⁴¹ and quality of life.⁴²

Intensive Insulin and Glycemic Control

Inadequately controlled blood sugar levels can result in increased morbidity and mortality in all patients whether diabetic or not. Hyperglycemia is associated with increased inflammation, infectious complications (including sepsis), ventilator dependence, length of hospital stay, and mortality. Deleterious consequences on the nervous, immune, respiratory, and renal systems arise from increased blood sugar levels.⁴³ Low blood sugar is equally dangerous. Hypoglycemia adversely affects the circulatory and both the autonomic and central nervous systems. Clinical presentation of hypoglycemia includes fatigue, drowsiness, dizziness, tachycardia, seizures, and coma. Tight glycemic control is necessary for rapid wound healing and patient outcome. We and others have shown that in recent years, the emergence of protocols for tight glycemic control with intensive insulin administration has reduced complications and improved outcomes in critically ill and severely burned patients.⁴³ Aggressive glycemic control in line with these intensive insulin protocols reduces insulin resistance and hyperglycemia. Although most physicians agree that maintenance of normoglycemia is beneficial, controversy

persists regarding establishment of the target blood glucose levels and protocolization of indications for intensive insulin therapy initiation.

Summary

The stress response to surgery, critical illness, trauma, and burns encompasses derangements of metabolic and physiological processes that induce perturbations in the inflammatory, acute phase, hormonal, and genomic responses. Hypermetabolism and hypercatabolism result, leading to muscle wasting, impaired immune function and wound healing, organ failure, and death. Optimal nutrition support is required to insure positive patient outcomes following surgery, trauma, critical illness, and burn injuries. Amelioration of the systemic inflammatory, hormonal, and metabolic responses with nutrition supplementation, pharmacologic interventions, and exercise reduces the impact of the hypermetabolic and stress responses.

Discussion

Robert Martindale: David, I am very impressed with the work you are doing. Do you start all of these things on every patient and then sort out who is going to be the best fit? I know you just study adolescents and children.

David Herndon: I have spent most of my life in performing randomized controlled studies. I do one study at a time. I would recommend to clinicians that they consider the multicentered long-term studies that we are doing and participate in them with enthusiasm and zeal so that we can really change standard of care. If I had my choice, I would give Oxandrolone and propranolol to a 60% total body surface burn, initiate exercise, and feed at 1500 kilocalories per meter squared burned. I would do that starting at admission and proceeding for 1 year post-injury. The diet would be high protein, high sugar, and low fat. I would also give selenium, zinc, copper and a variety of other minerals that have been proven necessary under these circumstances. I do not believe that immune enhancing diets have necessarily been proven yet in these patients.

Rosemary Kozar: I am going to start with a controversial question. You talked about the evils of TPN. What about the patient that has an ileus that cannot be fed enterally?

David Herndon: I do give supplemental TPN when patients develop an ileus and cannot tolerate enteral feeding. Their livers do get worse and they are at risk of infection. I change lines every 4–5 days based on an article that I wrote in 1975 and I am true to my principals. Use TPN but only when really necessary.

Rosemary Kozar: My understanding is that long term, many burn patients become obese. I seem to see this same

phenomenon in my sick trauma patients. What happens with the genetic changes and alterations and all the things that you talked about with time? It almost seems like they are reversed. Patients now have low muscle mass and a high percentage of body fat.

David Herndon: We have looked extensively at obesity in burn patients; fat people get fatter after burns, and thin people get thinner. Unfortunately, it is not easily summarized as everybody gets fat. I think that exercise and proper nutrition and seeing your patient every couple of months and addressing such issues on an individualized basis is what is required.

Marco Braga: What percentage of your patients need to be supplemented with parenteral nutrition in order to cover the nitrogen intake, especially in the early phase after thermal injury? The second question is what is your opinion about the potential of glutamine in terms of adding it into enteral nutrition to protect the barrier function?

David Herndon: In answer to the first question, the people that I treat who require parenteral nutrition are those people who become septic and develop enteral feeding intolerance such that they do not tolerate oral calories. I did a randomized study in 1980 that showed if we tried to supplement with parenteral nutrition, we increased morbidity and mortality. It is only in those patients with an ileus that prevents me from feeding the gut that I use TPN. I have worked with Doug Wilmore for a long time and I think that glutamine probably is a conditionally necessary additive in this patient population. I personally have not studied glutamine but I am looking forward to the multicentered Canadian study addressing that issue.

Paul Wischmeyer: Our lab is starting to show propranolol can have the very same effects in sepsis models and perhaps in trauma models that you report in your burn patients. We are thinking of moving forward to a multicenter trial some day with that. Do you think the effects are only in burn patients? In our burn unit at least, we start at day 7 post-burn with anabolic agents when the patients are out of the acute phase. When do you start and why? In response to your answer on the glutamine question, we have about 57 patients enrolled in Re-Energize study now, so it will be a little while until we have the answer.

David Herndon: I think that the catecholamine overdrive is common to all types of surgical stress and occurs in an additive fashion in septic individuals. I think trials are needed for beta blocking agents. Tachycardia is pathologic and beta-blockers are simple drugs to use. Obviously, you lose tachycardia as an indicator of hypovolemia or stress. I think that tachycardia is an incredibly important marker of the prolonged stress response and that it is an adaptive response that has gone awry. We can and should modulate it appropriately.

Paul Wischmeyer: Should we be waiting until day 7?

David Herndon: Cuthbertson described an ebb and flow response to major catabolic stress. In burn patients, we do excision and grafting within 24 hours of the time of injury then we start propranolol. For surgical patients, I think you first have to drain the abscess and get out of the ebb phase before you start an agent that is going to depress the heart rate.

Beth Taylor: I wanted to bring back your comments to surgery patients and the prolonged stress response. I think that after patients leave the hospital they continue to have complications from this prolonged stress response. What type of complications would you see months down the road? Would they be related to the loss of lean body mass? Should we define "success" not based on discharge alive from the hospital but rather on one-year mortality? For CMS, if a patient is readmitted too soon for congestive heart failure, you are not reimbursed. Can we convince our surgeons that if prescribe a postoperative plan to include nutrition and exercise, patients we have less readmissions? Maybe in the end we will get support for those programs from the government?

David Herndon: That is a wonderful discussion. I think you have really identified the area we need to study. There are postop pressure sores, aspirations, and pneumonias that lead to admission to SNIF units. I think the time back to work or the time out of work should be an indicator of our success rate and not just whether we get them out of the hospital alive. I also think we can make tremendous improvements in world health by concentrating on rehabilitation and return to work and looking at long-term quality of life outcomes as opposed to short-term surgical morbidity and mortality outcomes.

David Flum: I want to build on Beth's question. Tell us about the signs of the hypermetabolic state after surgery? What can we learn from burns about the length of time after one of these events when you are hypermetabolic and when you could benefit from nutrition intervention? If you look at patients who have had colon surgery, about 3 weeks after surgery, they are taking in only about 40% of their normal caloric load. If you look at bariatric patients, it is 30%. We view this as a success and clearly, these patients are still hypermetabolic. How long does that last and is their a role for nutrition supplementation either by total load or specific type that we should be trying in our patients?

David Herndon: I feel that specific long-term outcome studies that are geared toward these end points need to be done. It is my prejudice and my feeling that this is a huge worldwide health problem that has been ignored. We should do studies looking at the duration of the catabolic response and the effect of strength on return to work and quality of life. We should treat those catabolic phenomena not just with

nutrition but with a balanced program that would improve health. I do think a balanced program compared with standard of care would absolutely shock people if a proper study were to be done.

Ken Kudsk: In obese patients, probably the best way to break insulin resistance is exercise. Do you break insulin resistance in your burn patients through exercise? Have you measured that?

David Herndon: We are in the process of writing a manuscript in that regard and the answer is yes. Our patients are insulin resistant for up to a year or 2 after injury and exercise profoundly decreases the duration.

Ken Kudsk: I was quite intrigued about your experience using an insulin clamp. Are you using it during the immediate phase or during the flow phase?

David Herndon: We use a continuous insulin infusion for about 40 days throughout the patient's hospital course.

Ken Kudsk: Is that when you see protein balance improved?

David Herndon: Yes, it takes about 30-40 days.

Ken Kudsk: Do you also find that at this point you reduce your glucose intake overall because your energy expenditure is decreased?

David Herndon: We did see a decrease in resting energy expenditure and a decrease in caloric intake in those patients who were given insulin. It was marginal but it was statically significant.

Ken Kudsk: Do you think everybody should have his or her metabolic response blunted? The reason that I ask is, it is not unusual that we will get a young trauma patient who for the first 4-5 days is tachycardic but otherwise doing well. My concern is that you can miss other diagnoses if you mask the tachycardic response.

David Herndon: I think that is the critical question that still gives us equipoise to do randomized prospective trials with beta-blockers. I do not know that in the adult population there has been enough studies to look at the risk of missed injuries or complications. There are physiologic benefits to beta-blockade. The question is which patients will have dangerous sequelae if you allow the catabolic response to persist.

Ken Kudsk: I think with the burn patients, you can predict that they are going to be catabolic for a long period of time, but with trauma patients, they could go into either group. Either they could go into the group that recovers very quickly or they could go into the group that stays in your ICU for a prolonged period of time.

David Herndon: I think that patients who get an additional septic insult will go on to have a prolonged course. I think

the elderly do not bounce back from big operations and critical care interventions. I think that any therapy needs to be used selectively, even nutrition.

Robert Martindale: I just have a question about the enteral intolerance that we referred to earlier in the conversation. I am wondering if we can identify high-risk patients who are likely to develop enteral intolerance. Based what you know about the metabolic response to injury, is there a role for prophylactic use of motility agents? We tend to use them reactionary when the problem develops but should we be recommending their use in high risk patients at the same time we are starting enteral nutrition?

David Herndon: I certainly think there is a place for motility agents and I do not have enough knowledge to know exactly what that would be. The vast majority of patients with burns can begin on enteral feeding within 2 hours of time of injury. If you start feeding right away, patients generally do not get an ileus. I also think there are many people that can be fed through an ileus.

John Drover: Is there much known about individual genetics determining the metabolic response to injury? Is there a way of looking at your data to say that there are groups of patients that respond differently?

David Herndon: I think we can use the genetic response within the first 24 hours of a massive burn to predict that one individual is going to do worse than another individual. But, what do we do with that particular kind of information? Do we expend more resources on a person who has a more distinct genetic response with down regulation of immune system and up regulation of inflammatory systems and treat them with care that is more assiduous? I think that is probably what I would do right now but obviously much more data needs to be done in that regard.

Bob Martindale: I think your point of feeding within a couple of hours of injury really sets home to this patient population. I know that you published in the '80s with McDonald that if we feed early we prevent the progression of ileus and prevent bowel wall edema. It has now taken us 30 years in the ICU setting to learn that again. The general principles learned from surgical and trauma population have not really caught on yet.

Steve McClave: This persistent catabolic response to the injury that goes out 2 years resembles the persistent inflammation, immunosuppression, and catabolism (PICS) that Fred Moore has described. Should we be monitoring for that so that we know if it is still going or if it has been turned off? How do we best monitor that syndrome?

David Herndon: I have used stable isotope studies. I also think that dual interjectory absorptiometry is useful and when you get away from the fluid balance problems of the first acute days, it is a good way of looking at lean body

mass vs fat mass, bone mineral density, and bone mineral content over time. I would encourage each of you to think of using a DEXA scan to follow your patients over time.

Paul Wischmeyer: Should we be following urinary or plasma cortisol? I have just completed analyzing some recent data where we could show that there is a longitudinal increase in risk of mortality from increases in cortisol over time. The patient whose cortisol continued to be persistently elevated, died.

David Herndon: I think that clearly 24-hour urinary catechols can be measured. I would not follow serum, it is just not too variable.

Keith Miller: Who should follow patients over time? The multidisciplinary team has been accepted in the care of the cancer patient, but many times at our burn center, we as the burn surgeons do not typically follow these patients over time. They go back to their primary care physician.

David Herndon: Well, I really think that is one of the messages that I would like to leave to the next generation. We should follow our patients until they are completely recovered since we know best when that occurs.

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References

- Gore DC, Jahoor F, Wolfe RR, Herndon DN. Acute response of human muscle protein to catabolic hormones. *Ann Surg.* 1993;218(5):679-684.
- Burton D, Nicholson G, Hall G. Endocrine and metabolic response to surgery. *Continuing Ed Anaesthesia Crit Care Pain.* 2004;4(5):144-147.
- Jeschke MG, Chinkes DL, Finnerty CC, et al. Pathophysiologic response to severe burn injury. *Ann Surg.* 2008;248(3):387-401.
- Wilmore DW, Long JM, Mason AD Jr, Skreen RW, Pruitt BA Jr. Catecholamines: mediator of the hypermetabolic response to thermal injury. *Ann Surg.* 1974;180(4):653-669.
- Jeschke MG, Gauglitz GG, Kulp GA, et al. Long-term persistence of the pathophysiologic response to severe burn injury. *PLoS One.* 2011;6(7):e21245.
- Kulp GA, Herndon DN, Lee JO, Suman OE, Jeschke MG. Extent and magnitude of catecholamine surge in pediatric burned patients. *Shock.* 2010;33(4):369-374.
- Song J, Finnerty CC, Herndon DN, et al. Thermal Injury activates the eEF2K-dependent eEF2 pathway in pediatric patients. *JPEN J Parenter Enteral Nutr.* 2012;36(5):596-602.
- Jeschke MG, Finnerty CC, Herndon DN, et al. Severe injury is associated with insulin resistance, endoplasmic reticulum stress response, and unfolded protein response. *Ann Surg.* 2012;255(2):370-378.
- Hart DW, Wolf SE, Mlcak R, et al. Persistence of muscle catabolism after severe burn. *Surgery.* 2000;128(2):312-319.
- Mlcak RP, Jeschke MG, Barrow RE, Herndon DN. The influence of age and gender on resting energy expenditure in severely burned children. *Ann Surg.* 2006;244(1):121-130.
- Norbury WB HD. *Total Burn Care.* 3rd ed. Philadelphia, PA: Saunders Elsevier; 2007.
- Sneve H. The treatment of burns and skin grafting. *JAMA.* 1905;45:1-8.
- Cuthbertson DP. Post-shock metabolic response (Arris-Gale Lecture to the Royal College of Surgeons of England). *Lancet.* 1942;239:433-437.
- Cope O, Nardi GL, Quijano M, Rovit RL, Stanbury JB, Wight A. Metabolic rate and thyroid function following acute thermal trauma in man. *Ann Surg.* 1953;137(2):165-174.
- Moore FD. *Metabolic Care of the Surgical Patient.* Philadelphia, PA: Saunders; 1959.
- Dudrick SJ. Early developments and clinical applications of total parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2003;27(4):291-299.
- Wolfe RR, Allsop JR, Burke JF. Glucose metabolism in man: responses to intravenous glucose infusion. *Metabolism.* 1979;28:210-220.
- Rodriguez NA, Jeschke MG, Williams FN, Kamolz LP, Herndon DN. Nutrition in burns Galveston contributions. *JPEN J Parenter Enteral Nutr.* 2011;35:704-714.
- Norbury WB. Modulation of the hypermetabolic response after burn injury. In: Herndon DN, ed. *Total Burn Care.* Philadelphia, PA: Saunders Elsevier; 2007:420-433.
- Hall KL, Shahrokhi S, Jeschke MG. Enteral nutrition support in burn care: a review of current recommendations as instituted in the Ross Tilley Burn Centre. *Nutrients.* 2012;4:1554-1565.
- Thorell A, Nygren J, Ljungqvist O. Insulin resistance: a marker of surgical stress. *Curr Opin Clin Nutr Metab Care.* 1999;2(1):69-78.
- Sato H, Carvalho G, Sato T, Lattermann R, Matsukawa T, Schrickler T. The association of preoperative glycemic control, intraoperative insulin sensitivity, and outcomes after cardiac surgery. *J Clin Endocrinol Metab.* 2010;95(9):4338-4344.
- Jeschke MG, Kulp GA, Kraft R, et al. Intensive insulin therapy in severely burned pediatric patients: a prospective randomized trial. *Am J Respir Crit Care Med.* 2010;182(3):351-359.
- Tuvdendorj D, Zhang XJ, Chinkes DL, et al. Intensive insulin treatment increases donor site wound protein synthesis in burn patients. *Surgery.* 2011;149(4):512-518.
- Olah G, Finnerty CC, Sbrana E, et al. Increased poly(ADP-ribosylation) in skeletal muscle tissue of pediatric patients with severe burn injury: prevention by propranolol treatment. *Shock.* 2011;36(1):18-23.
- Kobayashi M, Jeschke MG, Asai A, et al. Propranolol as a modulator of M2b monocytes in severely burned patients. *J Leukoc Biol.* 2011;89(5):797-803.
- Williams FN, Herndon DN, Kulp GA, Jeschke MG. Propranolol decreases cardiac work in a dose-dependent manner in severely burned children. *Surgery.* 2011;149(2):231-239.
- Jeschke MG, Norbury WB, Finnerty CC, Branski LK, Herndon DN. Propranolol does not increase inflammation, sepsis, or infectious episodes in severely burned children. *J Trauma.* 2007;62(3):676-681.
- Baron PW, Barrow RE, Pierre EJ, Herndon DN. Prolonged use of propranolol safely decreases cardiac work in burned children. *J Burn Care Rehabil.* 1997;18(3):223-227.
- Herndon DN, Barrow RE, Rutan TC, Minifee P, Jahoor F, Wolfe RR. Effect of propranolol administration on hemodynamic and metabolic responses of burned pediatric patients. *Ann Surg.* 1988;208(4):484-492.

31. Herndon DN, Rodriguez NA, Diaz EC, et al. Long-term propranolol use in severely burned pediatric patients: a randomized controlled study. *Ann Surg.* 2012;256(3):402-411.
32. Jeschke MG, Finnerty CC, Suman OE, Kulp G, Mlcak RP, Herndon DN. The effect of oxandrolone on the endocrinologic, inflammatory, and hypermetabolic responses during the acute phase postburn. *Ann Surg.* 2007;246(3):351-360; discussion 360-362.
33. Przkora R, Herndon DN, Suman OE. The effects of oxandrolone and exercise on muscle mass and function in children with severe burns. *Pediatrics.* 2007;119(1):e109-e116.
34. Porro LJ, Herndon DN, Rodriguez NA, et al. Five-year outcomes after oxandrolone administration in severely burned children: a randomized clinical trial of safety and efficacy. *J Am Coll Surg.* 2012;214(4):489-502; discussion 502-504.
35. Kim C, Moon CJ, Lim MH. Safety of monitoring exercise for early hospital-based cardiac rehabilitation. *Ann Rehabil Med.* 2012;36(2):262-267.
36. McEntire SJ, Chinkes DL, Herndon DN, Suman OE. Temperature responses in severely burned children during exercise in a hot environment. *J Burn Care Res.* 2010;31(4):624-630.
37. Al-Mousawi AM, Williams FN, Mlcak RP, Jeschke MG, Herndon DN, Suman OE. Effects of exercise training on resting energy expenditure and lean mass during pediatric burn rehabilitation. *J Burn Care Res.* 2010;31(3):400-408.
38. Neugebauer CT, Serghiou M, Herndon DN, Suman OE. Effects of a 12-week rehabilitation program with music & exercise groups on range of motion in young children with severe burns. *J Burn Care Res.* 2008;29(6):939-948.
39. McEntire SJ, Herndon DN, Sanford AP, Suman OE. Thermoregulation during exercise in severely burned children. *Pediatr Rehabil.* 2006;9(1):57-64.
40. Celis MM, Suman OE, Huang TT, Yen P, Herndon DN. Effect of a supervised exercise and physiotherapy program on surgical interventions in children with thermal injury. *J Burn Care Rehabil.* 2003;24(1):57-61; discussion 56.
41. Suman OE, Mlcak RP, Herndon DN. Effect of exercise training on pulmonary function in children with thermal injury. *J Burn Care Rehabil.* 2002;23(4):288-293; discussion 287.
42. Rosenberg M, Celis MM, Meyer W III, et al. Effects of a hospital based wellness and exercise program on quality of life of children with severe burns. *Burns.* 2013;39(4):599-609.
43. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med.* 2001;345:1359-1367.