Chapter 6
Physiological Resilience

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In aging studies, resilience is often used to suggest an ability to recover from stressors and the relative degree of resilience depends on the stressor in question. Individuals may have adequate physiologic reserves to recover from moderate stressors yet lack sufficient resilience to recover from severe stressors. We have examined the recovery process from the relatively significant physiologic stressor of hip fracture. Following a hip fracture, there is a sudden loss of physical function (as measured by ability to walk independently and walking speed) followed by a period of recovery that can continue for a year or more depending on the area of function examined. The trauma of hip fracture and subsequent surgical repair may result in an oxidative stress and inflammatory response that, if excessive, can result in a detrimental effect on muscle strength and function. Antioxidant vitamins, vitamin D, and the statin class of medications and exercise may exert a beneficial effect, in part through a favorable modification of the post-traumatic inflammatory response.

In its most common usage, the term resilience refers to an ability to recover from change. In aging studies, resilience is often used to suggest an ability to recover from stressors. Using this definition it is possible to conceptualize resilience as the opposite of the geriatric syndrome of frailty. Frailty has increasingly been described as a biologic syndrome of*, decreased* reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes. Although there has been an extensive amount of research that has been recently conducted into the frailty syndrome, significantly less research has been directed toward the concept of resiliency. In contrast to frailty, resilience represents a state of*, adequate* reserve and resistance to stressors.

The relative degree of resilience obviously depends on the stressor in question. Individuals may have adequate reserves to recover from moderate stressors yet lack sufficient resilience to recover from severe stressors. Given the demographic trends in this aging population, older adults will, with increasing frequency, continue to encounter severe stressors (i.e. myocardial infarction, stroke, hip fracture, surgeries)

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that will challenge their physiologic reserve. We have examined the recovery process from the relatively significant physiologic stressor of hip fracture.

Because hip fracture is an acute traumatic and disabling condition that affects older adults, it is a good model for the examination of the physiologic processes that might influence resilience.

Following a hip fracture, there is a sudden loss of physical function (as measured by ability to walk independently and walking speed) followed by a period of recovery that can continue for a year or more depending on the area of function examined (Magaziner et al. 1990, 2000). By the end of a year, half of those who were able to walk independently before their fracture are not able to walk independently (Magaziner et al. 1990, 2000), which translates into an excess loss of function of about 25% when compared to loss in similar persons who do not have a hip fracture (Magaziner et al. 2003). In elders post-hip-fracture, the average one-year mortality is 18–33 percent (Magaziner et al. 1997). The duration of recovery and the period of increased mortality risk extend beyond that required for fracture healing, implying that the hip fracture event may trigger other adverse physiologic consequences.

In the following sections, we outline some aspects of the physiologic responses to the trauma of hip fracture that may explain the propensity for the adverse consequences of physiologic stress is older adults. We then discuss how possible modifiers of this response might influence resilience in older adults.

Inflammatory Response in Older Adults

Inflammatory cytokines are intercellular signaling molecules that mediate various aspects of cell function. They are essential for the coordination of the inflammatory response and immune function. Aging is associated with increased levels of circulating inflammatory cytokines (Bruunsgaard et al. 1999; Wei et al. 1992). These chronic, low-grade increases are typically two to four times the normal level of young adults, which, although well below the levels seen during acute infections (Krabbe et al. 2004), may have adverse effects. In studies of older adults, higher serum levels of markers of chronic inflammation have been associated with sarcopenia, decreased strength, functional loss and the frailty syndrome (Cappola et al. 2003b; Cesari et al. 2004b; Cohen et al. 1997; Ferrucci et al. 1999; Payette et al. 2003; Reuben et al. 2002; Walston et al. 2002).

Frailty and Resilience

Elders who are frail have decreased resilience to physiologic stressors. The frailty syndrome has been defined as a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes in elders (Fried et al. 2001).

There is evidence to suggest that older adults, and in particular frail older adults, may respond differently to inflammatory stimuli compared to younger adults or non-frail older adults. Peripheral blood mononuclear cells (PBMC) taken from frail elderly subjects had a higher IL-6 production after lipopolysaccharide (LPS) stimulation than those from non-frail elders (Leng et al. 2004), and elders are believed to also have a prolonged response following an inflammatory stimulus with slower normalization of cytokine levels compared to younger adults (Bruunsgaard et al. 1999; Krabbe et al. 2001). Following abdominal surgery, older adults have been reported to have both an increased and delayed interleukin-6 (IL-6) response, compared to younger patients (Kudoh et al. 2001).

Older adults who suffer hip fractures are often frail, and following the trauma of hip fracture and subsequent surgical repair, inflammatory cytokines have been found to be elevated up to one year post-fracture (Miller et al. 2006). These levels are higher than published values in disabled older women who have not suffered a hip fracture (Cappola et al. 2003a).

An inflammatory reaction following an acute medical event or traumatic event such as hip fracture is a reflection of the normal physiologic response to the initial insult. However, in some older adults, for example frail older adults, this response may be prolonged and become detrimental to recovery. The inflammatory response may therefore be a physiologic factor that influences the resilience of older adults to these physiologic stressors, and may explain the decreased resilience to physiologic stressors that may be seen in frail elders.

Effect of Inflammation on Muscle

Remote inflammatory processes, such as cancer, congestive heart failure (CHF), arthritis, and chronic obstructive pulmonary disease (COPD), have been observed to be associated with muscle catabolism and loss of muscle function that have been attributed to circulating cytokines (Gosker et al. 2003; Reid and Li 2001; Vescovo et al. 2000). Inflammation can contribute to muscle weakness by two main mechanisms: accelerated protein loss and contractile dysfunction (Reid and Li 2001). Inflammatory cytokines have long been associated with catabolic states (Beutler et al. 1985). This effect is believed to result from nitrogen loss and catabolism of muscle protein, which is strongly linked to tumor necrosis factor alpha (TNF-α). In addition, the inflammatory response can also suppress trophic hormone production and activity, for example insulin-like growth factor 1 (IGF-1), which similarly results in decreased muscle mass (Barbieri et al. 2002; Cappola et al. 2003b; De Benedetti et al. 1997; Fernandez-Celemin et al. 2002; Fernandez-Celemin and Thissen 2001).

Muscle weakness, however, has also been found to occur without overt loss of muscle protein (Budgett 1998) suggesting that inflammation may result in changes intrinsic to the muscle itself. In fact, inflammatory cytokines have been associated with altered contractile protein composition and contractile dysfunction in

laboratory animals and humans (Li et al. 2000; Vescovo et al. 2000). In addition to the catabolic effect of chronic inflammatory states (Beutler et al. 1985; Kotler 2000), TNF-α is believed to depress contractile force at the myofilament level, by a mechanism mediated by reactive oxygen species (ROS) and nitric oxide (NO) derivative generation (Reid et al. 2002).

In adults undergoing elective hip arthroplasty, peak IL-6 levels shortly after surgery were associated with time to recovery of walking (Hall et al. 2001). In hip fracture patients, serum levels of inflammatory markers were adversely associated with function, as individuals with higher serum inflammatory cytokine levels were observed to have worse performance on tests of lower extremity function in the year post-fracture than those with lower serum levels (Miller et al. 2006). If cytokine levels do in fact rise and remain high in some individuals following exposure to physiologic stressors, then this may result in similar consequences on muscle mass and function as seen in other chronic inflammatory conditions.

Oxidative Stress

Dating back to the 1950s, it has been suggested that oxidative damage, caused by free radicals, might be associated with the age-related functional decline and the development of frailty seen in older adults (De La Fuente 2002). Free radicals have been described as "any species capable of independent existence that contains one or more unpaired electrons" (Halliwell and Gutteridge 1999). Due to the unstable nature of these free radicals, biologic systems can be placed in a state of disequilibrium resulting in oxidative damage (Aust et al. 1985; Sevenian and Hochstein 1985). It has been theorized that oxidative damage may be, in large part, responsible for the sarcopenia (loss of muscle mass and strength) and resultant functional decline seen with typical aging (Fano et al. 2001). These sarcopenic changes are thought to be due to oxidative damage to DNA, proteins, and lipids that increases in human skeletal muscle (Semba et al. 2007b).

Early in the course of surgery an increase in ROS and a decrease in plasma antioxidant levels have been measured, suggesting that oxidative stress is one of the early responses to surgical stress (Clermont et al. 2002; Luyten et al. 2005). ROSs are important mediators and regulators of the inflammatory response, and are important to the intercellular messaging systems of nuclear factor Kappa B (NF-κB). Relatively low concentrations of hydrogen peroxide or a moderate oxidative shift in thiol-disulfide redox status have been shown to enhance NF-κB activation in various cell types. Expression of the inflammatory TNF-α is commonly induced by NF-κB and is accordingly increased under oxidative conditions (Dröge 2002). And NF-κB itself has been strongly implicated in pathological processes involved in muscle wasting (Cai et al. 2004).

In response to oxidative damage, the body has a natural antioxidant defense system that counters the rate of oxidation (Maxwell 1995; Clarkson and Thompson 2000). If the antioxidant system does not function properly in response to the

oxidative damage caused by the proliferation of free radicals, then DNA damage and an acceleration of functional decline are likely consequences (Cesari et al. 2004a). Therefore, it is critically important that antioxidant levels are properly maintained among older adults to deal with the severe stressors that occur.

Potential Modifiers of Physiologic Resilience

Antioxidant Vitamins

Inflammation and oxidative stress are believed to play a significant role in many age-associated conditions such as sarcopenia, decreased strength, functional loss, and the frailty syndrome (Cappola et al. 2003b; Cesari et al. 2004b; Cohen et al. 1997; Ferrucci et al. 1999; Payette et al. 2003; Reuben et al. 2002; Semba et al. 2007a; Walston et al. 2002). Given the importance of ROS in the processes of inflammation and muscle wasting (Cai et al. 2004; Dröge 2002), there has been significant attention paid to the role of antioxidant vitamins in retarding these processes. Of these, vitamin E and the carotenoids are among the best studied. Vitamin E is a term that encompasses a group of potent, lipid-soluble, chain-breaking antioxidants that include four tocopherols and four tocotrienols (Brigelius-Flohe 1999). The carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein, zeaxanthin, and lycopene) occur in a wide variety of fruits and vegetables. They are best known for their pro-vitamin A activity but in addition they are believed to be efficient scavengers of free radicals (Di Mascio et al. 1989). Selenium is an essential element and adequate selenium intake is required for optimal activity of key antioxidant enzymes, including glutathione peroxidases and thioredoxin reductases (Rayman 2000).

Because of their anti-oxidant effects, vitamin E, the carotenoids, and selenium have been extensively studied for their potentially preventive effects in chronic diseases believed to have an oxidative stress component such as cardiovascular diseases, atherosclerosis, and cancer (Navas-Acien et al. 2008; Rimm et al. 1993; Stampfer et al. 1993; Voutilainen et al. 2006). In studies of older adults, higher levels of both the tocopherols, carotenoids, and selenium have been associated with decreased frailty, increased muscle strength, and reduced disability (Bartali et al. 2008, 2006; Lauretani et al. 2007; Michelon et al. 2006; Semba et al. 2006; Semba et al. 2007b, 2007c).

In contrast to these observational studies, results from interventional studies with antioxidant vitamins have been less favorable. These studies have shown either no benefit or a risk of harm with the administration of supplemental antioxidant vitamins (Miller et al. 2005; Vivekananthan et al. 2003; Voutilainen et al. 2006). Many theories have been proposed for this disconnect between observational and interventional studies. One obvious explanation is that the serum markers of antioxidant vitamins may be markers of healthy lifestyle factors aside from diet that may result in the benefit seen in observational studies (Lichtenstein 2009). Another explanation is that the majority of intervention studies have relied on supplementation with single compounds, ignoring the complexity of whole food intake. For example, most

carotenoid interventional studies have used high-dose β-carotene as the agent of supplementation, whereas intake of foods rich in carotenoids may also contain lycopene, α-carotene, lutein, zeaxanthin, and β-crytoxanthin (Voutilainen et al. 2006).

It is believed that in vivo the carotenoids exhibit their antioxidant properties in different locations in cellular structures, based upon their chemical composition. β-Carotene is a highly lipophilic structure and so would be located primarily deep within the interior of cell membranes, whereas zeaxanthin also has polar components and can span the cell membrane. Due to its lipophilicity, β-carotene would not be as effective a scavenger of water soluble peroxyl radicals, whereas zeaxanthin would (El-Agamey et al. 2004). It has been postulated that the carotenoids therefore act in concert to scavenge free radicals across cellular structures; again suggesting that supplementation cannot easily replicate the complexity of whole food intake.

Also, β-carotene is believed to have paradoxical pro-oxidant effects at high serum concentrations, and this pro-oxidant effect has been suggested as a potential explanation for the observed negative effects in intervention studies that have typically utilized high-dose β-carotene. The water soluble vitamin C is believed to inhibit the pro-oxidant effects of high concentrations of β-carotene. Because smoking generates a high burden of oxidizing radicals, and smokers are typically deficient in vitamin C, this has been suggested as one explanation for the observation that smokers have fared particularly poorly in studies on β-carotene supplementation (El-Agamey et al. 2004).

Similarly, interventional studies using vitamin E have primarily used α-tocopherol as the agent of supplementation. Here too this may ignore the complexity of whole-food intake. A recent study has suggested a mechanism by which that unbalanced intake of α-tocopherol may be harmful, as it can result in a depletion of two other forms of vitamin E, γ-tocopherol, and δ-tocopherol; both powerful antioxidants (Huang and Appel 2003).

In response to a more potent inflammatory stimulus, the role of inflammatory markers and free radicals is even more pronounced. Key to the pathogenesis of sepsis and the systemic inflammatory response syndrome (SIRS) is the production of free radicals and inflammatory cytokines (Berger and Chiolero 2007). In an effort to minimize the devastating effects of sepsis, numerous immunotherapeutic approaches have been attempted, with little success (Nasraway 2003). It has been suggested that the immune dysregulation and organ dysfunction that is seen in the sepsis syndrome may be too complex to be significantly modified by therapies directed at single molecules, such as the anti-TNF-α antibodies (Abraham 1999).

Plasma concentrations of antioxidant vitamins have been found to be depressed during critical illness and sepsis, and supplementation with selenium, vitamin E, and carotenoids appears to offer some protection from the effects of sepsis and SIRS in observational studies and in small human or animal intervention studies (Sakr et al. 2007; Berger and Chiolero 2007). The first randomized trial of enteral pharmaconutrition in sepsis has recently been published. This study demonstrated that the administration of nutritional supplementation, including vitamins C, E, β-carotene, and selenium, early in the course of sepsis, resulted in a significantly faster recovery of organ function compared to controls (Beale et al. 2008). Although it is premature

to draw strong conclusions from a single study, it may be that this more holistic approach to nutritional therapy be of benefit. In contrast to sepsis, the levels of inflammatory cytokine elevations that have been observed following hip fracture or in post-operative patients are generally lower, and so may not require aggressive immunotherapy. For example, after cardiac surgery where serum levels of vitamin E have been observed to decrease shortly after surgery (Luyten et al. 2005), pre-operative supplementation was found to offer some protective effects in one small study (Yau et al. 1994).

Vitamin D

The importance of vitamin D in the maintenance of calcium homeostasis is well known. Vitamin D is now believed to also have important effects related to muscle strength and function, via both a direct influence and through its regulation of parathyroid hormone (PTH) levels (Bischoff-Ferrari et al. 2004b; Visser et al. 2003). Vitamin D deficiency may result in decreased muscle strength from both an increase in muscle protein degradation as well as altered contractile properties of muscle (Rodman and Baker 1978; Wassner et al. 1983). The vitamin D receptor (VDR) is present on skeletal muscle (Simpson et al. 1985), and muscle protein synthesis is initiated by the binding of 1,25-dihydroxyvitamin D3 [1,25 $(OH)_2$ D3] to its nuclear receptor with subsequent gene transcription. The influence of 1,25 $(OH)_2$ D3 on calcium homeostasis in skeletal muscle is believed to influence the contractile properties of muscle cells via both a VDR-mediated genomic pathway and a non-genomic rapid mechanism involving membrane effects of 1,25 $(OH)_2$ D3 (Boland et al. 1995).

Vitamin D has also been studied for its immunomodulatory effects. The VDR, through which the majority of the biologic effects of vitamin D are mediated, has been identified in almost every tissue in the body including most cells of the immune system (Holick 2005; van Etten and Mathieu 2005). 1,25 $(OH)_2$D3 has been shown to inhibit the maturation of dendritic cells (DC) in vitro as well as the secretion by DCs and other antigen-presenting cells of the immuno-stimulatory cytokine IL-12. Since IL-12 stimulates the development of CD4+ T-helper 1 cells (Th-1) and inhibits the development of CD4+ T-helper 2 cells, this results in a shift away from a relatively pro-inflammatory Th1 profile (Ex: IL-1, TNF-α, IL-17, 1L-18, IFN-γ) and toward a relatively anti-inflammatory Th2 type (Ex: IL-4, IL-10, IL-13) (van Etten and Mathieu 2005). In addition, the transcription of several key Th-1 cytokines such as IFN-γ and IL-2 is also inhibited by vitamin D (van Etten and Mathieu 2005). Vitamin D deficiency has been associated with an increased risk of Th-1 cytokine-mediated autoimmune diseases such as inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis, and type 1 diabetes mellitus (Peterlik and Cross 2005). Furthermore, although vitamin D attenuates the antigen-presenting function of monocytes and macrophages, the chemotactic and phagocytic function of these cells is enhanced by exposure

to 1,25 $(OH)_2$ D_3, suggesting an immune-modulating effect rather than merely an immunosuppressive one.

Unfortunately, vitamin D deficiency is common in older adults, especially among several groups of minority elders (Yetley 2008). We have found that the serum level of 25 (OH) D measured shortly after hip fracture is associated with IL-6 response post-fracture, with subjects deficient in vitamin D at the time of the fracture displaying higher serum levels of IL-6 at all follow-up time points in the year post-fracture. Vitamin D deficiency itself has also been associated with worse function post-hip fracture (LeBoff et al. 2008).

Vitamin D deficiency has been associated with functional decline, sarcopenia, and the frailty syndrome with studies indicating that vitamin D deficiency increases risk for decreased muscle strength, sarcopenia, falls, and frailty (Bischoff-Ferrari et al. 2004a; Puts et al. 2005; Visser et al. 2003), many of the same outcomes are associated with chronic inflammatory processes in elders. Whether the relative pro-inflammatory state that is conferred by vitamin D deficiency may explain, in part, the adverse effect of this deficiency is not known. Furthermore, if vitamin D deficiency is associated with frailty, then this deficiency may explain, in part, the increased cytokine response and the decreased functional resiliency to stressors in frail elders (Leng et al. 2004). If individuals who are deficient in vitamin D at the time of the fracture respond with a greater inflammatory response than those with sufficient levels following hip fracture surgery, then this would suggest that vitamin D may offer some protective effects from a detrimental inflammatory response following the inflammatory stimulus of hip fracture and surgical repair.

Exercise

Physical activity and exercise have also been associated with elevations in anti-inflammatory cytokines and cytokine inhibitors as well as lower levels of pro-inflammatory cytokines (Abramson and Vaccarino 2002; Colbert et al. 2004; Okita et al. 2004; Ostrowski et al. 1999, 2000; Wannamethee et al. 2002). In response to exercise, IL-6 is typically the first cytokine to appear, followed by interleukin-1 receptor antagonist (IL-1ra) and interleukin-10 (IL-10). The rise in IL-6 levels occurs shortly after initiation of exercise, peaking at approximately 3–4 hours after exercise termination, returning to baseline levels 24–48 hours post-exercise (Toft et al. 2002). Both IL-10 and IL-1ra have anti-inflammatory effects, while the effects of IL-6 are more complex, in this context it is believed to exert an inhibitory effect on TNF-α and IL-1β.

There is evidence that exercise may have prolonged anti-inflammatory effects and may result in blunting of the response to inflammatory stimuli. In healthy subjects, the performance of a cycling exercise at 75% of their VO_2 max had a blunted TNF-α response to an endotoxin bolus (Starkie et al. 2003). This suggests that exercise might also offer some protection against chronic systemic low-grade inflammation resulting from external stimuli. We have found that a low-intensity

generalized exercise program can reduce levels of soluble TNF-α receptor 1 (sTNF-α R1) in the year after hip fracture.

The effect of exercise on resistance to oxidative stress is more complex, as exercise itself can generate oxygen-free radicals. Low levels of exercise-induced oxidative stress are believed to result in increased expression and synthesis of anti-oxidant enzymes, through a mechanism involving NF-κB as several important antioxidant enzymes contain NF-κB binding sites in their promoter region (Ji 2002; Gomez-Cabrera et al. 2008). In studies of older adults, physical activity has been found to be associated with an increased level of the intrinsic anti-oxidant enzyme glutathione peroxidase, but with a decreased level of carotenoids, perhaps as a result of consumption following the oxidative stress of exercise (Rousseau et al. 2006; Karolkiewicz et al. 2003).

In a randomized study, preoperative exercise was found to reduce the duration of stay at hospital and ICU stay in patients awaiting coronary artery bypass grafting surgery (Arthur et al. 2000). Cardio-pulmonary bypass results in the significant generation of free radicals and oxidative stress (Clermont et al. 2002). Whether the observed beneficial effects of pre-operative exercise may be due to a favorable attenuation of the oxidative stress and inflammatory responses following surgery is not known.

Statins

Key to the pathogenesis of sepsis and the SIRS is the production of free radicals and inflammatory cytokines (Berger and Chiolero 2007). 3-Hydroxy-methyl-glutaryl-COA reductase inhibitors (statins) are a class of medications that have been shown in observational studies to improve survival in sepsis (Almog et al. 2004). Statins have important anti-inflammatory effects; however statins do not target individual inflammatory mediators, but instead may reduce the overall magnitude of the systemic response (Ando et al. 2000; Terblanche et al. 2006, 2007). This broad action is believed to be an important distinguishing feature in the modulation of the host response to septic insults. A recent study estimated that between 1999 and 2004 over 24% of men over 50 and women over 60 had taken statins (Spatz et al. 2009), but whether these agents might favorably alter the inflammatory response in those who are exposed to acute stressors is unknown.

Conclusion

The physiologic response to stressors in older adults is complex, and tremendous variability exits in the ability of older adults to recover from physiologic stress. The oxidative stress and inflammatory response may suggest potential explanations for this variability. Early observational and experimental data suggest that modifiers of

the inflammatory response and antioxidant vitamins may favorably impact resilience in older adults to physiologic stress. The disappointing results from anti-oxidant intervention trials, however, would argue for caution before advocating for the widespread use of these agents in older adults. Instead, diets rich in foods that contain anti-oxidants, the maintenance of adequate vitamin D levels, and physical activity are likely to be the most beneficial for the enhancement of physiologic resilience in elders.

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