

# Anesthesia, Microcirculation, and Wound Repair in Aging

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## ABSTRACT

Age-related changes in skin contribute to impaired wound healing after surgical procedures. Changes in skin with age include decline in thickness and composition, a decrease in the number of most cell types, and diminished microcirculation. The microcirculation provides tissue perfusion, fluid homeostasis, and delivery of oxygen and other nutrients. It also controls temperature and the inflammatory response. Surgical incisions cause further disruption of the microvasculature of aged skin. Perioperative management can be modified to minimize insults to aged tissues. Judicious use of fluids, maintenance of normal body temperature, pain control, and increased tissue oxygen tension are examples of adjustable variables that support the microcirculation. Anesthetic agents influence the microcirculation of a combination of effects on cardiac output, arterial pressure, and local microvascular changes. The authors examined the role of anesthetic management in optimizing the microcirculation and potentially improving postoperative wound repair in older persons. (**ANESTHESIOLOGY 2014; 120:760-72**)

**S**URGICAL wound repair is a major problem in the older population,<sup>1</sup> who are at increased risk of wound dehiscence and infection.<sup>2</sup> As a specific example, surgical site infections (SSIs) are common (approximately 500,000 cases annually in the United States), lead to worse patient outcome (patients who develop SSI are twice as likely to die),<sup>3</sup> and are an enormous economic burden (1–10 billion dollars annually).<sup>4</sup> Many factors contribute to age-related changes in skin<sup>5</sup> and subsequent vulnerability to impaired wound healing and infection. Changes in skin with age (fig. 1) include a decline in epidermal and dermal thickness and composition, as well as a decrease in the number of most resident cell types. The dermal–epidermal junction is flattened and the microcirculation is diminished.<sup>6</sup> The latter is defined as blood flow through arterioles, capillaries, and venules and is the key system that affects the entire skin surface. In the aging patient, the microcirculation in the skin is reduced by 40% between the ages of 20 and 70 yr.<sup>7</sup> The microcirculation provides tissue perfusion, fluid hemostasis, and delivery of oxygen and other nutrients. It also controls temperature and the inflammatory response. Surgical incisions cause disruption of the microcirculation in the skin as manifested by local edema resulting from vasodilation and increased vascular permeability.

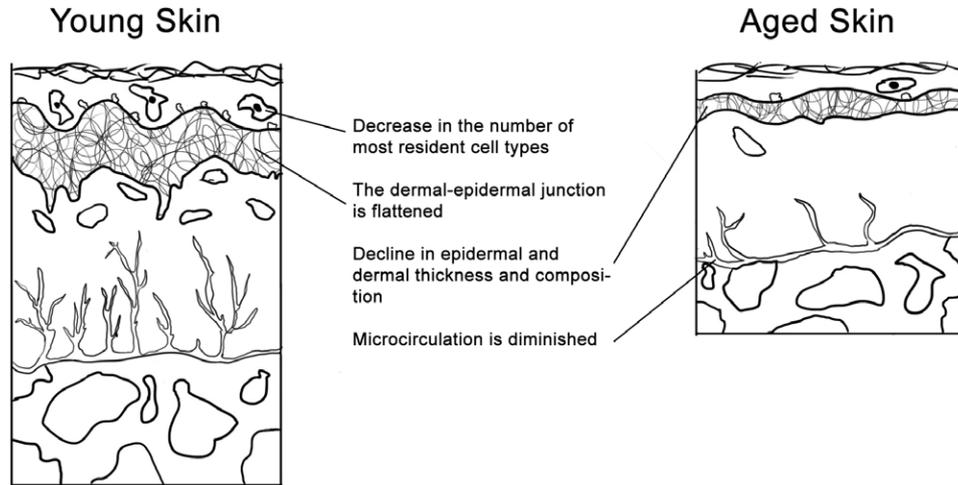
Perioperative management can be modified to optimize the microcirculation. Measures that support the microcirculation include careful use of fluids, normothermia, pain control, and smoking cessation.<sup>8</sup> Factors that can be influenced by intraoperative management (judicious use of fluids, maintenance of normal body temperature, pain control, and increased tissue oxygen tension) have been suggested to be beneficial as well. Most anesthetic agents also influence the microcirculation: a reduction in cardiac output and arterial pressure decreases flow in the microcirculation, whereas anesthetic-induced local microvascular changes and vasodilatation can increase perfusion.<sup>9</sup> Optimization of these variables plays an important role in enhancing the microcirculation in all patients, but is especially relevant if modifications could improve postoperative wound healing in the older population.

In this review, we will use skin as a representative organ to describe age-related changes that negatively affect the microcirculation and have subsequent impacts on wound healing and the incidence of postoperative infection. We will then examine the role of anesthesia management in minimizing detrimental effects on the microcirculation. A greater understanding of these variables could promote improvements that lead to better outcomes with respect to wound repair in older patients.

This article is featured in “This Month in Anesthesiology,” page 1A.

Submitted for publication January 18, 2013. Accepted for publication September 24, 2013. From the Department of Anesthesiology and Pain Medicine (I.B.) and Division of Gerontology and Geriatric Medicine, Department of Medicine (M.J.R.), Harborview Medical Center, University of Washington, Seattle, Washington.

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**Fig. 1.** Numerous changes in skin with age contribute to impaired wound healing.

**Summary of Wound Repair and Aging**

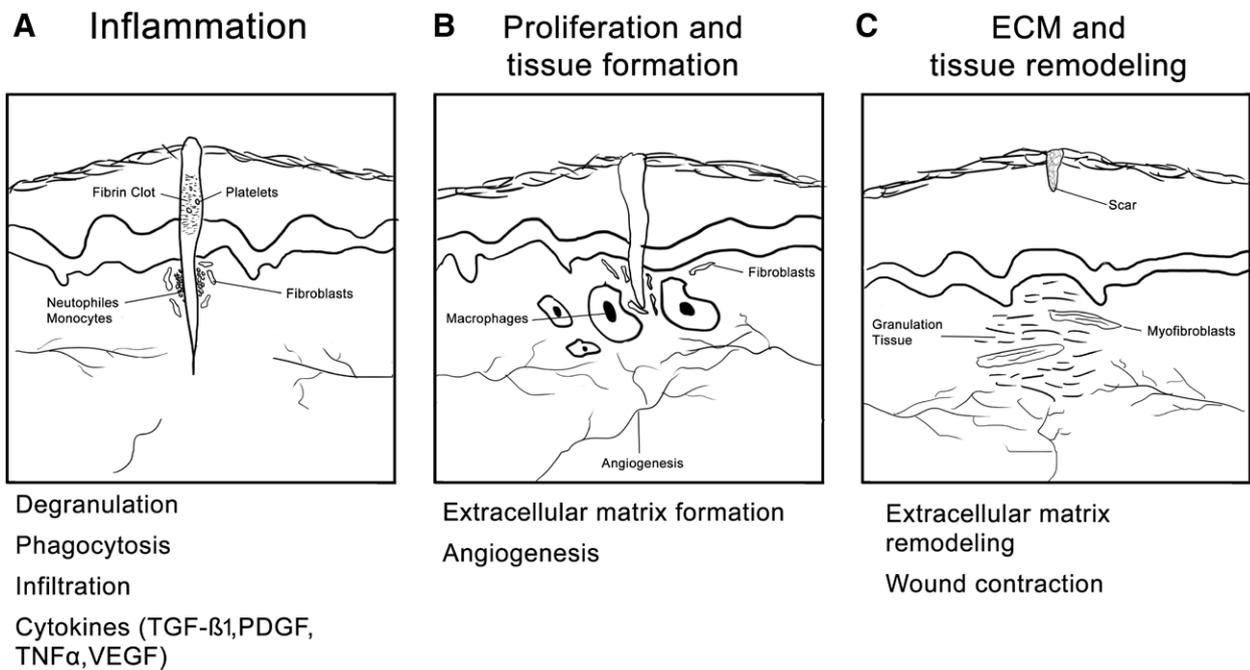
It has been nearly a century since it was noted that the rate of cutaneous scar formation after a wound is inversely related to the age of the patient.<sup>10</sup> Four decades ago, it was observed that older age was associated with an increased risk of postoperative disruption of the surgical wound, leading to higher mortality.<sup>11</sup> Recent data suggest that in patients older than 65 yr, development of SSI is associated with a two-fold increase in cost and a staggering four-fold increase in mortality.<sup>12</sup>

Wound healing ensues *via* a sequential chain of events (with variable overlap) that includes inflammation, tissue

formation, and remodeling<sup>13</sup> (fig. 2). Circulating factors have a pivotal role in each of these phases. Accordingly, as we will discuss below, immediate changes in the microcirculation influence each stages of the wound-healing response in aging. As human data is lacking, we have taken data from established animal models of aging. Although animal models are not uniformly predictive of responses in human tissues,<sup>14</sup> several animal models of wound healing are generally accepted.<sup>15</sup>

**Inflammation**

Immediately after injury to the skin, local blood vessels constrict and circulating platelets attach to the endothelial



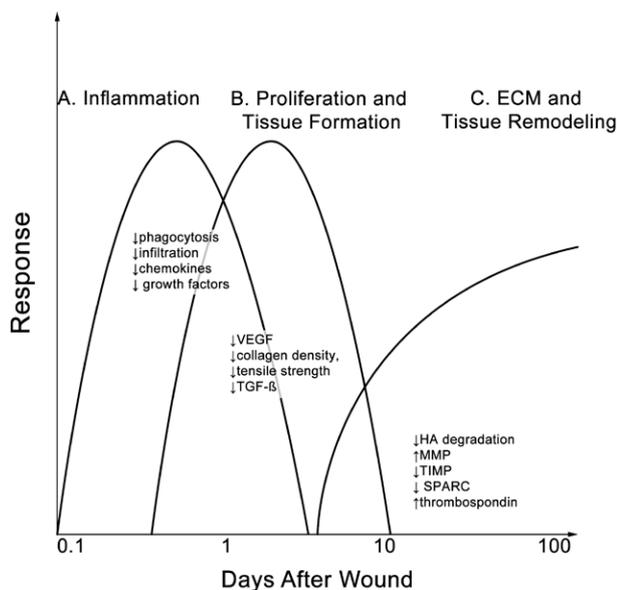
**Fig. 2.** The stages of wound healing are a sequential chain of events that include: (A) inflammation, (B) proliferation and granulation tissue formation, and (C) extracellular matrix (ECM) deposition and tissue remodeling. PDGF = platelet-derived growth factor; TGF-β1 = transforming growth factor-β1; TNF-α = tumor necrosis factor-α; VEGF = vascular endothelial growth factor.

wall to prevent further bleeding. The platelets aggregate and release their granules to form a fibrin clot. During this process, several mediators and cytokines that are also regulators of cell proliferation, extracellular matrix synthesis, and angiogenesis are released. As examples, transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) and platelet-derived growth factor elicit rapid chemotaxis of neutrophils, monocytes, and fibroblasts to the injured area, which stimulates generation of additional cytokines. The latter include the angiogenic factor vascular endothelial growth factor (VEGF) and the proinflammatory molecules tumor necrosis factor- $\alpha$  and interleukin-1 $\beta$ .<sup>16</sup>

Age-related changes in the inflammatory response (fig. 3A) result in alterations in cell adhesion, cell migration, and cytokine production. In an aged mouse model of impaired wound healing, reduced phagocytosis by macrophages and delayed T-cell infiltration into wounds were found in the aged mice relative to young mice. As expected, the production of most chemokines (as measured by messenger RNA levels) declined by 20–70% with age,<sup>17</sup> but levels of some proinflammatory cytokines increased. Subsequent studies highlighted the critical role of macrophages: when young mice were injected at a biopsy wound site with anti-macrophage serum, they exhibited delayed closure of the wounds, similar to that of aged mice.<sup>18</sup> In contrast, aged mice wounds that were given peritoneal macrophages from young mice showed enhanced wound healing.<sup>19</sup> Interestingly, in old female mice, healing of full-thickness dermal wounds on the upper dorsum was accelerated by treadmill

exercise, potentially reflecting an exercise-induced anti-inflammatory response in the wound.<sup>20</sup> Similarly, adult men (mean age, 61 yr) who exercised before an experimental wound showed a reduction in stress-related neuroendocrine responses that was accompanied by an accelerated wound healing.<sup>21</sup> Another therapeutic intervention is suggested by the finding that castration of male mice is associated with a reduced inflammatory response and results in acceleration of cutaneous wound healing.<sup>22</sup> This might reflect suppression of the androgen receptor, which enhances the inflammatory response through an increase in tumor necrosis factor- $\alpha$  expression.<sup>23</sup> The quantity and distribution of several growth factors are also different between aged and young mice. Expression of platelet-derived growth factor, epidermal growth factor, and their cognate receptors is delayed with increasing animal age.<sup>24</sup> Alterations of the inflammatory response are also found in aged humans. Although total leukocyte and neutrophil counts are slightly lower in samples from older individuals,<sup>25</sup> granulocyte adherence is greater in aged subjects especially in women.<sup>26</sup> Phagocytosis is decreased in neutrophils from old, compared with young, healthy donors, potentially secondary to reduced neutrophil CD16 expression in the aged.<sup>27</sup>

In summary, inflammation is an important part of the initial host response to injury and pathogens. Aging is sometimes associated with a persistent proinflammatory state; at the same time, there is a reduction in the ability to generate an acute inflammatory response during injury. This paradox can result in disrupted wound healing due to lack of synchronization between pro- and anti-inflammatory responses.



**Fig. 3.** Age-related changes in every stage of the wound-healing process may delay and impair surgical wound repair in older patients. ECM = extracellular matrix; HA = hyaluronan; MMP = matrix metalloproteinases; SPARC = secreted protein acidic and rich in cysteine; TGF- $\beta$  = transforming growth factor- $\beta$ ; TIMP = tissue inhibitor of matrix metalloproteinases; VEGF = vascular endothelial growth factor.

### Proliferation and Tissue Formation

Several hours after injury, reepithelization begins.<sup>28</sup> Wounded epidermal cells express integrin receptors, produce collagenase, and activate plasmin by plasminogen activator. These changes allow them to separate from neighboring cells, interact with and degrade extracellular matrix proteins, and enable movement from the dermis into the margins of the wound area. Epidermal cells in the wound margins begin to proliferate approximately 1 or 2 days after the injury, producing a scaffold of basement membrane proteins from the margins inward. During this process, mediators and cytokines (interleukins and  $\alpha$ - and  $\beta$ -chemokines) that regulate angiogenesis and influence the microcirculation are released.<sup>29</sup> Several days after the injury, macrophages, fibroblasts, and blood vessels simultaneously invade the wound.<sup>30</sup> Macrophages produce growth factors, such as TGF- $\beta$ 1 and platelet-derived growth factor. Fibroblasts synthesize a new matrix (first a provisional matrix of fibrin, collagen III, fibronectin, and hyaluronan; later a structural matrix of primarily collagen I replaces the provisional matrix). Blood vessels supply oxygen and nutrients, which is essential to sustain the newly formed granulation tissue. As an example, the deposition of collagen relies on proline hydroxylase, an oxygen-dependent enzyme.<sup>31</sup>

Studies based on animal models demonstrate that proliferation of the cell types responsible for tissue formation is reduced with aging<sup>32</sup> (fig. 3B). As an example, punch biopsy samples obtained repeatedly over the life span of hamsters found that *in vitro* proliferative capacity of dermal fibroblasts mimicked *in vivo* dermal wound repair.<sup>33</sup> In healthy human volunteers, superficial, split-thickness wound epithelialization is delayed in older persons (older than 65 yr) when compared with the control group (18–55 yr old).<sup>34</sup> Most studies suggest that wound angiogenesis is also decreased by approximately 70% 1 week after injury in aged animals.<sup>35,36</sup> Others propose an altered, dysregulated response with some extracellular matrix components increased, some decreased, and many showing disrupted ultrastructure.<sup>37</sup> Impaired endothelial cell function and reduced VEGF expression are possible mechanisms of age-related deficits in angiogenesis, which has an adverse effect on the development of an effective microcirculation.<sup>38</sup> In an explant model, age-related deficiencies in angiogenesis were reversed, in part, by stimulation with angiogenic growth factors.<sup>39</sup>

### Extracellular Matrix and Tissue Remodeling

During the last phase of wound healing, the extracellular matrix begins to remodel and the wound undergoes further contraction. Fibroblasts assume a myofibroblast phenotype characterized by bundles of  $\alpha$ -smooth muscle actin-containing microfilaments. Synchronized collagen reorganization occurs by synthesis and catabolism (although at a much slower rate than in previous stages), which allows the granulation tissue to turn into a scar. Deposition and remodeling of collagen are slower in aged animals resulting in less scar formation.<sup>40</sup> Moreover, the collagen deposited has a looser, more disorganized matrix that has decreased tensile strength. The changes in aged collagen matrix reflect decreases in circulating factors, in particular reduced levels of TGF- $\beta$ 1—a potent stimulator of collagen synthesis.<sup>41</sup> Of note, dermal fibroblasts from aged and young donors exposed to TGF- $\beta$ 1 exhibit similar biosynthetic and contractile properties.<sup>42</sup>

Other matrix components<sup>43</sup> that are altered with age (fig. 3C) include: decreases in osteonectin (also known as secreted protein acidic and rich in cysteine), increases in thrombospondin,<sup>44</sup> and alterations in fibronectin and laminin.<sup>45,46</sup> Nonprotein components of the extracellular matrix include glycosaminoglycans, such as hyaluronan, which interact with other matrix components to maintain hydration in the dermis. Hyaluronan is a linear disaccharide polymer that can range from 2 to 25,000 disaccharides with molecular masses up to  $2 \times 10^4$  kDa. Hyaluronan size determines its biologic properties: high molecular-weight forms can inhibit proliferation and migration of many cell types, whereas middle and lower molecular-weight forms usually promote tissue formation.<sup>46</sup> Hyaluronan content is maintained in aged wound dermis, but its degradation is reduced.<sup>47</sup> Wound healing also requires matrix metalloproteinases (MMPs), which promote cell proliferation

and vessel ingrowth by degrading the existing extracellular matrix. MMP activity is balanced, in part, by endogenous tissue inhibitors of metalloproteinases. Aged tissues are associated with dysregulation of MMP activity,<sup>48</sup> with a tendency toward overexpression of MMPs<sup>49</sup> and reduced levels of tissue inhibitors of metalloproteinases.<sup>50</sup>

As highlighted above, alterations occur during each stage of wound repair in aging, and many of these changes negatively impact the microcirculation. Nonetheless, given sufficient time, aged animals eventually (age-related delay is approximately 30–40%) catch up to their young counterparts with respect to most aspects of tissue repair.<sup>51</sup>

### The Surgical Context of Wound Repair and Aging

Measures that support the microcirculation improve wound repair, thereby reducing the risk of postoperative dehiscence and infection.<sup>52</sup> General preoperative measures such as smoking cessation and optimal management of comorbid medical conditions have been reviewed in other contexts.<sup>53,54</sup> For the purpose of this review, we will focus on interventions in the perioperative setting.

### Oxygen Administration

Wound healing is dependent upon adequate levels of oxygen.<sup>55</sup> Oxygen interacts with growth factor signaling and regulates numerous transduction pathways necessary for cell proliferation and migration.<sup>56</sup> It is also an indispensable factor for oxidative killing of microbes.<sup>57</sup> Consequently, the effects of oxygen tension on the outcome of surgical wounds have been best studied in the context of postoperative infection. Resistance to surgical wound infection is presumed to be oxygen dependent—with low oxygen tension viewed as a predictor of the development of infection,<sup>56</sup> particularly when subcutaneous tissue oxygenation (measured by a polarographic electrode) decreases to less than 40 mmHg.<sup>58</sup>

In two recent meta-analyses, one found that perioperative supplemental oxygen therapy exerts a significant beneficial effect on the prevention of SSIs,<sup>59</sup> whereas the other suggested a benefit only for specific subpopulations.<sup>60</sup> Although most authors suggest that supplemental oxygen during surgery is associated with a reduction in infection risk,<sup>61,62</sup> others propose it may be associated with an increased incidence of postoperative wound infection.<sup>63</sup> Notably, in the latter report, the sample size was small and there was a difference in the baseline characteristics of the groups. A prospective trial randomizing patients to either 30 or 80% supplemental oxygen during and 2 h after surgery did not find any difference in several outcome measures including death, pulmonary complications, and wound healing.<sup>64</sup> Of note, the administration of oxygen to aged subjects may be limited by the finding that although arterial oxygen tension did not decrease with age, there was reduced steady-state transfer of carbon monoxide in the lungs.<sup>65</sup> This indicates that oxygen transport could be

diffusion-limited in older subjects, especially when oxygen consumption is increased. Furthermore, longitudinal studies of five healthy men over 3 decades showed impaired efficiency of maximal peripheral oxygen extraction,<sup>66</sup> suggesting that tissue oxygen uptake is reduced in the aged subjects.<sup>67</sup> This likely reflects a decrease in the number of capillaries as well as a reduction in mitochondrial enzyme activity.<sup>68</sup> Animal models (rabbit<sup>69</sup> and mouse<sup>69,70</sup>) have suggested that aging and ischemia have an additive effect on disruption of wound healing. Consequently, the potential benefit of increasing tissue oxygen tension during surgical wound repair in older patients should be further evaluated.

### Fluid Management

Clinical signs of intravascular volume status are often difficult to evaluate in older persons.<sup>71</sup> Moreover, the repercussions of extremes of intravascular volume have harmful sequelae. As an example, hypovolemia decreases tissue oxygen concentrations,<sup>72</sup> whereas excessive fluid administration increases tissue edema, which can adversely affect healing.<sup>73</sup> Numerous types of fluids<sup>74</sup> and devices<sup>75</sup> have been evaluated as optimizers of volume status in the general surgical population, but lack of definition of liberal *versus* restrictive regimens precludes evidence-based guidelines.<sup>76</sup> When fluid administration was guided by subcutaneous oxygen tension rather than clinical criteria, patients received more fluids and accumulated more collagen in their surgical incisions.<sup>76</sup> However, in residents of nursing homes who are at a higher risk of impaired hydration (and subsequently reduced tissue oxygenation),<sup>77</sup> supplemental oral fluid intake neither reverses these deficits nor improves wound healing.<sup>78</sup> The need for more accurate determination of volume status is underscored by studies which showed that judicious use of fluids improves outcomes in the older population more than in the young population.<sup>79</sup> Goal-directed fluid therapy reduced the length of stay by an average of 2 days in general surgery cases where the mean age was 56–59 yr.<sup>80</sup> In an older group of patients (mean age, 75 yr) undergoing repair of femoral fractures, use of goal-directed therapy shortened the length of stay by 8 days.<sup>81</sup> Consequently, a strategy of administering fluids in a manner that maintains optimal hemodynamics and end-organ perfusion is recommended.

Anemia is common in the older population. More than 8% of men and 6% of women greater than 65 yr of age, and without severe comorbidities, have anemia as defined by hemoglobin levels less than 10 g/dl.<sup>82</sup> Perioperative anemia in the aged population is associated with worse outcome.<sup>83</sup> However, perioperative anemia results in an increase in erythrocyte transfusions, which are also correlated with adverse outcomes including SSI.<sup>84</sup> Low level of hemoglobin in young healthy subjects does not reduce subcutaneous tissue oxygenation,<sup>85</sup> suggesting that erythrocyte transfusions are not indicated to enhance wound healing. The optimal

hemoglobin level to maximize wound healing in older patients remains to be elucidated.

### Temperature

Mild perioperative hypothermia is common not only during general anesthesia but also during regional anesthesia.<sup>86</sup> Age is an independent risk factor for the development of hypothermia during anesthesia.<sup>87</sup> Mild hypothermia during the intraoperative period is associated with vasoconstriction as measured by skin temperature and subcutaneous tissue oxygen.<sup>88</sup> This markedly increases the risk of surgical wound infection, even after clean procedures such as hernia, breast, and varicose vein surgeries.<sup>89</sup> Thermoregulatory responses are decreased in the aged subjects,<sup>90</sup> mostly due to altered regulation of skin blood flow in the setting of a reduced microcirculation.<sup>91</sup> During general anesthesia with isoflurane<sup>92</sup> and sevoflurane,<sup>93</sup> the threshold for thermoregulatory vasoconstriction is reduced in the aged more than the young. The aged subjects are at additional risk of perioperative hypothermia because clinical signs (such as shivering) are absent at the same time thermoregulation is impaired.<sup>94</sup> Rewarming of the older patient takes significantly longer than younger adults, reflecting the same physiology that predisposes older adults to hypothermia.<sup>95</sup> Consequently, it is prudent to maintain euthermia for every aged patients during the intraoperative and postoperative periods, regardless of the type of anesthesia.

Strategies to maintain normothermia during anesthesia must take into account specific changes in the microcirculation. The initial decrease in core temperature results from the redistribution of heat to the peripheral microcirculation. Prewarming in the preoperative area might prevent redistribution of core heat.<sup>96</sup> Combined strategies that use multiple modalities (prewarming with use of warmed fluids and forced-air warming devices), are more effective in prolonged surgeries and in the older population.<sup>97</sup>

### Anesthetic Management Impacts the Microcirculation and Subsequent Wound Healing

The role of anesthesia technique in postoperative wound repair is not well studied. However, several lines of retrospective data analyses of outcomes after cancer surgery suggest that anesthesia technique can influence mechanisms that are relevant to tissue repair processes.<sup>98</sup> Wound healing and cancer progression share several pathways: cellular proliferation and migration are accelerated; the extracellular matrix undergoes greater turnover; and neovascularization is enhanced. These effects are mediated by a surge of inflammatory mediators, cytokines, and growth factors that are common to both wound repair and cancer. Although the endpoints in these studies were cancer recurrence or metastases, the subsequent changes in growth factor levels or activity of matrix-degrading MMPs<sup>99,100</sup> are likely relevant to tissue healing. It is notable, however, that the groups studied differed not only in the use of inhalational *versus* IV agents

but also in the use of other variables such as the amount of opiates used to control pain. Each of these components has collateral effects including changes in regional blood flow and the effective microcirculation. Nonetheless, the underlying mechanisms that influence cancer surgery outcomes should be noted when examining determinants of postoperative wound healing.

**The Effect of Anesthesia Technique: General versus Regional.** Although clinical and theoretical perceptions often advocate for regional anesthesia rather than general anesthesia in older patients, there is no difference in various outcome measures.<sup>101,102</sup> Comparisons are difficult: for example, in a retrospective analysis, neuroaxial anesthesia (epidural or spinal anesthesia) for total hip or knee replacement was associated with a lower risk of SSI than general anesthesia, but the general anesthesia group was older with more comorbidities making it difficult to form definitive recommendations.<sup>103</sup>

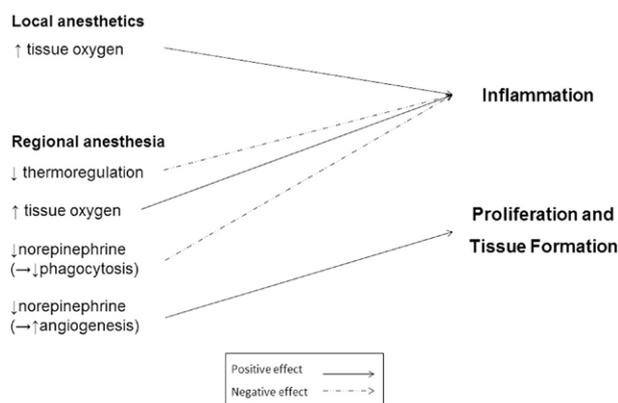
Effects of anesthesia on physiologic variables relevant to the microcirculation and subsequent wound repair have been examined and will be discussed here. For example, general anesthesia causes vasodilation by direct effects on the peripheral microcirculation<sup>104</sup> and indirectly by central inhibition of vasoconstriction.<sup>105</sup> Thoracic epidural anesthesia increases peripheral tissue oxygen tension, even outside the dermatome affected by the block.<sup>106</sup> Core hypothermia develops equally under general and epidural anesthesia due to vasodilation in the microcirculation in the skin and loss of thermoregulation. During epidural anesthesia, skin thermoregulation in the region affected by the epidural (lower body) is reduced independent of patient age. Not surprisingly, young patients are better able than older patients to maintain skin thermoregulation in the regions not affected by epidural anesthesia.<sup>107</sup>

Administration of typical doses of volatile or IV agents does not suppress the contribution of the endocrine response to the microcirculation.<sup>108</sup> In contrast, regional anesthesia (most notably neuroaxial blockade) blunts the endocrine stress response to surgery.<sup>109</sup> Continuous lumbar plexus and sciatic nerve blocks did not affect cortisol levels but attenuated the postoperative inflammatory response (lower C-reactive protein).<sup>110</sup> In a study of regional block after knee arthroplasty, clinical signs of inflammation were reduced although there were no detectable changes in levels of measured cytokines.<sup>111</sup> Epidural anesthesia reduces the plasma levels of norepinephrine during surgery when compared with general anesthesia.<sup>112</sup> This holds true when combined general and epidural anesthesia is compared with general anesthesia alone.<sup>113</sup> Norepinephrine and epinephrine induce vasoconstriction in the microcirculation<sup>114</sup> and also have effects on subsequent biological processes that influence wound repair, such as angiogenesis and inflammation. For example, norepinephrine significantly increased secretion of the angiogenic factor VEGF by ovarian cancer and melanoma cell lines.<sup>115,116</sup> Furthermore, epinephrine

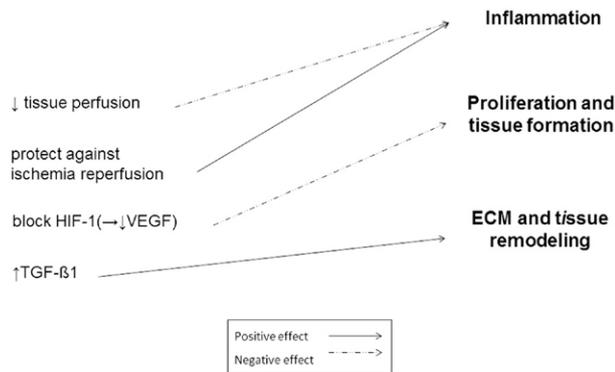
suppresses phagocytosis of soluble immune complexes (aggregated  $\gamma$ -globulin) by macrophages in a dose-dependent manner<sup>117</sup> (fig. 4).

**Volatile Anesthetics Agents.** Volatile anesthetic agents have several contradictory effects on microcirculatory flow. They decrease flow in the microcirculation by reducing arterial perfusion pressure and depressing myocardial contractility. At the same time, these agents can increase flow in the microcirculation by inducing a vasodilatory response.<sup>118</sup> As a result, clinically useful concentrations of volatile agents will often produce systemic hypotension and decrease regional tissue perfusion in a tissue- and agent-specific manner.<sup>119</sup> Muscle perfusion under anesthesia with volatile agents is better maintained in young subjects than in aged subjects.<sup>120</sup>

Not all effects of inhalation anesthesia are detrimental to tissue repair (fig. 5). Volatile anesthetics protect against ischemia–reperfusion injury of several organs (heart,<sup>121</sup> liver,<sup>122</sup> kidney,<sup>123</sup> and potentially others) by reducing necrosis and inflammation.<sup>124</sup> Several lines of evidence suggest that inhalation anesthetics exert their effects by affecting the microcirculation and influencing subsequent angiogenesis. For example, exposure to volatile anesthetics stimulates growth and proliferation of endothelial progenitor cells.<sup>125</sup> Conversely, volatile anesthetics, at clinically relevant doses, block transcription factor hypoxia-inducible factor-1 activity and expression of its downstream target genes. Hypoxia-inducible factor-1 is a transcriptional regulator of VEGF expression<sup>126</sup> and mediates angiogenic responses to reduced oxygen availability.<sup>127</sup> When renal proximal tubule cells were exposed to volatile anesthetics for 16 h, there was an increased production and release of TGF- $\beta$ 1, a potent stimulator of extracellular matrix synthesis, into the cell culture media. The role of TGF- $\beta$ 1 in the protective effect of volatile agents on ischemic injury to the kidney was specifically demonstrated *in vivo*—mice heterozygous for TGF- $\beta$ 1 (TGF- $\beta$ 1+/-) were not protected from ischemia–reperfusion injury by sevoflurane, and a neutralizing TGF- $\beta$ 1 antibody blocked renal protection with sevoflurane in TGF- $\beta$ 1+/+ mice.<sup>128</sup> Despite the data above, it is worth noting that volatile anesthetic agents differ



**Fig. 4.** The effects of local anesthetics and regional anesthesia on wound healing.



**Fig. 5.** The effects of volatile anesthetics on wound healing. ECM = extracellular matrix; HIF-1 = hypoxia-inducible factor-1; TGF- $\beta$ 1 = transforming growth factor- $\beta$ 1; VEGF = vascular endothelial growth factor.

in their effects on the microcirculation with respect to specific agents (desflurane *vs.* isoflurane *vs.* sevoflurane), target organs (heart *vs.* kidney *vs.* splanchnic), and clinical states (healthy *vs.* sepsis *vs.* hemorrhagic states).<sup>129</sup> Consequently, we cannot make meaningful recommendations regarding volatile anesthetics and wound-healing outcomes.

**Opioids.** Large doses of opioids are routinely used to achieve hemodynamic stability during the intraoperative period. Compared with other commonly used IV agents, opioids have the advantage of not depressing cardiac contractility.<sup>130</sup> Opioids have multiple effects on the microcirculation, which include inducing the release of nitric oxide<sup>131</sup> and directly relaxing smooth muscle cells.<sup>132</sup> Opioids can both increase and decrease body temperature. The hyperthermic response to opioids is mediated by the  $\mu$ -receptor and the hypothermic response is mediated by the  $\kappa$ -receptor.<sup>133</sup> Morphine has several downstream effects that can influence wound repair, such as activation of G-protein–coupled receptors to induce cellular proliferation<sup>134</sup> and activation of the VEGF receptor.<sup>135</sup> Activation of a receptor in a ligand-independent manner can occur through different mechanisms and includes cross-talk between signaling pathways. For example interleukin-8, an angiogenic factor, can transactivate VEGF receptor-2.<sup>136</sup> Human endothelial cells express the opioid responsive  $\mu$ -3 receptor,<sup>137</sup> but the effect of opioids on angiogenesis itself is still under investigation. Some suggest that opioids inhibit blood vessel growth<sup>138</sup> and that opioid antagonists promote angiogenesis,<sup>139</sup> probably *via* suppression of hypoxia-inducible factor-1  $\alpha$ -mediated VEGF transcription.<sup>140</sup> Others found that opioids stimulate angiogenesis and tumor growth by inhibition of apoptosis and promotion of cell cycle progression in breast cancers.<sup>141,142</sup>

There are conflicting findings regarding the direct effect of opioids on wound repair. The expression of  $\mu$ -receptors is decreased in the margins of chronic wounds.<sup>143</sup> Some describe opioid-induced, delayed wound healing that is dose dependent.<sup>144</sup> The latter is proposed to be mediated, in part, by the inhibition of peripheral neuropeptide release into the healing wound and reduced neurokinin receptor expression

in inflammatory and parenchymal cells.<sup>145</sup> Others suggest that topical opioids accelerate wound healing<sup>146</sup> by up-regulating nitric oxide synthase and the VEGF receptor-2.<sup>147</sup>

Pain<sup>148</sup> (as well as psychological stress)<sup>149</sup> delays wound healing. Conversely, inappropriately high doses of opioids can also impair organ function, delay mobilization, and subsequent healing after surgery.<sup>150</sup> A recent meta-analysis that compared analgesia after surgery with opioids alone as compared with a multimodal approach (in which an epidural was used in addition to general anesthesia) did not find a difference in mortality between the groups but found a lower complication rate in the multimodal group.<sup>151</sup> Wound-healing rates were not reported in the meta-analysis. Further studies are needed to elucidate the effects of opioids and other pain-alleviating modalities on subsequent wound repair.

**Other IV Anesthetic/Sedative Agents.** It is common for combinations of different agents to be used during induction and maintenance of anesthesia.<sup>152</sup> To our knowledge, the effects of the IV agents on the microcirculation have been best studied in different models of shock states, such as profound hemorrhage. Consequently, the observed effects are usually transient and are of uncertain relevance to wound healing.

In general, most agents either produce no change in hemodynamic parameters or cause vasodilation and cardiac depression. In normovolemic rats, regional blood flow was similar for all anesthetic agents<sup>153</sup> although some authors have described skeletal muscle arteriolar vasodilation with propofol. In a rat model of abdominal surgery, dexmedetomidine attenuated the reduction of the microcirculatory blood flow to the intestinal mucosa.<sup>154</sup> Ketamine is an exception as it usually induces vasoconstriction and produces an increase in blood pressure and cardiac output.<sup>155</sup> In certain models of hemorrhagic shock, at similar systolic blood pressures, propofol produced regional vasodilation, whereas ketamine resulted in vasoconstriction.<sup>156</sup> Of note, the potential benefit of propofol on end-organ perfusion may be offset by the finding that macromolecular leak occurred from venules during propofol/fentanyl administration, but not during ketamine anesthesia.<sup>157</sup> Midazolam (but not ketamine or propofol) stimulated the release of VEGF by smooth muscle cell cultures, which might induce further downstream changes in the microcirculation.<sup>158</sup> VEGF induces angiogenic responses by inducing proliferation and migration and inhibiting apoptosis of endothelial cells.<sup>159</sup>

Intravenous agents also have numerous effects on immune responses that might be relevant to subsequent wound healing. *In vitro*, clinically relevant concentrations of ketamine and midazolam (but not propofol) inhibited monocyte chemotaxis.<sup>160</sup> Thiopental and etomidate (but not ketamine, propofol, or methohexital) decreased chemotaxis by eosinophils.<sup>161</sup> Ketamine inhibits the inflammatory response of macrophages<sup>162</sup> and antigen-presenting cells.<sup>163</sup> Thiopental and midazolam, but not ketamine, suppressed neutrophil function.<sup>164</sup>

In summary, the choice of IV anesthetic agents could potentially have beneficial effects on the microcirculation and subsequent wound healing. It is premature to make any specific recommendations, as cell and animal studies are insufficient and well-designed clinical studies do not exist.

**Local Anesthetics.** The effect of local anesthetic infiltration on wound healing has been studied in numerous models with conflicting results. Some suggest that exposure to local anesthetics enhances wound repair, others propose no effect or a negative impact.<sup>165</sup> Local anesthetics may positively influence wound healing by reducing the stress response and alleviating pain.<sup>166</sup> Intraarticular lidocaine, used to achieve pain management after knee surgery, increased oxygen tension in the subcutaneous tissue.<sup>167</sup> Local anesthetics can be detrimental by delaying the synthesis of collagen<sup>168</sup> and by an antiproliferative effect on mesenchymal cells.<sup>169</sup>

The response of the microcirculation to local anesthetics is not consistent. The first-known local anesthetic, cocaine,<sup>170</sup> induces vasoconstriction, even at small doses, by inhibition of norepinephrine uptake.<sup>171</sup> Modern local anesthetics (lidocaine<sup>172</sup> and bupivacaine<sup>173</sup>) have a dose-dependent effect: low concentrations cause vasoconstriction of arterioles, whereas high concentrations cause vasodilation. Human studies suggest that dose-dependent properties of lidocaine may be pronounced in aged tissues. This likely reflects a longer drug half-life in older individuals, as a result of age-related decreases in hepatic blood flow and clearance.<sup>174</sup>

## Summary

Nearly every anesthesiologist who provides care to adults will participate in the care of geriatric patients.<sup>175</sup> A growing older population is undergoing surgical procedures that are increasing in number and complexity.<sup>176</sup> Poor healing of surgical wounds is a major cause of morbidity, mortality, and substantial economic burden. Wound healing is dependent on the microcirculation that supplies the incision area. Measures that support the microcirculation during the perioperative period have a profound effect on wound healing. Some measures such as maintenance of normal body temperature and control of postoperative pain are supported by ample evidence and have been implemented in routine clinical care. Other measures, for example, the choice of anesthesia technique and use of opioids are supported by basic research but need further clinical studies. A better understanding of the effect of aging and anesthesia on the microcirculation can potentially assist in improving postoperative wound repair, thereby benefiting a growing older population.

## Acknowledgments

The authors thank Mamatha Damodarasamy M.S., Division of Gerontology and Geriatric Medicine, Department of Medicine, Harborview Medical Center, University of Washington, Seattle, Washington, for her assistance and Yotam Bentov, Tufts University, for his skillful graphical support in designing and creating the figures for this article.

This work was supported by the National Institute of Aging, Bethesda, Maryland (grant No. R03 AG042353 to Dr. Bentov), and by the Institute of Translational Health Sciences and the Department of Anesthesiology and Pain, University of Washington, Seattle, Washington (pilot grant to Dr. Bentov).

## Competing Interests

The authors declare no competing interests.

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