reasons, the decreased compensation for female anesthesiologists in the study may have a plausible explanation that was not proffered in the article.

Competing Interests

The authors declare no competing interests.

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Reference

1. Baird M, Daugherty L, Kumar KB, Arifkhanova A: Regional and gender differences and trends in the anesthesiologist workforce. Anesthesiology 2015; 123:997–1012

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In Reply:

We thank Pivalizza *et al.* for the valuable input based on their experiences that they provided on our original article.[1] We agree that one of the potential drivers of gender differences in earnings could be the types of hours worked and the costs and benefits associated with that type of work. Given that after-hour, weekend, and holiday time may be less desirable for many anesthesiologists, employers may need to pay a premium wage to staff their facilities during these times. And, as you argue, it may be the case that women are less likely to work these hours (based on preference or necessity), and this tendency to work traditional hours may account for meaningful differences in earnings.

We are limited by the data we collected in the survey and are therefore unable to examine all of the potential explanations for the gender earnings gap. We also attempted to limit speculation on aspects of the gender wage gap we could not measure by noting that some of the gap may be driven by individual preferences or constraints female anesthesiologists have, while some of it may be employer-driven. We did try to account for the types of facilities in which hours were worked and the percentage of time allocated to various types of care to account for some of the potential difference in the value of the time anesthesiologists are working. Unfortunately, we did not collect data on the times of day or days worked, so we cannot directly test your hypothesis. While we understand that your hypothesis is focused on the timing of call hours rather than on the total number of hours, we do have average weekly call hours and average call hours spent actively providing care. A quick check indicates that including average weekly call hours in the wage regression does reduce the gender earnings gap by $329 (please refer to the coefficient shown in table 7 in our article[1]) or 0.5% of the total earnings gap.

Future research should continue to explore the important drivers of earnings differences for physicians beyond what we were able to examine in our study.

Competing Interests

The authors declare no competing interests.

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Reference

1. Baird M, Daugherty L, Kumar KB, Arifkhanova A: Regional and gender differences and trends in the anesthesiologist workforce. Anesthesiology 2015; 123:997–1012

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Specific or Nonspecific? There Is Very Little Light at the End of the Tunnel

To the Editor:

The article by Fragiadakis *et al.*[1] is an interesting attempt in an everlasting quest to establish reliable markers for postsurgical recovery. The authors hypothesized that by testing presurgical immunologic parameters, individuals with expected delayed recovery can be identified. Whole blood was stimulated with several ligands aimed at mimicking an immunologic environment in blood during surgery followed by a correlational study linking the activation of several pathways to the psychosomatic measures of recovery (fatigue, pain, and functional impairment). In conclusion, the authors showed an impressive correlation between the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and studied clinical endpoints.

Activation of the immune system is often a nonspecific act. NF-κB is one of the most ubiquitous proteins activated by virtually any stressor or insult to the immune system. It would be expected that NF-κB–mediated pathway will be activated during surgery-induced stress. The study confirmed a pretty well-established link between psychosomatic markers of well-being and generalized systemic inflammatory response heralded by activation of NF-κB. However, the nature of the study precludes a final determination that suggested pathways are truly a cause, not a bystander, of the impaired recovery. Another important question is whether any manipulation lowering the activation of NF-κB benefits patients and speeds up postsurgical recovery? The authors also pointed out that most of the immunologic pathways are interconnected; thus, affecting one of them will have widespread consequences. Furthermore, how much can the activation of the immune system be decreased or increased by manipulation of NF-κB or Toll-like receptor (TLR) 4 system?[2] The authors described a three- to five-fold difference between individuals with respect to the level of activation. Such a wide range of responses can affect statistical correlational analysis and

suggests the high interindividual variability in response. It is unclear what the underlying causes of such differences are. Can polymorphism of TLR and several other cytokine receptors as described in previous literature play a role?[3–5] It is unclear from the study how to modify these inflammatory responses to surgery from the perspective of an anesthesiologist. Investigation of different immunologic compounds in sepsis and other critical care grade of insults to the immune system failed to modify any outcomes. This is attributed at least partially to lack of sufficient fidelity in testing of the status of the immune system as well as lack of understanding how clinical interventions will affect incredibly convoluted and interdependent responses of the immune system to stress. Additionally, if polymorphism is to be blamed for the wide range of responses, our ability to affect these responses is very limited due to the underlying patient characteristics.

The stimulation used to activate samples of blood was lipopolysaccharide and several cytokines. Lipopolysaccharide should not be present in bloodstream during the elective "clean" surgery.[6–8] It is also worth mentioning that the primary mediators of the activation are intracellular danger signals like adenosine, low pH, heat-shock proteins, or high-mobility group box protein 1.[5] Some of these mediators share activation *via* TLR4/CD14 system, while some of them do not. Moreover, the concentration of lipopolysaccharide (1 μg/ml) was exceptionally high. At such concentration, activation of apoptosis is abundant, while other pathways mediated by lipopolysaccharide are less pronounced.[9] Similar remarks can be made with respect to cytokine cocktail used for stimulation. Therefore, it should be concluded that the stimulation mixture used in the study is artificial and may never be seen during elective surgery.

Finally, testing of several psychosomatic variables is highly dependent on the preexisting psychologic makeup of patients. One would presume that at least some of the patients had significant physical impairment, pain, and fatigue. In the discussion, the authors identified this problem as a potential shortcoming of the study, and I want to further emphasize its importance.

The study by Fragiadakis *et al.* is a valuable resource. In previous work, they analyzed several data pertaining to activation of the immune system in the aftermath of the surgery. This study is a valuable addition, but their conclusions have to be taken with a grain of salt, considering the "artificial" stimulation regimen, correlational nature of the study, and the lack of long-term outcome data.

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Competing Interests

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In Reply:

We appreciate the opportunity to respond to Dr. Laudanski's critical commentary. The key result of our study suggests that signaling activity of the Toll-like receptor 4 (TLR4) in a presurgical whole blood sample predicts the speed at which patients regain function of their operated hip.[1] We agree with Dr. Laudanski that nuclear factor kappa-light-chain-enhancer of activated B cells is ubiquitous. However, our findings are related to specific signaling events downstream of TLR4, including mitogen activated protein kinase-activated protein kinase-2, cyclic adenosine monophophate response element-binding protein, and ribosomal protein S6, that occurred in a precisely phenotyped subset of monocytes.[1,2] The detected signaling patterns were highly specific with respect to pathway and cell type, which diverges from Dr. Laudanski's view that "activation of the immune system is often non-specific." Our findings further highlight the sentinel role of TLR4 in detecting tissue damage and mediating sterile inflammation and extend previous work by linking TLR4 activation patterns to patients' functional recovery.[3,4] Functional recovery is at the very core of current enhanced recovery after surgery protocols, and delays of weeks, as reported by us and others, matter greatly to patients and healthcare providers.[2,5,6] A blood test identifying patients at risk