Can a blood test of immune responsiveness predict speed of recovery from pain and dysfunction after surgery?

James C. Eisenach, MD [Editor-in-Chief] and
Anesthesiology Chair, ASA Section on Journals

FM James III [Professor of Anesthesiology]
Department of Anesthesiology, Wake Forest School of Medicine, Winston-Salem, NC

The current issue contains a remarkable report on a blood test to predict how quickly patients recover from surgery.[1] This and other medical journals are full of predictive tests and tools for a good reason - doctors and patients are interested in what to expect from disease and treatment (see for example a Web-based tool to predict your own likelihood of dying in the next 5 years at www.ubble.co.uk/riskcalculator). In addition to more informed decision making, better prediction is key to more targeted prevention, speedier diagnosis, more effective treatment, and better understanding of mechanisms of disease. Better predictive tools for morbidity and mortality after surgery are particularly needed, given the high risk of death and permanent disability in the perioperative period beyond the operating room doors.[2]

The report by Fragiadakis and colleagues[1] is remarkable for several reasons: its focus on patient centered outcomes, an exciting, innovative hypothesis, and the unexpected strength of the predictor it uncovers. Let's briefly review each.

Recovery from Surgery as a Primary Outcome

Most patients understand that surgery will cause temporary pain, dysfunction, and disability. They consider these burdens to be acceptable, provided the disability is not too great or lasts too long. We know surprisingly little beyond the broad strokes of this recovery process – considerable disability and pain for a few days, somewhat better in a few weeks, and most likely gone in a few months. What little we do know relies on cross-sectional incidence data with infrequent assessments – pain present yes or no at 2, 6, or 24 weeks, for example. This data-poor approach does little to help patients understand how quickly they will recover, and may well mislead the study mechanisms of recovery. An alternative approach, exemplified in the recent validation of an assessment tool to define disability-free survival after surgery,[3] examines both severity and time course of dysfunction.

The current study[1] is one of the first to examine patient centered outcomes at frequent intervals during the period of rapid recovery. They recorded 3 primary measures of recovery after hip arthroplasty, pain, hip dysfunction, and disability, every few days for up to 6 weeks after surgery. From this they calculated the speed of recovery in each of these three domains for each individual, and observed a significant correlation within patients in the speed of recovery from pain and from hip dysfunction after surgery, but no such correlation with the speed of recovery from disability / reduced quality of life. They then leveraged the large inter-individual variability in speed of recovery to examine predictors.

An Innovative Hypothesis

Surgery induces a neuro-hormonal stress response and an immune response. These two responses interact with each other to speed recovery, but can also create dysfunction. The literature over the past decades is replete with studies of isolated aspects of these responses following surgery. In their previous paper,[4] the current research group tested the novel hypothesis that cataloging the detailed types of signaling systems activated in the postoperative period within individual immune cell types might yield novel predictors of recovery, and that different aspects of recovery might be predicted by different cell types and different signaling systems within their repertoire of responses. The methods they employed are complex, expensive, and available at only a few centers, but allowed them to describe nearly as many individual phenotypes of immune response as there were phenotypes of slow to fast recovery. They observed a remarkably strong ability of one type of signaling induced by toll-like receptor 4 (TLR4) activation following surgery in two types of cells (CD14+ monocytes and dendritic cells) to predict individual recovery across the patient-centered domains.

In the current study[1] the investigators reasoned that perhaps the strength of this particular type of activation in these particular cells from factors released after surgery might also be seen in samples taken <u>before</u> surgery and stimulated exogenously *in vitro*. In other words, might not the strength of TLR4 activation and signaling in CD14+ monocytes in response to surgery reflect individual differences in immune cell response, which could be tested *in vitro* before surgery? So they cataloged immune cell type-specific responses to *in vitro* activation of key receptors, especially TLR4 activation by lipopolysaccharide (LPS), in preoperative samples from the same patients from their previous study. LPS is a convenient probe, although surgical trauma induces release of other substances, such as high mobility box 1 protein (HMBX-1) to stimulate TLR4 receptors. This hypothesis, that the "immune phenotype" of the patient could be measured before surgical injury, was largely supported – the strength of LPS induced signaling in CD14+ monocytes in preoperative samples also predicted speed of recovery in some domains.

An Amazingly Potent Predictor

In the primary analysis, the strength of LPS-induced activation of CD14+ monocytes in preoperative blood explained approximately 50% of the variability in recovery of hip function and in a secondary analysis it also explained a large amount of the variability in recovery from pain. Other signaling pathways and ligands were also examined, and in

secondary analyses they appeared likely to predict variability in recovery in hip function and pain, although no significant predictors were identified for recovery from disability and reduced quality of life.

The authors put this in perspective, noting that key predictors for recovery from pain after surgery, including age, sex, cognitive style, presence of pre-existing chronic pain, psychophysical response to pain stimuli, and genetics, account for only 10-15% the variability in cross sectional incidence of pain at times remote from surgery. So the current study using a single sample of blood was 3-4 times better at prediction than these known factors. This amazing predictive ability might well reflect the advantage of the data-rich measure of recovery using serial measurements compared to the traditional, data-poor cross sectional incidence approach or over-fitting predictive models to a single very small number of healthy patients with nearly uniform, rapid recovery. Only replication by this and other research groups in large number of patients with wider variability in recovery and using standard measures of sensitivity and specificity such as the area under the receiver operating curve will tell. Should these data be replicated, the authors speculate that a much simpler method to analyze a single signaling pathway in one subset of immune cells may be widely applied in the future.

One could speculate that the speed of recovery after surgery could be related to responsiveness of CD14+ monocytes to TLR4 agonists because of the proposed role of cells of this lineage and this pathway in postoperative cognitive dysfunction as they enter the brain[5] and in central sensitization of pain pathways.[6,7] Another contribution of the current study is to generate the hypothesis that the degree to which responsiveness of immune cells in peripheral blood prior to injury in animals predicts neuroinflammatory responses in the central nervous system and the mechanisms by which this association occurs. Finally, this work will likely spur research to determine whether a high-risk group can be easily identified for interventional trials and whether preoperative or postoperative immune modulation, such as with glucocorticoids[8] might speed recovery.

Patients and physicians want to know how much pain and dysfunction will occur after surgery, and how quick recovery will be. The current study uses patient-centered outcomes, frequent sampling during the time of recovery, and an innovative hypothesis to suggest that a blood test might possibly tell us a great deal about recovery from pain and hip function. This represents an important step forward in the prediction and potential manipulation of speed of recovery. Yet, biomarkers for arguably the most important measure, recovery from disability and reduced quality of life after surgery, remain elusive.

Acknowledgments

References

1. Fragiadakis GK, Gaudilliere B, Ganio EA, Aghaeepour N, Tingle M, Nolan GP, Angst MS. Patient-specific Immune States before Surgery are Strong Correlates of Surgical Recovery. Anesthesiology. 2015; 123:XXX.

2. Bartels K, Karhausen J, Clambey ET, Grenz A, Eltzschig HK. Perioperative organ injury. Anesthesiology. 2013; 119:1474–1489. [PubMed: 24126264]

3. Shulman SA, Myles PS, Chan MTV, McIlroy DR, Wallace S, Ponsford J. Measurement of Disability-free Survival after Surgery. Anesthesiology. 2015; 122:524–536. [PubMed: 25689757]

4. Gaudilliere B, Fragiadakis GK, Bruggner RV, Nicolau M, Finck R, Tingle M, Silva J, Ganio EA, Yeh CG, Maloney WJ, Huddleston JI, Goodman SB, Davis MM, Bendall SC, Fantl WJ, Angst MS, Nolan GP. Clinical recovery from surgery correlates with single-cell immune signatures. Sci Transl Med. 2014; 6:255ra131.

5. Vacas S, Degos V, Tracey KJ, Maze M. High-mobility group box 1 protein initiates postoperative cognitive decline by engaging bone marrow-derived macrophages. Anesthesiology. 2014; 120:1160–7. [PubMed: 24162463]

6. Cao L, Tanga FY, Deleo JA. The contributing role of CD14 in toll-like receptor 4 dependent neuropathic pain. Neuroscience. 2009; 158:896–903. [PubMed: 18976692]

7. Agalave NM, Larsson M, Abdelmoaty S, Su J, Baharpoor A, Lundback P, Palmblad K, Andersson U, Harris H, Svensson CI. Spinal HMGB1 induces TLR4-mediated long-lasting hypersensitivity and glial activation and regulates pain-like behavior in experimental arthritis. Pain. 2014; 155:1802–13. [PubMed: 24954167]

8. de la Motte L, Kehlet H, Vogt K, Nielsen CH, Groenvall JB, Nielsen HB, Andersen A, Schroeder TV, Lonn L. Preoperative methylprednisolone enhances recovery after endovascular aortic repair: a randomized, double-blind, placebo-controlled clinical trial. Ann Surg. 2014; 260:540–8. discussion 548-9. [PubMed: 25115430]
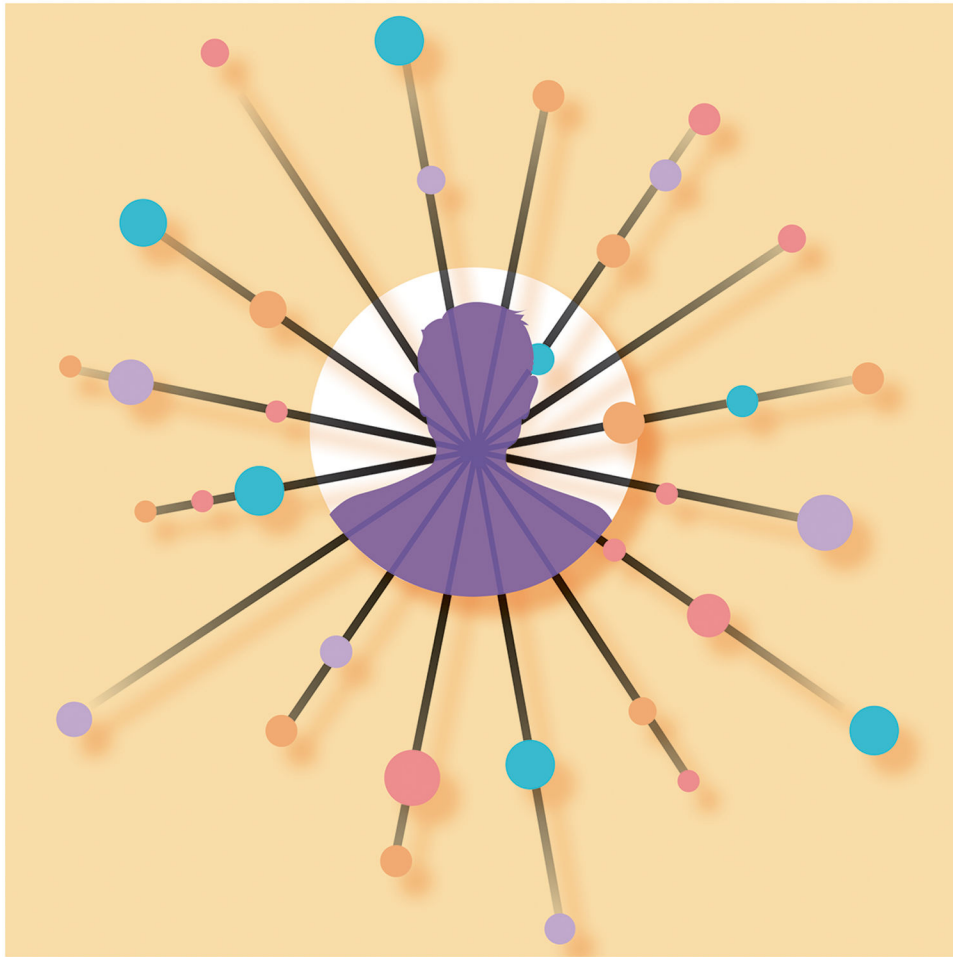
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