Published in final edited form as:

J Cardiovasc Transl Res. 2008 ; 1(2): 171–173. doi:10.1007/s12265-008-9018-0.

Understanding the Transition to Acute Illness:

The Promise of Perioperative Genomics

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Abstract

Over the last decades, tremendous advances have been made in understanding the genomic basis of a large number of chronic human diseases. Such advances were made possible by studying large numbers of patients over relatively long periods of time. It is increasingly recognized that acute robust stress stimulates pathways activated in chronic disease, facilitating mechanistic studies in much shorter time frames. A new field of molecular medicine, called perioperative genomics, uses robust surgical stress as a perturbation designed to explore such mechanisms. This new field is described briefly below.

Keywords

Perioperative Care; Genomics; Risk Assessment; Postoperative Complications; Acute Disease

Importance of the Perioperative Period

More than 40 million patients undergo surgery in the United States each year, and that number is expected to rise by 25% by 2020 [1]. In terms of monetary costs, the numbers are staggering with current estimates of \$450 billion spent annually in the perioperative period [2]. Adverse events such as perioperative myocardial injury, renal failure, cognitive dysfunction, and stroke are devastating. Cardiovascular complications can occur after procedures even in patients without known heart disease. This problem is increasing as the population ages and cardiac risk factors, such as hypertension and diabetes mellitus, become more prevalent.

Outside of its overall economic impact, the perioperative period provides an ideal model of acute illness. Although a dynamic and complicated environment, the operating room offers unique advantages for studying patients. In this environment, physiologic changes from baseline with robust stress can be prospectively quantified (e.g., hemo-dynamic parameters or plasma biomarkers). Even perturbations such as drug administration and organ ischemic time can be studied. Exposure to extremes of physiology offers the advantage of revealing (uncovering) phenotypes which might otherwise be dormant or take years to be expressed. Indeed, for patients at risk for proinflammatory activation, the operating room may transition an otherwise healthy individual into one who is acutely ill and at risk for postoperative complications and organ dysfunction.

Coronary thrombosis is one example of how perioperative genomics can aid our understanding of illness beyond the operating room. There are more than one million spontaneous myocardial infarctions annually in the United States, but despite this incidence, molecular events triggering

this event remain largely unknown. Because it is impossible to predict when acute coronary plaque rupture will occur, studying perturbations underlying the transition from stable to unstable plaque is unfeasible in an outpatient setting. There is a predictable rate of perioperative myocardial infarction after surgery (up to 20–25% after noncardiac vascular surgery [3], for instance), and in a relatively controlled environment, patients can be profiled in both clinical and molecular detail before and after surgical stress to dissect pathways involved in the pathogenesis of thrombosis. A similar paradigm would operate for other cardiovascular disorders, such as cardiac arrhythmias and cerebrovascular events.

How Do We Study Patients in the Perioperative Period?

Perioperative genomics utilizes familiar high-throughput “-omic” technologies (e.g., transcriptomics, metabolic profiling) to study the transition from “health” to “illness.” These techniques are used in a novel fashion by profiling the *same* patients over a very short period of time (i.e., minutes to days). This is ideal for small molecule markers, such as metabolic intermediates or plasma proteins, where marked interindividual differences in concentrations may exist, as patients can serve as their own baseline control. As mediators and end-products of all diverse signaling pathways bombard the system, small molecule “-omics” (i.e., metabolomics and proteomics) have the potential to deconvolute pathways responsible for maladaptive stress responses. In addition, intraoperative access to both tissue as well as efferent and afferent blood-feeding specific organs (such as the arterial and coronary sinus venous blood to measure transcatheter metabolism) has the potential to provide information on organ-specific changes in metabolic and protein profiles in response to robust surgical stress.

As inflammation is a universal process in the perioperative period, which is clearly linked to many postoperative complications, gene expression analysis using peripheral leukocyte profiling has considerable potential to improve care. Peripheral gene expression signatures have been shown to change acutely with surgery [4], and it is possible that some combination of “baseline” and “poststress” leukocyte profiles may be proven capable of predicting patients at high risk for complications with a known inflammatory component, such as atrial fibrillation or myocardial injury. Furthermore, leukocyte activation patterns may help gain mechanistic understanding of how inflammation is involved in the process of end-organ dysfunction (e.g., humorally mediated or cytotoxicity).

Ultimately, improved mechanistic understanding of molecular pathways of maladaptive stress responses will guide the identification of *genes* involved in such predispositions. In this way, the other “-omic” platforms will feedback to the genetic level, allowing the development of screening tests to help guide management by predicting patients at risk for complications (and what type), potentially altering perioperative management (e.g., selective use of antiarrhythmics in patients at high risk for atrial fibrillation, prophylactic antiinflammatory drugs to suppress predicted overly robust immune activation, etc.). Ultimately, whole genome analysis of a large cohort of patients undergoing surgery may prove to be the most effective method of identifying candidate genes. Such candidates will require validation, either by replication in another population or, as recently shown for postcardiac surgery neurocognitive dysfunction, by complementing data from across “-omic” platforms [5].

Studies to date have already yielded significant results. Perioperative complications, including acute kidney injury [6], postoperative bleeding [7], myocardial injury [8], and stroke [9], have been correlated with a variety of proinflammatory genotypes. The fact that a number of these genes (and/or gene products) identified in these association studies, such as the inflammatory mediators IL-6 and CRP as well as the endothelial adhesion molecules E-selectin and ICAM, have been previously implicated in the natural history of chronic inflammatory diseases provides proof of principle that this model is robust and can be extrapolated beyond the

perioperative context. Identification of such candidate genes and polymorphisms by studying adverse *acute* outcomes can serve as a starting point for establishing which genes are important in chronic disease progression.

Because the operating room is such a robust proinflammatory environment, candidate genes thus far chosen for investigation have largely focused around these and related pathways. In the future, however, a large-scale whole genome analysis of patients presenting to the operating room may serve to overcome this limitation. Information from such an undertaking may reveal mechanistic pathways associated with disease not appreciated by traditional biased approaches.

In conclusion, the perioperative environment holds considerable promise, a promise which has only begun to be realized by clinical and genomics investigators. Clinical factors alone do not account for all variability in individual perioperative risk. Translational genomics has the potential to improve prediction, and perhaps more importantly, offer mechanistic insight into the physiology of the transition from health to acute perioperative illness.

References

1. Mangano DT. Perioperative medicine: NHLBI working group deliberations and recommendations. *Journal of Cardiothoracic and Vascular Anesthesia* 2004;18(1):1–6. [PubMed: 14973791]
2. Kozak LJ, Owings MF, Hall MJ. National Hospital Discharge Survey: 2002 annual summary with detailed diagnosis and procedure data. *Vital and Health Statistics* 2005;13(158):1–199. [PubMed: 15853196]
3. McFalls EO, et al. Coronary-artery revascularization before elective major vascular surgery. *New England Journal of Medicine* 2004;351(27):2795–2804. [PubMed: 15625331]
4. Feezor RJ, et al. Genomic and proteomic determinants of outcome in patients undergoing thoracoabdominal aortic aneurysm repair. *Journal of Immunology* 2004;172(11):7103–7109.
5. Mathew JP, et al. Genetic variants in P-selectin and C-reactive protein influence susceptibility to cognitive decline after cardiac surgery. *Journal of the American College of Cardiology* 2007;49(19):1934–1942. [PubMed: 17498578]
6. Stafford-Smith M, et al. Association of genetic polymorphisms with risk of renal injury after coronary bypass graft surgery. *American Journal of Kidney Diseases* 2005;45(3):519–530. [PubMed: 15754274]
7. Welsby IJ, et al. Genetic factors contribute to bleeding after cardiac surgery. *Journal of Thrombosis and Haemostasis* 2005;3(6):1206–1212. [PubMed: 15892865]
8. Podgoreanu MV, et al. Inflammatory gene polymorphisms and risk of postoperative myocardial infarction after cardiac surgery. *Circulation* 2006;114(1 Suppl):I275–I281. [PubMed: 16820586]
9. Grocott HP, et al. Genetic polymorphisms and the risk of stroke after cardiac surgery. *Stroke* 2005;36(9):1854–1858. [PubMed: 16051899]