Impact of Genetics on Perioperative Outcome: The Long and Short of It

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Perioperative organ dysfunction in the myocardium, pulmonary, neurologic and renal systems varies based on techniques used for assessment, and ranges from mild (sometimes silent) injury and enzyme leak to profound organ injury, coma or death. While it has been easy to understand the implications of the more immediate and severe injury occurring in the perioperative period, it has only more recently been noted that injury thought to be transient may also have long-term implications.

The measurable response or outcome associated with perioperative stress, anesthetic agents, hemodynamic challenges, and the pharmacopeia response is strikingly variable. Current risk stratification based on patient demographics, comorbidities, physiologic reserve, and procedural variables explains only a small part of observed variability in incidence of perioperative complications. Evidence is accumulating that genetic variations, or polymorphisms, can significantly affect an individual's susceptibility to adverse postoperative events. A new field, coined *perioperative genomics*, aims to apply functional genomic approaches to uncover the biological mechanisms underlying why similar patients have dramatically different outcomes after surgery.

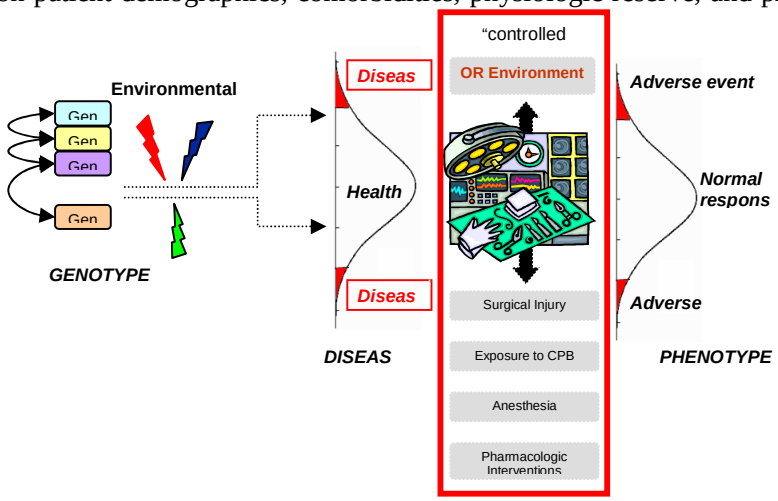

Figure 1: Interaction between genetics, environmental factors, and perioperative controlled trauma alter the probability of periop events.

In the perioperative period, patients with various burdens of complex comorbid conditions are exposed to "controlled trauma" in the operating room environment, consisting of surgical injury, anesthesia, pharmacologic interventions, and, in the case of cardiac surgery, extracorporeal circulation. As an environmental stimulus, perioperative injury can be characterized as: 1) robust and extreme; 2) multifactorial (i.e., outcomes are the cumulative result of both *direct* initial operative injury and the host's *responses* to injury, both interacting with an individual's genetic background); 3) quantifiable (e.g., for cardiac surgery, duration of cardiopulmonary bypass [CPB] and aortic cross-clamping, number of coronary bypass grafts, volume, type and route of cardioplegia, perioperative medications, and so on); 4) defined onset of exposure; and 5) defined time course, usually shorter than for common chronic diseases, although in some cases predictive of future natural history of disease (e.g., cognitive decline). Characteristic phenotypes studied by perioperative genomics include immediate postoperative adverse events (incidence/ severity of organ dysfunction), as well as long-term outcomes. Overall, an individual's genetic susceptibility to adverse perioperative events stems not only from genetic contributions to the development of comorbid risk factors (like CAD) during the patient's lifetime, but also from genetic variability in specific biological pathways participating in pathophysiological events during and after surgery. Thus, the term *perioperative genomics* is justified by a combination of unique environmental insults and postoperative phenotypes that characterize surgical and critically ill patient populations.

Specific Organ System Information

Perioperative Myocardial Infarction

The inflammatory response triggered by cardiac surgery with cardiopulmonary bypass (CPB) is a primary mechanism in the pathogenesis of postoperative myocardial infarction (PMI), a multifactorial disorder with significant inter-patient variability poorly predicted by clinical and procedural factors. We tested the hypothesis

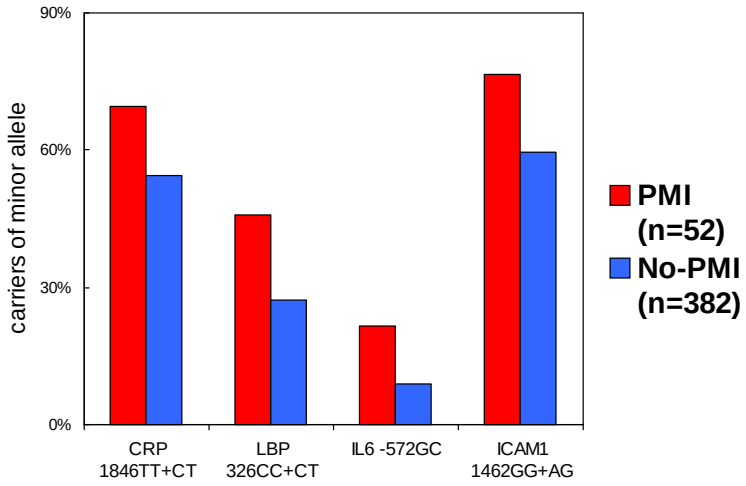

Figure 2: Genetic variants associated with an increased risk of perioperative MI.

that candidate gene polymorphisms in inflammatory pathways contribute to risk of PMI after cardiac surgery. We genotyped 48 polymorphisms from 23 candidate genes in a prospective cohort of 434 patients undergoing elective cardiac surgery with CPB. PMI was defined as creatine kinase-MB isoenzyme level > or = 10x upper limit of normal at 24 hours postoperatively. A 2-step analysis strategy was used: marker selection, followed by model building. To minimize false-positive associations, we adjusted for multiple testing by permutation analysis, Bonferroni correction, and controlling the false discovery rate; 52 patients (12%) experienced PMI. After adjusting for multiple comparisons and clinical risk factors, 4 polymorphisms were found to be independent predictors of PMI (adjusted P<0.05; false discovery rate <10%). These gene variants (two of which are included in Figure 2) encode the proinflammatory cytokine interleukin 6 (IL6 -572G>C; odds ratio [OR], 2.47), and 2 adhesion molecules: intercellular adhesion molecule-1 (ICAM1 Lys469Glu; OR, 1.88), and E-selectin (SELE 98G>T; OR, 0.16). The inclusion of genotypic information from these polymorphisms improved prediction models for PMI based on traditional risk factors alone (C-statistic 0.764 versus 0.703). Functional genetic variants in cytokine and leukocyte-endothelial interaction pathways are independently associated with severity of myonecrosis after cardiac surgery. This may aid in preoperative identification of high-risk cardiac surgical patients and development of novel cardioprotective strategies.

Perioperative Stroke Genetics

Patients undergoing cardiac surgery utilizing cardiopulmonary bypass surgery were studied. DNA was isolated from preoperative blood and analyzed for 26 different single-nucleotide polymorphisms. Multivariable logistic regression modeling was used to determine the association of clinical and genetic characteristics with stroke. Permutation analysis was used to adjust for multiple comparisons inherent in genetic association studies. A total of 1635 patients experiencing 28 strokes (1.7%) were included in the final genetic model. The combination of the 2 minor alleles of C-reactive protein (CRP; 3'UTR 1846C/T) and interleukin-6 (IL-6; -174G/C) polymorphisms, occurring in 583 (35.7%) patients, was significantly associated with stroke (odds ratio, 3.3; 95% CI, 1.4 to 8.1; P=0.0023). In a multivariable logistic model adjusting for age, the CRP and IL-6 single-nucleotide polymorphism combination remained significantly associated with stroke (P=0.0020). We demonstrate that common genetic variants of CRP (3'UTR 1846C/T) and IL-6 (-174G/C) are significantly associated with the risk of stroke after cardiac surgery, suggesting a pivotal role of inflammation in post-cardiac surgery stroke.

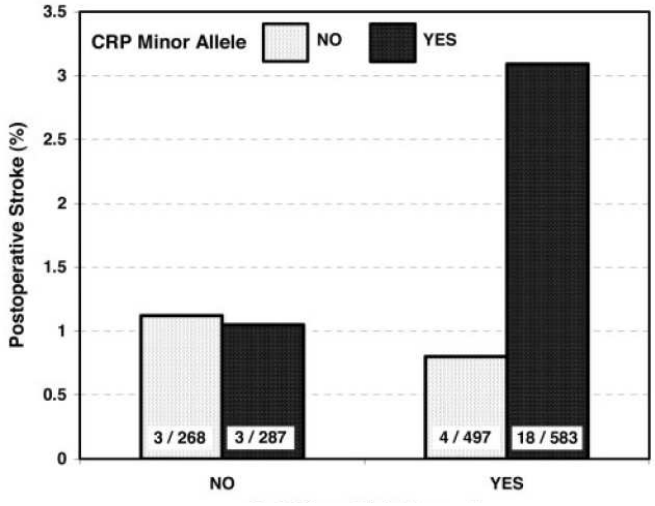

Figure 3: Incidence of postoperative stroke in patients possessing the combination of SNPs in both CRP (3'UTR 1846C/T) and IL-6 (--174G/C). This SNP combination significantly increased the risk of stroke (OR, 3.3; 95% CI, 1.4 to 8.1; *P*=0.0023).

Genetics of Perioperative Cognitive Decline

Cognitive decline is a common complication of coronary artery bypass graft (CABG) surgery and is associated with a reduced quality of life. We hypothesized that candidate gene polymorphisms in biologic pathways regulating inflammation, cell matrix adhesion/interaction, coagulation-thrombosis, lipid metabolism, and vascular reactivity are associated with postoperative cognitive deficit (POCD). In a prospective cohort study of 513 patients (86% European American) undergoing CABG surgery with cardiopulmonary bypass; a panel of 37 single-nucleotide polymorphisms (SNPs) was genotyped by mass spectrometry. Association between these SNPs and cognitive deficit at 6 weeks after surgery was tested using multiple logistic regression accounting for age, level of education, baseline cognition, and population structure. Permutation analysis was used to account for multiple testing. RESULTS: We found that minor alleles of the CRP 1059G/C SNP (odds ratio [OR] 0.37, 95% confidence interval [CI] 0.16 to 0.78; p = 0.013) and the SELP 1087G/A SNP (OR 0.51, 95% CI 0.30 to 0.85; p = 0.011) were associated with a reduction in cognitive deficit in European Americans (n = 443). The absolute risk reduction in the observed incidence of POCD was 20.6% for carriers of the CRP 1059C allele and 15.2% for carriers of the SELP 1087A allele. Perioperative serum C-reactive protein (CRP) and degree of platelet activation were also significantly lower in patients with a copy of the minor alleles, providing biologic support for the observed allelic association.

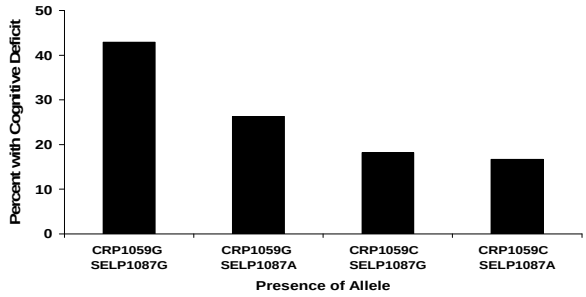

Figure 4. Incidence of postoperative cognitive deficit by *CRP* 1059G/C and *SELP* 1087G/A genotypes. The incidence of cognitive deficit was 16.7% in carriers of minor alleles at both of these loci compared to 42.9% in patients homozygous for the major allele.

The results suggest a contribution of P-selectin and CRP genes in modulating susceptibility to cognitive decline after cardiac surgery, with potential implications for identifying populations at risk who might benefit from targeted perioperative anti-inflammatory strategies.

Genetics of Perioperative Bleeding

Postoperative bleeding remains a common, serious problem for cardiac surgery patients, with striking inter-patient variability poorly explained by clinical, procedural, and biological markers. Objective: We tested the hypothesis that genetic polymorphisms of coagulation proteins and platelet glycoproteins are associated with bleeding after cardiac surgery.

Seven hundred and eighty patients undergoing aortocoronary surgery with cardiopulmonary bypass were studied. Clinical covariates previously associated with bleeding were recorded and DNA isolated from preoperative blood. Matrix Assisted Laser Desorption/Ionization, Time-Of-Flight (MALDI-TOF) mass spectroscopy or polymerase chain reaction were used for genotype analysis. Multivariable linear regression modeling, including all genetic main effects and two way gene-gene interactions, related clinical and genetic predictors to bleeding from the thorax and mediastinum. Results: Nineteen candidate polymorphisms were assessed; seven [GPIaIIa 52C>T and 807C>T, GPIba 524C>T, tissue factor 603A>G, prothrombin 20210G>A, tissue factor pathway inhibitor 399C>T, and angiotensin converting enzyme (ACE) deletion/insertion] demonstrate

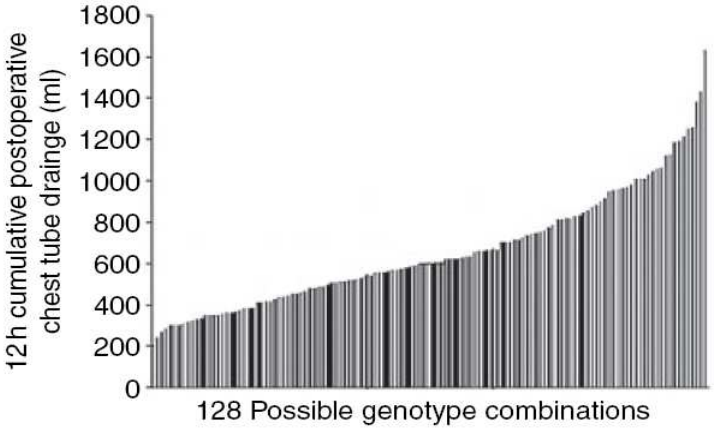

Figure 5. Twelve hour postoperative chest tube drainage predicted from statistical model for all 128 (2^7) possible allele combinations of seven prothrombotic polymorphisms associated with postoperative bleeding.

significant association with bleeding ($P < 0.01$).Adding genetic to clinical predictors results improves the model, doubling overall ability to predict

We identified seven genetic polymorphisms associated with bleeding after cardiac surgery. Genetic factors appear primarily independent of, and explain at least as much variation in bleeding as clinical covariates; combining genetic and clinical factors double our ability to predict bleeding after cardiac surgery. Accounting for genotype may be necessary when stratifying risk of bleeding after cardiac surgery.

Conclusions

The challenge for coming years is the integration of genetic information to provide a better understanding of the intact organism, its responses to various environmental stimuli, and translating the knowledge into daily clinical practice. For the perioperative physician, this will translate into prospective risk assessment based on genomic profiling of markers important in inflammatory, thrombotic, neurologic, and vascular responses to perioperative stress, allowing the development of more comprehensive cross-disciplinary treatment paradigms for stress-induced organ dysfunction in each individual patient.

References

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