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Pharmacogenomics and End-Organ Susceptibility to Injury in the Perioperative Period

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Abstract

Genomic medicine has provided new mechanistic understanding for many complex diseases over the last 5–10 years. More recently genomic approaches have been applied to the perioperative paradigm, facilitating identification of patients at high risk for adverse events, as well as those who will respond better/worse to specific pharmacologic therapies. The consistent biological theme emerging is that while inflammation is important in healing from surgical trauma, patients who are too robustly proinflammatory appear to be at higher risk for adverse perioperative events. Precise predictors of each adverse event are being elucidated so that corrective therapeutics can be instituted to improve outcomes in high-risk patients. While the field of perioperative genomics could be considered in its infancy, such approaches are the wave of the future.

Keywords

Anesthesiology; adverse event; genetic; genomic; human; intensive care; outcome; prediction; surgery

Introduction

The ability to identify patients at high risk for perioperative and peri-procedure adverse events is critical so that interventions can be identified that optimize outcome. Over 40 million patients undergo surgery annually in the U.S., resulting in costs of \$450 billion per year [1], a number which continues to rise with the aging population worldwide. The operating room is a unique setting where acute, robust, and generalized proinflammatory cascades are initiated on a reproducible basis (see perioperative physiology discussion below). An advantage of using a robust surgical perturbation to elucidate novel mechanisms underlying perioperative adverse events is that the surgical stressor is usually elective, predictable (occurs on the day of surgery), graded (magnitude of insult increases with length of surgery, cardiopulmonary bypass [CPB] and/or aortic cross-clamp or other ischemia/reperfusion injury), adverse cardiovascular outcomes peak within days (e.g. perioperative myocardial ischemia/infarction peaks on postoperative day 1–2), sufficiently common to be

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studied (e.g. 7–15% of cardiac surgery patients have perioperative myocardial ischemia/injury [2,3]), and patients are routinely invasively monitored and treated using routes that facilitate obtaining unique human specimens (e.g. arterial and coronary sinus blood, human atrium, adipose tissue, etc.). These characteristics make the surgical environment a unique perturbation capable of revealing latent phenotypes and mechanisms underlying acute perioperative adverse events.

Despite advances in surgical, anesthetic, and cardioprotective strategies, the incidence of perioperative adverse events continues to be significant, and is associated with reduced short and long-term survival [4]. Since all surgical patients are exposed to perturbations that potentially activate inflammation, coagulation, and other stress-related pathways, but only a subset experience adverse perioperative events (even after controlling for co-existent disease), a genetic component is likely involved. To explore this further, the next sections will review general genetic/genomic concepts, complex physiologic pathways activated during surgery, generalizability of the perioperative physiology paradigm, effects of genetic variability on such physiology, and finally data associating genetic variants related to adverse perioperative events.

Genetic and Genomic Analysis

In simplistic terms, genetics refers to gene variants in DNA. Single nucleotide polymorphisms (SNPs) are DNA variants that alter a single nucleotide in the sequence of DNA. Often SNPs travel in groups together in genes, a concept called a haplotype block. Other DNA variants include insertions and/or deletions of “chunks” of DNA as well. DNA variants may be transcribed into altered RNA sequences and/or alter levels of otherwise “normal” RNA, findings that can be determined using traditional molecular biology approaches of measuring RNA levels and examining transcription rates, splice variant production, and RNA stability. Since altered RNA may be translated into altered proteins, either in level or function, biochemical approaches can be utilized to determine protein structure and function. Finally, since proteins work in concert to coordinate function of cells and organs, examination of resulting metabolites within the cell can be very informative.

What is genomics and how does it differ from genetics? Genomics can be described as the “ramping up” of genetics, in that it represents analysis of many genetic processes and pathways concurrently, not one-by-one (Figure 1). For example, genomic analysis of DNA variants would include examination of many SNPs across all chromosomes and mitochondria as well as analysis of many haplotypes; such studies might include whole genome-wide association approaches. Genomic analysis at the RNA level is provided by microarrays where thousands of RNA species are examined simultaneously, with changes in patterns of RNA expression compared over time or between conditions. Analysis of many proteins simultaneously is called proteomics and simultaneous analysis of metabolic pathways is called metabolomics. The advantage of using genomic approaches is that patterns of genes, RNA, proteins, or metabolites can be identified that predict disease or response to drug therapy. Since genomic analysis does not presume the role of physiologic pathways already known exist in medicine, it is thought to be a more unbiased way of analyzing the effect of drugs and/or disease. Instead, patterns of DNA, RNA, proteins, or metabolites are identified which better characterize physiologic states. The end result of this era of medical research will be the subdividing of major diseases (e.g. diabetes) into many more sub-diseases, each characterized in more refined ways. Ultimately this should have positive benefits for patients since it will more accurately predict whether specific pharmacologic drugs work in some subtypes of disease *versus* others—bringing a greater likelihood that initial therapy will benefit a given patient. This represents a new way of thinking about personalized medicine. However, such progress cannot be made until one

connects genetic variants with biological pathways activated in complex disease or (in our case), perioperative physiology resulting in adverse events. This process is called a systems biology approach and is an important part of analyzing genomic data. But to be most effective, systems biology analyses should be guided by physiology principles and acknowledged intersections between biochemical pathways. Hence we next review perioperative physiology, highlighting known relevant pathways activated during surgery that may lead to adverse events.

Perioperative Physiology

Anesthetized surgery patients undergo physical trauma, including events such as skin incision, vascular cannulation, and excision of partial/total organs (Figure 2). In cardiac surgery, cannulation is required so that venous blood returning from the body to the heart is able to drain passively to the CPB machine, from whence oxygenated blood is then pumped back to the aorta. Atriotomy alone has been shown to induce right atrial edema [5], accompanied by 2-fold increase in myeloperoxidase (MPO) activity (1.5-fold even with pericardiotomy alone) and neutrophil invasion; inhomogeneity of atrial conduction correlates with MPO activity [5]. In dog models, the degree of atrial edema correlates with incidence of new-onset postoperative atrial fibrillation [5], a common and vexing problem for 25–50% of patients after cardiac surgery. Stress hormones increase precipitously (2–10-fold) during cardiac surgery, including catecholamines and cortisol-mediated responses [6,7]. Robust sympathetic stimulation results in norepinephrine spill-over from nerve fibers during surgery, while unphysiologic non-pulsatile flow occurring during CPB is thought to increase epinephrine levels. Generalized proinflammatory cascades are also robustly activated [8]. Hyperglycemia is common during surgery and has been shown to result in adverse perioperative outcomes including death, neurologic injury, and infection in both diabetics and non-diabetics [9,10]. Maintenance of euglycemia via continuous intra/postoperative insulin infusions is currently standard during many surgeries; this practice has been shown to be of benefit in critical care settings as well [11]. Tight glucose control is important since hyperglycemia mediates release of IL-6 from monocytes via upregulation of protein kinase C [12], amplifying the proinflammatory state.

Surgery patients are often starved (not fed) for 12 hours prior to surgery, inducing a catabolic state designed to provide energy through various mechanisms [13]; this process is exaggerated by surgical trauma [14]. The metabolic response to surgery, trauma, and sepsis is characterized by muscle protein breakdown and mobilization of amino acids, thought to furnish glutamine and other amino acids to the immune system, gut, and liver [15]. This hypercatabolic response is characterized by increased metabolic rate, severe muscle wasting and negative nitrogen balance [16]. Interestingly, total parenteral nutrition does not counteract the decrease in muscle protein synthesis observed 24hrs postoperatively [17]. A hepatic catabolic stress response continues for up to 1 week post uncomplicated surgery, characterized by twice as much amino-nitrogen excreted as urea-nitrogen compared to control; hence amino acids are lost that otherwise could have been used for protein synthesis [18].

Temporary limb/organ ischemia is induced for defined times during various surgeries. The length of ischemia (in the case of cardiac surgery this is tracked as aortic cross-clamp time), is a clinical variable that predicts perioperative myocardial events [3] and therefore must be taken into account as a co-variate in analysis of this endpoint. Both myocardial ischemia and catecholamine-induced stress induce IL-6 and tissue factor (TF) production in patients with coronary artery disease [19], and decrease the PI3-kinase survival pathway [20]. Ischemia inactivates oxidative phosphorylation, leading to loss of adenine nucleotides and cytochrome c, accumulation of free phosphate, fatty acids, lactic acid, increased cellular calcium, and a

decrease in cellular pH [21]. Interleukin-8 (IL-8) promotes adhesion, activation, and transmigration of polymorphonuclear leukocytes (PMNs) associated with production of tissue injury in reperfused myocardium, a process attenuated by hypoxia induction factor-1 (HIF-1) activation [22].

In addition to ischemia, termination of ischemia results in reperfusion injury, characterized by production of free radicals, lipid peroxidation (oxygen free radicals attack double bonds in polyunsaturated fatty acids leading to formation of conjugated dienes), and loss of cardiolipin (a mitochondrial protein) [23]. Upon reperfusion, oxygen interacts with the damaged mitochondrial respiratory chain to produce a burst of reactive oxygen species leading to ischemia/reperfusion (I/R) injury [24]. I/R induces translocation of d-protein kinase C (dPKC; the redox sensitive PKC isoform) to cardiac mitochondria, preventing pyruvate dehydrogenase reactivation (via phosphorylation of the aE1 subunit of pyruvate dehydrogenase [PDH] via PDH kinase 2) [25]. Apoptosis-inducing factor is a ubiquitous flavoprotein localized in the mitochondrial intermembrane space that is important in protecting against peroxide injury in heart [26]. Oxidant tolerance of myocytes (made inflammatory by I/R) is dependent on induction of manganese superoxide dismutase (Mn-SOD) and endothelial nitric oxide synthetase (eNOS) [27]. I/R also activates coagulation pathways by increasing TF mRNA/protein [28]. The importance of TF in I/R injury is demonstrated by decreased infarct size in rabbits given a TF monoclonal antibody before or during ischemia and/or by functionally inhibiting thrombin; in contrast, defibrinogenating rabbits with ancrod has no effect on infarct size [28]. A mechanism for increasing TF appears to be H₂O₂ and thrombin-induced increases in the stress transcription factor Sgk-1 which enhances TF expression and procoagulant activity [29]. Confirming this observation are data demonstrating that antioxidant therapy at the time of I/R, decreases TF expression [29].

Surgery activates a complex set of humoral and cellular interactions via numerous pathways; these pathways are redundant and amplification occurs [30]. Monocyte activation (CD11b expression) occurs with CPB and is associated with postoperative atrial fibrillation and renal dysfunction [31]. Macrophages become proinflammatory when activated by calcium during surgery [32]. Calcium crystals are internalized into vacuoles of human monocyte-derived macrophages and are associated with secretion of proinflammatory cytokines tumor necrosis factor (TNF)- α , IL1b, and IL-8 [32]. CD163 (a macrophage scavenger receptor for uptake of haptoglobin-hemoglobin [Hp-Hb] complexes, and an overall anti-inflammatory molecule) increases in plasma and surface in patients undergoing coronary artery bypass graft (CABG) surgery [33]. Specifically glucocorticoids, IL-10, and IL-6 increase macrophage CD163; soluble CD163 increases by 1 hour post aortic cross-clamp release, with significant increases in monocyte CD163 occurring on postoperative day 1 [33]. In addition, inflammation and coagulation pathways are closely linked.

Inflammatory cytokines and cytokine networks are intimately associated with injury response systems, including the coagulation system that controls fibrinogenesis and fibrinolysis, proteases, metabolites, fibrin, thrombin, plasmin, fibrinopeptide, and fibrin metabolites, etc [34]. Central to coagulation is the transmembrane glycoprotein tissue factor (TF), which controls clot formation via the extrinsic pathway. Cytokines IL-1, TNF, IL-6 are known to induce TF in a variety of cells; conversely, fibrin and fibrin degradation products are known to induce expression of proinflammatory cytokines such as IL-6, and IL-8 [34]. In an analogous situation, inducible myocardial ischemia increases plasma levels of biomarkers, especially IL-6 and TF leading to persistent left ventricular (LV) dysfunction during recovery from dobutamine stress testing [35].

Finally, intravascular hemolysis with increased extravascular plasma hemoglobin (Hb) occurs during surgery, especially cardiac surgery with CPB. Excess cell free plasma Hb results in Hb-mediated NO scavenging and resultant endothelial dysfunction [36]. Since the reaction of NO with intravascular oxyHb (16g/dL) is fast ($10^7 \text{ M}^{-1}\text{s}^{-1}$) and irreversible, most NO produced by vascular endothelium is immediately scavenged by free Hb and therefore incapable of paracrine diffusion to smooth muscle. NO plays a major role in vascular homeostasis (smooth muscle relaxation and vasomotor tone, endothelial adhesion molecule expression, and platelet activation and aggregation), so excess Hb results in dystonias of gastrointestinal, cardiovascular, pulmonary, and urogenital systems, as well as clotting disorders [36]. Erythrocyte hemolysis also leads to decreased NO synthesis since arginase increases conversion of L-arginine to ornithine [36]. Lack of functional NO in local vascular beds leads to the no-reflow phenomenon, a finding sometimes noted after successful revascularization. A recent study demonstrated that the NO donor, sodium nitroprusside, facilitates better coronary flow in such situations [37].

Generalizability of the Perioperative Paradigm

Studies of exhaustive exercise and sepsis suggest perioperative studies in “healthy” individuals provide an excellent environment where new mechanisms of human physiology can be explored. As a model of exhaustive exercise, half-marathon runners have been examined at baseline (prior to a race), immediately after the race, and 24 hours later, with blood and urine examined for inflammatory markers. Peripheral mononuclear blood cells have been examined using a microarray approach, with upregulation of mitogen-activated protein kinase-activated protein kinase-2 (MAPKAP-K2), L-selectin, IL-1 receptor antagonist (IL-1ra), and thioredoxin (which may play a role in oxidant defense) observed, as well as downregulation of CD81 (which promotes B and T cell activation and T cell maturation) [38]. Others have found increases in cortisol and adrenaline, increased cytokines (TNF- α , IL-1, IL-6, IL-8, IL-1 receptor antagonist [IL-1ra]) in plasma or urine (levels which decrease by the following day [39,40]), and generation of reactive oxygen/nitrogen species [41]. Acute endurance exercise also affects gene expression of metabolic transcriptional co-activators and transcription factors [42]. Effects on the immune system and inflammation resulting from exhaustive exercise are similar in many ways to findings from the perioperative environment.

In addition, the inflammatory response to sepsis has been extensively studied, most commonly by administering bacterial endotoxin IV over 24hr to healthy volunteers. Acute-phase cytokines in serum have been studied [43], as well as a recent network-based approach using biologic targets defined from 200,000 published articles [44]. In general, 2–4 hours post endotoxin, secreted proinflammatory cytokines and chemokines increase (TNF, IL1A, IL1B, GRO α , GRO-b, MCP-1, IL-8), consistent with early activation of innate immunity [44]. Decreased expression of several nuclear factor kappa/relA family of transcription factors (NFKB1, NFKB2, RELA, RELB) reach their zenith during this time period. The 4–6 hrs post endotoxin time is critical, with increased expression of a number of transcription factors, both those that initiate and those that limit immune response. General themes that emerge suggest that the leukocyte response to acute inflammation includes transient dysregulation of leukocyte bioenergetics and modulation of translational machinery, widespread suppression (at a transcriptional level) of mitochondrial energy production and protein synthesis machinery, decreased high-energy substrates in muscle and liver (supported by patients with sepsis or burns, and animal models), and direct disruption of mitochondrial complexes by cellular-stress-derived mediators (e.g. reactive oxygen species), leading to necrotic cell death (supported by animal models of sepsis and reperfusion injury) [44]. Other studies have demonstrated that TNF- α increases and lipopolysaccharide (LPS) impair thrombin responses for at least 24hr [45]. In summary,

although the response to sepsis is fundamentally distinct in initial activation of innate immunity, the resultant whole body response to the stress of infection is remarkably similar to the surgery model.

Genomic Variability and Complex Disease

As stated above, one feature of perioperative physiology is striking variability in patient response to perioperative perturbations. Studies are mounting suggesting that genetic variation can significantly affect an individual's risk of adverse perioperative events [46–48]. Perioperative genomics is a new field that uses functional genomic approaches to discovering underlying biological mechanisms that explain why similar patients have dramatically different outcomes after surgery [49].

In this context, it has been noted that several complex cardiovascular diseases, such as myocardial infarction [50] and stroke [51] have been identified using genome-wide linkage analysis. However many such studies rely on analysis of family pedigrees, something impractical in the perioperative setting where patients often have surgery late in life. In addition, perioperative adverse events are more likely to represent the sum of multiple smaller genetic effects, rather than single gene variants, thereby limiting classic linkage analysis approaches. This is the predominant reason that most perioperative genetic discoveries published to date are derived from association studies utilizing appropriately matched unaffected controls. One needs to carefully consider what SNPs are chosen in these studies since there is increasing evidence that variability in gene expression levels present in complex diseases may represent SNPs/polymorphisms in regulatory regions of genes that affect transcription, splicing, and translation efficiency in tissue-specific and stimulus-specific manners [52].

Genetic variants have been found for adverse events such as myocardial ischemia [53], postoperative arrhythmias [54], vein graft restenosis [55], transplant rejection [56], renal compromise [57,58], neurocognitive dysfunction [59,60], stroke [61], and death [62], as well as more systemic outcomes such as bleeding [63], thrombosis [64], inflammatory responses and severe sepsis [65], and alterations in vascular reactivity [66] (see Podgoreanu [2]). Even more broadly, genetic variants affecting inflammatory responses have been identified. Variants in the IL-6 gene promoter significantly increase inflammatory response to cardiac surgery with CPB [67] and increase length of hospitalization after coronary artery bypass graft surgery [68]. Both APOE genotype [69] and SNPs in TNF genes are associated with proinflammatory effects in patients undergoing CPB [70]. In addition, a SNP modulating expression of anti-inflammatory cytokine IL-10 in response to CPB has been associated with postoperative cardiovascular dysfunction [71], and association between SNPs in 2 inflammatory genes (IL-6 and TNF- α) alters incidence of composite postoperative complications lung resection for cancer [72].

As described above, the metabolic consequences of surgery and anesthesia are complex. Perioperative assessment of global metabolite profiles (metabolomics) should shed light on metabolic derangements associated with surgical stress. A principal advantage of metabolomics is that metabolite information is readily transferable between species. Preliminary studies reveal metabolic signatures characterizing overall effects of stress [73], impact of ischemia-reperfusion injury on allograft function [74], and effectiveness of cytoprotective therapy in preventing lung injury in models of surgical sepsis [75] or myocardial ischemia-reperfusion injury [76]. A recent study examining metabolic alterations induced with exercise stress testing, comparing individuals with inducible ischemia to those without (n=36 total), and analyzed using functional pathways analysis, novel metabolites predictive of ischemia were identified [77]. Of the 23 most altered in the group with

inducible ischemia, 6 metabolites are members of the citric acid pathway and capable of differentiating cases from controls with a high degree of accuracy (c-statistic 0.83) [77].

Genetics and Adverse Perioperative Outcomes

The Duke Perioperative Genomics investigative team initiated a prospective study called **Perioperative Genomics And Safety Study, U.S.**, or PEGASUS, in 2001. In recent years, broader multi-institutional perioperative genomics groups have been formed in the US (PeriGReN) and internationally (iPEGASUS). The goal of the PEGASUS group of investigators is to use genetic variability to determine which individuals are at risk for adverse events after surgery. This initiative not only solidified ongoing focused efforts by Drs. Newman, Reves, and Mathew on the role of APOE isoforms on neurocognitive outcome after cardiac surgery [78], it also greatly expanded the effort to include prospectively enrolling all cardiac surgery patients (and some targeted intensive care and general thoracic patients), with a broader series of adverse outcomes and more in-depth genetic/genomic approaches. Perioperative genomics teams are multidisciplinary groups of physician scientists, statistical geneticists, and genome scientists. Studies published over the last several years demonstrate feasibility of performing genetic analysis of complex phenotypes in the perioperative environment. These studies should ideally focus on mechanistic pathways with carefully defined clinical endpoints and include all appropriate clinical covariates in order to optimize reproducibility of the final results. End-points examined thus far include bleeding, renal injury, stroke, neurocognitive deficits, myocardial injury, sepsis, and arrhythmias [3,58,61,63,69,79–81]; analysis typically includes creation of clinical models, genetic models, and combined clinical/genetic models for these adverse outcomes, with careful adjustment for multiple comparisons. A recent invited review [2] introduced the concept of perioperative genomics to the broader cardiovascular community.

As an example of the power of perioperative genetic/genomic approaches, the PEGASUS group recently examined the perioperative myocardial injury/infarction (PMI) endpoint by genotyping 48 polymorphisms from 23 candidate genes in a prospective cohort of 434 patients undergoing elective cardiac surgery with CPB [3]. PMI was defined as CK-MB level $\geq 10\times$ upper limit of normal at 24 hr postoperatively. A 2-step analysis was used--marker selection, then model building. To minimize false-positive associations, adjustment was made for multiple testing by permutation analysis, Bonferroni correction, and controlling the false discovery rate (FDR). 52 patients (12%) experienced PMI. After adjusting for multiple comparisons and clinical risk factors, 3 polymorphisms were found as independent predictors of PMI (adjusted $p < 0.05$; $FDR < 10\%$) (Figure 3). These represent SNPs in genes encoding IL-6 (-572G>C, OR 2.47) and 2 adhesion molecules, ICAM-1 (Lys469Glu, OR 1.88), and E-selectin (*SELE* 98G>T, OR 0.16). Inclusion of genotypic information from these SNPs improves prediction models for PMI based upon traditional risk factors alone. The study concluded that functional genetic variants in cytokine and leukocyte-endothelial interaction pathways are independently associated with severity of myonecrosis following cardiac surgery.

In describing these pathways further, it is important to note that the 2 proinflammatory SNPs that increase PMI both activate the coagulation system, but via distinct mechanisms. IL6 -572G>C is associated with significantly higher postoperative plasma IL-6 levels [67] and longer hospital stay [68]. IL-6 is also known to induce TF expression in a variety of cells, giving it procoagulant properties [19,34]. ICAM1 1462A>G is a non-conservative SNP encoding Lys469Glu, located in an immunodominant epitope involved in integrin-mediated B-cell adhesion and neutrophil transmigration; it has been associated with a variety of pro-inflammatory phenotypes such as transplant rejection, vasculopathy, vascular restenosis, multiple sclerosis, and asthma [82,83]. ICAM1 469Glu is highly associated with serum

soluble ICAM1 (sICAM1) levels [83]; increased sICAM1 levels have been correlated with silent cerebral infarction[84]. Thrombin contributes to local inflammation, stimulating neutrophils and endothelial cells to express chemoattractants including the chemokine ICAM1, thus providing a distinct thrombin-mediated, cytokine independent pathway for ICAM1 expression [28]; the increased ICAM1 mRNA and protein peak over 24 hrs. ICAM1-activated endothelial cells support monocyte adhesion *in vitro* [85], and such an interaction has been shown to induce monocyte TF expression [86] as well as leukocyte recruitment and ultimately platelet aggregation which leads to thrombus formation [87].

In contrast, SELE98G>T decreased risk of PMI in the study. E-selectin is an endothelial membrane protein absent in quiescent endothelial cells, but upregulated over several hours in response to inflammatory stimuli [88]; it is cleaved to a soluble form (sE-selectin) which is controversial in its role in stratifying ACS risk. SELE98 (which is located in the untranslated region of exon 2) has been shown to be a predictor of premature CAD (even after controlling for the SELE S128R mutation) [89,90]. Further, in healthy volunteers given lipopolysaccharide (LPS), E-selectin S128R is associated with 20% higher monocyte counts and 50–80% increase in thrombin generation at 24hrs in spite of not altering basal/inducible sE-selectin, TNF, or IL-6 levels [91]. However, TNF-induces localized chromatin modification that affect E-selectin expression [92], yet in a lung surgery model E-selectin expression is not a consequence of TNF- α triggering [93], and E-selectin SNPs do not consistently alter sE-selectin levels or risk of CV disease [94]. E-selectin also downregulates expression of LFA-3 and ICAM-1 mRNAs in lung [93], is required for anti-angiogenesis actions of endostatin [95], and has been reported to mediate P-selectin glycoprotein-1-dependent and independent rolling and the latter effect is down-regulated by systemic activation [96]. It is also interesting to note that SELE98G>T and SELE A561C have similar effects in influencing susceptibility and course of multiple sclerosis [97]. This fits with a trend toward decreasing PMI by SELE561A>C, in addition to the clear protective effect of SELE98G>T, seen in the study (Figure 3 [3]).

In spite of important information gleaned by association studies, it is important to go beyond perioperative associations to utilizing more global genomic approaches. Recent publications using animal models of cardiac surgery with CPB [98] demonstrate the utility of genomic approaches such as microarrays to determine novel candidate genes in an unbiased manner. Further analysis using proteomic and metabolomic approaches (see Figure 1) should augment clinical genetic studies in humans over the coming years, providing new mechanistic insights. Putting together all perioperative genetic/genomic studies published thus far suggests that the key biological theme emerging in adverse perioperative outcomes is inflammation. While inflammation is important in healing from surgical trauma, patients who are too robustly proinflammatory appear to be at higher risk for adverse perioperative events.

But in the end, do genetic/genomic studies result in practical information capable of facilitating therapeutic interventions designed to improve outcome? Indeed, a landmark study on the effects of a 5-lipoxygenase-activating protein inhibitor on biomarkers associated with the risk of MI demonstrates that by defining at risk patients for 2 genes in the leukotriene pathway, one can predict who will respond to targeted drug therapy [99]. Specifically, in patients with genetic variants in the gene encoding 5-lipoxygenase activating protein (FLAP; variant described as the haplotype HapA based on haplotype and genotype information from databases of Decode Genetics Inc [Reykjavik, Iceland] [100]), use of the drug DG-031 (an inhibitor of FLAP) leads to significant and dose-dependent suppression of biomarkers associated with increased risk of myocardial infarction events [99]. This demonstrates that identification of at-risk patients using genetic/genomic approaches provides more rational, targeted, and effective use drug therapies designed to lower risk

clinically. While this study does not take place during surgery, it is expected that similar principles will be operational in the perioperative period. Hence perioperative genomics is the wave of the future for predicting and preventing organ-specific adverse events during surgery.

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Appendix

Practice Points

- Perioperative perturbations invoke inflammatory cascades with far reaching consequences and possible adverse events.
- Genetic variants in genes encoding various aspects of biological pathways initiated during anesthesia/surgery may amplify or dampen resulting responses with clinical consequences.
- Testing for various genetic variants important to perioperative outcomes should be available in the near future.

Research Agenda

- Confirmation of existing perioperative associations between genetic variants and perioperative outcome is key.
- Unbiased approaches (e.g. whole genome analysis and other targeted organ specific approaches) are needed to elucidate key pathways affecting outcome.
- National and international multidisciplinary groups of investigators need to work together to tackle this important area.
- Genomic studies should use all available tools (e.g. DNA, RNA, protein, metabolite approaches).

Figure 1. Genetics *versus* Genomics

Genomics can be described as the scaling up of genetics, where thousands of DNA, RNA or protein molecules are studied simultaneously. Various scientific approaches are used at each level. For example whole genome analysis (WGA) refers to large scale examination of DNA sequences across the entire genome, microarrays refers to interrogating thousands of RNA molecules simultaneously, proteomics refers to examination of many proteins at once, and metabolomics refers to elucidation of hundreds of metabolites.

Figure 2. Physiologic Mechanisms Underlying Adverse Postoperative Events

See text for details. Abbreviations: Coag = coagulation, Endoth = endothelial cells, Macro = macrophage, Mol = molecules, Ornith = ornithine, Perox = peroxidation, Plts = platelets, TF = tissue factor, WBCs = white blood cells.

Polymorphism	Inheritance Mode	Univariable		Multivariable		Multivariable, risk factor adjusted		PDR
		OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	
IL6 -572G>C	Autosomal	2.81 (2.03-3.8)	0.0077	2.70 (2.04-3.6)	0.007	2.47 (1.68-3.7)	0.005	+
ICAM1 1462A>G	Autosomal	1.91 (2.02-1.9)	0.003	1.62 (1.12-2.29)	0.009	1.86 (1.12-3.04)	0.009	+
SELE 895C>T	Dominant	0.178 (0.09-0.33)	0.0007	0.198 (0.09-0.39)	0.002	0.168 (0.08-0.32)	0.003	+
CRP 1046C>T	Dominant	1.86 (1.04-3.3)	0.0319	2.50 (2.25-2.8)	0.001	2.28 (1.14-4.53)	0.03	-
LDH 1980T>C	Dominant	2.30 (1.24-4.2)	0.0086	2.37 (1.34-4.2)	0.009	2.91 (1.4-6.0)	0.003	-
CAT 844G>T	Autosomal	0.87 (0.42-1.84)	0.0030	0.87 (0.39-0.9)	0.001	0.89 (0.34-0.93)	0.03	-
IL1B -411T>C	Autosomal	1.10 (0.56-2.18)	0.0046					
IL1B -887C>T	Dominant	0.96 (0.51-1.0)	0.0088					
IL6 -887G>A	Autosomal	0.62 (0.31-1.0)	0.0002					
CD14 -380C>T	Dominant	0.88 (0.51-1.08)	0.0194					
SELE 855A>C	Dominant	0.10 (0.03-0.48)	0.0031					

Figure 3. Genetic Variants and Perioperative Myocardial Injury/Infarction

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