

Multilead Precordial ST-segment Monitoring

"The Next Generation?"

A QUARTER century has passed since the first reports describing use of precordial lead V_5 to monitor for intraoperative ischemia were published, and over a decade has passed since we documented its sensitivity (75%) using continuous 12-lead monitoring in 100 patients.^{1,2} Since then, V_5 has become "a clinical routine." In this issue, Landesberg *et al.* present "the next generation," monitoring a larger cohort (185 patients) undergoing higher-risk surgery (all vascular surgery), for a longer period of time (48-72 h).³ Their results extend our knowledge and add controversy, given their finding that leads V_3 (75%) and V_4 (83%) are either equal or more sensitive than V_5 (75%). They recommend use of V_4 over V_5 since its ST-segment is most commonly isoelectric on the baseline electrocardiogram, extrapolating that this makes it more likely to reflect ischemic changes. They also recommend the use of two precordial leads to approach 95% sensitivity to detect ischemia or infarction.

Should this study alter our current clinical practice? Should we "move to the right" in favor of V_3 or V_4 and abandon V_5 ? Should we encourage bipartisanship by monitoring two precordial leads (requiring equipment modification)? Or should we take the Libertarian approach by encouraging simplicity in monitoring? I would argue that with the clinical data accumulated over the past 10-15 yr. documenting associations of perioperative tachycardia and ST-segment depression to adverse outcome and beneficial effects of β -blockade, that sophisticated monitoring is considerably less important than adequate prophylaxis and therapy.^{4,5} However, since it is known that β -blockade cannot ensure suppression of ischemia nor prevention of infarction in all patients, evaluation of the current status of multi-lead monitoring remains worthy of serious consideration.⁶

Reference cardiology texts state that subendocardial ischemia induced by demand-related stress is manifested by ST-segment depression in lead V_5 and does not localize the anatomic site of coronary obstruction.⁷ Yet even Mason and Likar, the first to use the now universal

torso-mounted axial leads during exercise treadmill testing (ETT), reported that V_6 , not V_5 , was the most sensitive lead!⁸ Subsequent investigators have reported varying sensitivity, particularly between V_4 , V_5 , and V_6 .⁹⁻¹³ (table 1).

How can we reconcile these differences? Examination of these studies reveals differences in ST-segment criteria, (including magnitude and timing after the J-point, varying even with the number of leads involved); the time period considered (during exercise, during recovery, perioperatively, etc.); temporal duration (with Landesberg *et al.* requiring prolonged duration > 10 min.);³ mode of analysis (visual *vs.* computerized); incorporation of other physiologic parameters; and less frequently, but of considerable theoretical interest, normalization based on the height of accompanying R-wave.¹⁴ With all of these factors, any simple explanation is likely impossible. Given the common adage that the ST-segment vector during subendocardial ischemia is directed towards the apex of the ventricle (which V_5 is said to be closest to), it is possible that anthropomorphic factors influencing the position of the heart in the chest such as gender, body habitus, and chest diameter may be important. However, this has not been studied. Complex physiologic approaches using noninvasive body surface mapping have been used, and more recently invasive endo- and epicardial potentials with three-dimensional computer modeling has provided an alternative approach.¹⁵

Why is there not greater interest in the cardiology community to nail down the precise sensitivities? Possible explanations include (1) nearly all stress tests in this country use computerized 12-lead systems, (2) there is strong evidence that a positive response in multiple leads (along with greater magnitude of depression and presence of a downsloping ST-segment) is related to a larger area of myocardium at risk^{16,17} and (3) despite calls for cost containment, thallium imaging, even after a positive endotracheal tube is very common (as is cardiac catheterization). In clinical practice, the whole of the 12-lead electrocardiogram is clearly greater than the sum of its parts.

Another factor is the growing interest in continuous 12-lead monitoring for patients with acute coronary syndromes (ACS). With transmural ischemia, lead sensitivity is closely associated with the site of coronary occlusion (whether transient or permanent) with leads V_2 and V_3 most sensitive for left anterior descending occlusion, and lead III most sensitive for the right coronary artery. In this setting, ST-segment elevation is a nearly universal

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Table 1. Studies of 12-lead Sensitivity

Reference	N (Points)	Setting	Comparison	Results
Weyne <i>et al.</i> 1991 ⁹	28	PTCA	12-lead vs. VCG	V2 and V3 each 51%, V2 and V4 most sensitive for isolated LAD occlusion
Jensen <i>et al.</i> 1994 ¹⁰	30	PTCA	12-lead vs. VCG	V2 (69%) superior to V5 (42%)
Gannedahl <i>et al.</i> 1997 ¹¹	38	Vascular surgery	12-lead vs. VCG	V4 (69%) superior to V5 (54%)
Klootwijk <i>et al.</i> 1997 ¹²	130	Unstable angina	12-lead vs. 3 lead electrocardiogram	V2,V3,V4 highest and equally sensitive
Viik <i>et al.</i> 1997 ¹³	128	ETT	12-lead, various ST and HR related parameters	V5 and V6 superior to V4 based on ROC analysis

CAD = coronary artery disease; ETT = exercise treadmill testing; LAD = left anterior descending coronary artery; PTCA = percutaneous transluminal angioplasty; ROC = receiver operator characteristic; VCG = computerized vectorcardiography.

finding. Circumflex occlusion results in a variable response with primary elevation in posterior precordial leads (*i.e.*, V₇, V₈, etc.) or reciprocal ST-depression in other precordial or axial leads.¹ A recent multidisciplinary working group recommends leads III, V₃, and V₅ as the most sensitive combination for patients with ACS.¹⁸

Krucoff *et al.* were the first to make a serious argument for the value of continuous 12-lead electrocardiogram monitoring in ACS patients with the concept of the "12-lead fingerprint," a unique pattern of leads and ST segment magnitude sensitive to detecting reocclusion after percutaneous transluminal coronary angioplasty (PTCA).¹⁹ This approach has been used in major studies of thrombolysis. Many intensive care unit bedside monitors (and telemetry monitors) are now "12-lead ECG capable" with a precordial lead cable and continuous ST segment trending of all 12 leads. Recent American and European ACS Guidelines now acknowledge the utility of this approach but make no firm recommendations for it.^{20,21} However, this approach includes a high rate of false-positive responses (40%) because of changes in QRS amplitude or vector with positional changes, arrhythmia/pacing artifact and heart-rate-related changes in ST-segment contour.²² In the perioperative setting, the array of catheters, monitors, and drains and the need to mobilize patients quickly are major logistical obstacles. Artifact issues and the economically unfavorable task of investigating episodes are formidable factors.

Aside from the monitoring issues raised by this study, there is important information on perioperative ischemia. As noted in the parent publication, duration of ischemia is a significant predictor of peak cTn-I level, ischemic events associated with infarction are preceded by increased heart rate (32 beats/min). People with diabetes and patients with left ventricular hypertrophy (LVH) are at highest risk.²³ Diabetics are already known to be at high risk for adverse outcome.²⁴ Less is known about LVH since many studies excluded these patients because of concerns that the increased QRS voltage may exaggerate the ST-segment response.¹⁴ We previously noted that LVH was the strongest preoperative factor

multivariately associated with postoperative ischemia.²⁵ Left ventricular hypertrophy is associated with accelerated atherosclerosis, subendocardial ischemia, and adverse long-term outcome.²⁶ But its association with *plaque disruption*, likely the necessary ingredient for overt morbidity, is suggested by a recent study comparing angiographic results over a 6 months interval.²⁷ The strongest adverse multivariate associations were LV mass and elevated heart rate (> 80 bpm), while the strongest protective association was with chronic β -blocker use.

Integrating the monitoring and clinical data, it seems reasonable that sophisticated monitoring may be of value to people with diabetes and those with LVH. A targeted study in these cohorts of the value of therapeutic intervention guided by multi-lead monitoring (in the setting of concurrent β -blockade) would be most helpful. My clinical observations are that precordial lead placements by physicians and nurses at all levels of training remain imprecise (and are unavoidably affected by surgical factors). Thus, I recommend that clinicians use a "true" V₄ or V₅ along with an inferior axial lead, control heart rate and pain, and use β -blockers as tolerated for all patients at risk.

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Genetics Infuses New Life into Human Physiology

Implications of the Human Genome Project for Anesthesiology and Perioperative Medicine

GENETICS has revolutionized medicine. The human genome project has succeeded in sequencing almost all 3 billion nucleotides present in the human genome, an accomplishment that has been hailed as one of the greatest achievements of our time. Although more than 99% of human DNA is identical between individuals, residual vari-

ability not only makes each person unique but also, in the context of medicine, may contribute to disease onset or disease progression. As a result, the next step in the human genome project is designed to investigate DNA variability between species as well as between humans. Harnessing genetic information from clinical studies to examine the impact of genetic variability on disease characterization and outcome is called functional genomics. In this issue of *ANESTHESIOLOGY*, the study by Lasocki *et al.*¹ provides an example of how genetic variation in a common gene (the angiotensin converting enzyme [ACE] gene) alters pressure and flow relations during cardiopulmonary bypass. In this study, the authors use the unique environment of the operating room to answer a potentially important and clinically relevant physiologic question and, in the process, give new meaning to the operating room as the "last human physiology laboratory in medicine."

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Anesthesiologists have long recognized that response to drug administration or stress depends on the individual. In fact, a bell-shaped curve of responses to various environmental perturbations (drug administration, hemodynamic challenge, inflammatory response to stress of surgery, and others) shows that although most patients respond in predictable patterns, others respond either more or less vigorously. In fact, much of the art of anesthesiology is the astute clinician being prepared to deal with outliers. Increasingly clinicians are appreciating that an individual patient's response to stress may alter perioperative outcomes such as incidence of respiratory distress syndrome, perioperative myocardial infarction, survival, and response to pain management—but what are the mechanisms underlying pharmacodynamic and physiologic variability to stress? The answer to this complex question includes understanding how the unique genetic background an individual brings to the operating room affects his or her perioperative outcome.

To understand genetic variability in patients, it is important to briefly review some basics of genetics. The human genome consists of the aggregate of DNA present in 23 chromosomes (22 chromosome pairs plus sex chromosomes X/Y). DNA consists of a collection of nucleotides (A, C, G, or T) that form a code used to produce proteins. The expression of genetic information in the cell is generally a one-way system. In simple terms, the sequence of nucleotides in DNA determines the sequence of RNA *via* transcription, and then a sequence of three nucleotides of RNA encodes one amino acid (out of 20 possible amino acids) *via* translation; these amino acids are the building blocks for proteins, which perform virtually all chemical reactions and functions in the body. Only a small proportion of the entire DNA in a cell actually codes for RNA and proteins. Some of the nontranscribed DNA has controlling functions over transcription; thus, certain DNA nucleotide sequences may silence or enhance transcription. The word polymorphism refers to an altered DNA sequence compared with the most common, or wild-type, DNA. Polymorphisms can either be small or large insertions or deletions of nucleotides, repetitive sequences (often repeated pairs of DNA called microsatellites), or a change in a single nucleotide (single-nucleotide polymorphism). Some genetic variation provides us with unique (but nonmedically important) aspects of our bodies, such as facial expression, hair color, and body stature, but other variations have been shown to be important in determining onset and severity of disease, as well as response to drug therapy. Polymorphisms may directly alter the amino acid sequence of a protein and therefore potentially alter protein function, but other variants may alter regulatory sequences in DNA, thereby altering concentrations of otherwise normal proteins. Distinguishing background genetic variation that make us unique and provides a

genetic fingerprint, from clinically important polymorphisms that lead to disease is one of the most important tasks for clinical researchers today. Classically, pharmacologists have concentrated on genetic variability that alters drug metabolizing enzymes to explain variation in pharmacokinetic responses to drug therapy; however, it is now apparent that the genetic variability can alter many other proteins important to pharmacodynamic responses. In the operating room, clinical research needs to go one step further and examine how genetic variability affects responses to acute stress as well.

Historically, human genetic studies have focused on relatively rare Mendelian-inherited, single-gene diseases. Diseases such as sickle cell anemia are the result of a single-nucleotide polymorphism in the DNA sequence encoding the β chain of adult human hemoglobin; the disease is entirely the result of this single-nucleotide polymorphism and thus is relatively easy to investigate. In less-well-characterized inherited diseases, genetic studies often focus on linkage of a genetic locus (region of DNA within a chromosome) with patterns of inheritance within families. In contrast to single-gene disorders, most common diseases prevalent today involve a complex interaction between a number of disease-enhancing or -altering genes, environmental stimuli, and variable (and sometimes age-dependent) penetration of those genes.² Diseases such as hypertension, coronary artery disease, and some forms of cancer are examples of complex common diseases. Association studies analyze the incidence of a disease trait (or phenotype) and its association with a particular DNA polymorphism. Specifically, association studies test whether a genetic marker (or polymorphism) occurs more frequently in cases than in controls. The study by Lasocki *et al.*¹ in this issue of ANESTHESIOLOGY is an association study focusing on a candidate gene (the ACE gene) in which a well-described biologic effect occurs as a result of an insertion/deletion (I/D) polymorphism; this polymorphism impacts serum and renal concentrations of ACE. The authors are to be commended on using cardiopulmonary bypass as a unique and reproducible physiologic environment where blood flow can be altered and resulting arterial pressure (and systemic vascular resistance) can be documented, giving a measure of pressure-flow relations. Genetic association studies are only as good as the clinical characterization of end points (or phenotyping). The authors are therefore careful to include many factors that might affect systemic vascular resistance on cardiopulmonary bypass (*e.g.*, age, sex, hypertension history, medications, type of surgery) to ensure their results occur because of the ACE polymorphism and not some other clinical variable; however, other clinical covariates may also be important, such as body mass index, race, and central venous filling (which could be controlled by ensuring similar central venous pressure before beginning the study in all patients). Despite these limitations,

the authors seem to demonstrate in a new setting that the specific ACE polymorphism tested is associated with permutations in pressure-flow relations in humans undergoing surgery.

Because association studies are difficult to perform well, especially in patient populations where genetic admixture is an issue (patients originating from many distinct genetic backgrounds), it is important to take this opportunity to stress some ideal standards for future genetic association studies.³ First, it is important to study a large sample population when testing for association with a genetic marker or polymorphism and disease.⁴ Citizens from Western countries originate from all over the world, bringing unique and varied genetic backgrounds that may have nothing to do with disease. In simplistic terms, this introduces genetic "wobble" that can only be overcome by either properly powering a study for a primary main end point with thousands of patients, or by carefully screening the populations to be as homogeneous as possible. Second, genetic association studies are only as good as the clinical phenotyping. Clinical end points must be quantifiable and reproducible. Clinical covariates that might explain different outcomes must be taken into account (*e.g.*, the effect of body mass index in a study designed to examine blood pressure may be far more important than variation in DNA sequence of a candidate gene). Third, use of surrogate markers or intermediate end points often augment a genetic association study. In the study in this issue of *ANESTHESIOLOGY*, measurement of serum ACE concentrations might have validated the authors' final conclusions. Fourth, rigorous quality control must be in place to define the presence of a genetic polymorphism. There are currently many laboratory methods available for polymorphism detection. On careful examination, a single-nucleotide polymorphism that occurs in 2 patients out of 100 might be missed or overcounted if the method of detection is only 92–96% accurate. Fifth, smart genetics must be used; a genetics collaborator can often be enlisted for this aspect of the trial. The use of appropriate and accurate genetic language is important so that concepts and results are universally recognizable. For example, it is more informative to list allele (or marker) frequencies (range, 0–0.50) rather than genotype frequencies (often listed as 0–100%) when describing variants. Race has been shown to be an important determinant of allele frequency in many studies, so allele

frequencies for the overall group and then for each racial subgroup should be examined. If not appropriately taken into account, varying allele frequencies in subgroups might significantly influence final results of an association test. It is also important to test genetic markers to see if they are in Hardy-Weinberg equilibrium so that statistical genetics tools that require this condition are appropriately applied. Sixth, appropriate statistical analysis must be applied. Seventh and last, genotypes exist either as homozygous or heterozygous. Heterozygous genotypes may present as intermediate phenotype and therefore cannot necessarily be grouped together with homozygous genotype for the purpose of statistical analysis. A common mistake in association studies is to perform repeated comparisons without altering the final *P* value required for significance. As a general approach, overall significance should be sought, followed by analysis of covariates, determination of specific *P* values, and possible interaction between genes or polymorphisms. Appropriately performed analysis for association studies may be complicated, so statistical genetics expertise should be sought.

In summary, the study by Lasocki *et al.*¹ provides a first step in demonstrating the usefulness of association studies in the anesthesiology literature. Association studies can be useful in determining the pathogenesis of disease, variability in physiologic end points, or response to treatment. If one is visionary, such studies may hold the key to unlock the secret of predicting perioperative outcomes based on individual preoperative genetic information. As such, they have the potential to revolutionize clinical research.

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