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Section Editor

Blood Pressure Variability: Can Nonlinear Dynamics Enhance Risk Assessment During Cardiovascular Surgery?

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AS THE POPULATION AGES, increasing numbers of elderly patients with multiple comorbid conditions are presenting for high-risk cardiovascular surgical procedures. The commensurate increase in perioperative major adverse events (MAEs) increases mortality by 1.4- to 8-fold,[1] with an estimated 1 billion dollars annually spent on managing these complications.[2] Current MAE risk prediction indices[3,4] typically are based on *static* or "snapshot" measures such as the presence or absence of a comorbid condition like hypertension. Unfortunately, these indices have failed to adequately predict which high-risk patients will have MAEs;[5–7] possibly, at least in part, because they do not take into consideration the complex (nonlinear), time-varying features of physiologic hemodynamic signals. Furthermore, a one-size-fits-all risk prediction model approach is unlikely to accurately identify patients at high risk,[5–7] particularly at extremes of age and predicted risk.[8–13]

A major motivation for the program outlined here was that current risk prediction tools may be improved by incorporating dynamic properties of physiologic signals, thereby enhancing (a) individual patient risk assessment and counseling, (b) design of timely interventions to prevent disabling or fatal complications (eg, stroke, renal failure, atrial fibrillation and myocardial infarction), and (c) the accuracy of comparisons of provider and hospital performances. Toward this end, the authors' goal was to develop a real-time blood pressure variability (BP variability) indices or set of indexes incorporating a patient's own baseline and evolving pathophysiologic characteristics into current snapshot scoring systems.[4,5,14]

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One of the most important physiologic signals obtained in the perioperative period is the continuously recorded systemic BP signal.[15] While the optimization of BP is a major perioperative target, there is no universally accepted guideline for defining hypotension. Furthermore, hypotensive episodes are dynamic, not static, phenomena and not only vary from patient to patient but also within a patient at different surgical stages.

Therefore, measures of BP variability, quantified using different metrics, have been the focus of considerable interest. For example, in 1 study,[16] BP variability was defined as the time spent above or below a target systolic blood pressure range of 95 to 135 mmHg, and an increased BP variability value was associated with higher 30-day mortality. In another study, BP variability was defined as the root mean successive square difference of a moving 5-second time period. In this investigation,[17] decreased intracranial pressure and BP variability were shown to predict long-term adverse outcome after aneurysmal subarachnoid hemorrhage.

An intuitive limitation of traditional measures of variability is the fact that they do not take into consideration the temporal structure of a sequence of measurements. For example, the following 2 sequences, $A = \{1\ 2\ 3\ 2\ 1\ 2\ 3\ 2\ 1\ 2\ 3\ 2\ 1\}$ and $B = \{1\ 1\ 1\ 1\ 2\ 2\ 2\ 2\ 2\ 2\ 2\ 3\ 3\ 3\}$,[16] have the same variability, as measured by amplitude of range and standard deviation but completely different structures. In fact, while sequence A defines a triangular wave, sequence B is a step function. Measures that are sensitive to the temporal organization of a signal have been essential in characterizing and discriminating different dynamic systems.

The authors assessed BP fluctuation (variability) dynamics via 2 complementary metrics, (1) traditional standard deviation of BP time series, and (2) the degree of complexity of their dynamics. The motivating framework for quantifying the degree of complexity of nonlinear physiologic signals, such as BP, is that complexity reflects the degree of robustness/resilience of the underlying control mechanisms, and it decreases with aging and pathology (http://physionet.org/tutorials/cv/, accessed Oct 21, 2013).

The term, "nonlinear", may be unfamiliar to readers of physiologic and clinical journals. Linear systems exhibit 2 properties, proportionality and superposition. Proportionality, as implied by the term, means that there is a straight-line relationship between input and output. Superposition indicates that clinicians can completely understand the system (eg, a

Rube Goldberg-type device) by breaking it down into multiple subcomponents. In contrast, the subcomponents of a non-linear system do not add up to the whole because of either constructive or destructive interactions between those subcomponents. In these cases, reductionist strategies will fail to provide full understanding of a given system.[18,19] Furthermore, in nonlinear systems, unanticipated (off-target) effects are likely since small input changes may induce major changes in the output (the so-called butterfly effect).

The authors propose that complex (nonlinear) fluctuations of hemodynamic variables (including systemic blood pressure parameters) during cardiovascular surgery contain information relevant to risk assessment and intraoperative management. Preliminary analysis of a pilot study supports the feasibility and potential merits of performing a larger, prospective study to assess the clinical utility of such new dynamic measures and to evaluate their potential role in enhancing contemporary approaches to risk assessment of major adverse events.

In this pilot study, the authors tested the feasibility of (1) acquiring BP waveform data of sufficient length and quality for nonlinear complexity analyses, and (2) converting the data from a proprietary to an open-source format. The authors' specific hypothesis is that the complexity of the dynamics of systolic arterial pressure (SAP), diastolic arterial pulse (DAP), and pulse pressure (PP) from the post-bypass period is lower for the group of patients with MAEs (cases) than for a control group with comparable risk but no MAEs. The authors included pulse pressure dynamics in light of evidence that abnormalities in pulse pressure has been associated independently with an up to 3-fold increase in MAEs following cardiac surgery.[20]

METHODS

The authors' institution collaborates in the Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC II) data collection program with the Massachusetts Institute of Technology (MIT).[21] The MIMIC II project involves collection of all clinical and bedside monitoring data from patients in critical care beds and has been approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center and MIT. Recently, the authors expanded the MIMIC II project to the operating room (OR) by collecting all monitoring data during cardiovascular surgery.

Metadata including type and duration of surgery, preoperative medications, intraoperative anesthetic, and surgical events (anesthetic induction, surgical incision, bypass time, post-bypass period, chest closure, and surgery end) were collected from the Anesthetic Information Management Systems (AIMS; Philips CompuRecord). Time-stamped data reporting the anesthetic dosage (end-tidal agent concentration, minimal alveolar concentration of anesthetic) and details of circulatory support were collected from the hospital's AIMS systems; The deidentified metadata then were integrated into the STS system, which also served as the source of preoperative ontology definitions, including demographic data, comorbid conditions, inotropic support, STS predictive risk index for morbidity and 30-day mortality, surgery type, and postoperative adverse outcome information. Standard STS definitions were used to adjudicate endpoints (http://www.sts.org/doc/4862; Accessed Sep 25, 2010) and to report the postoperative outcome.

Twenty patients with MAEs admitted for cardiac surgery at the Beth Israel Deaconess Medical Center between the months of November 2009 and Feb 2010 were chosen for the pilot study. Twenty controls, without MAEs, matched for age, gender, and body surface area were chosen from the same period.

The monitoring data from the ORs were streamed at 125 Hz and 12-bit amplitude resolution to a dedicated, data-archiving server located within the secure environment of the Beth Israel Deaconess ORs. The data were retrieved from the server after completion of surgery and translated from a commercial system's (Philips, Andover, MA) proprietary data format to an open-source waveform data format (WFDB). After data conversion, signal quality assessment was performed by visual inspection. The authors then used an open-source software algorithm[22] to identify and annotate the onset of the arterial BP waveforms. They derived the beat-to-beat systolic and diastolic sequences of values that constitute the systolic and diastolic time series by determining the minimum and the maximum values of the BP waveforms in a neighborhood of the previously identified onsets. Finally, for each beat, the authors coded and archived the stage to which the surgical procedure had progressed (pre-induction, induction, vessel harvesting, bypass, post-bypass). These procedure-specific hemodynamic data were integrated with the intraoperative surgical events and postoperative STS database.

For the pilot study presented here, the authors focused on the analysis of post-bypass SAP, DAP, and PP time series segments with a minimum of 95% usable data. The selection of data from this time period was based on the assumption that the period of time during which chest closure is being performed is likely to be a hemodynamically stable phase of surgery and relatively comparable between subjects.

Such segments (1 per subject, Fig 1) were available in 12 cases (1 in-hospital death, 2 patients with postoperative renal failure, and 9 patients with new-onset postoperative atrial fibrillation) and 11 control subjects. Segment length varied between 12 and 30 minutes (Table 1).

An automated algorithm, used to eliminate artifacts, excluded SAP values <50 mmHg and >250 mmHg, DAP values <20 mmHg and >150 mmHg, and DAP $\geq$SAP and SAP -DAP <10 mmHg.

SIGNAL ANALYSIS

For each SAP, DAP and PP signal the authors calculated (1) the mean, (2) the standard deviation for the entire length of the time series, a measure of the amount of variability around the mean value, and (3) a complexity index, computed using the multiscale entropy (MSE) method, which quantifies the information content of the signal over a range of scales ($\sim$1-10 seconds). Table 3 presents the group mean and standard deviation values for each of these measures.

In addition to the original data segments, the authors also analyzed detrended time series, since nonstationarities, due to factors such as slow drifts of the baseline of a time series can lead to misleadingly low complexity values. For an example of the type of nonstationarity (drift) that the authors removed, see the PP signal (original and detrended) shown in the middle plot of Figure 1. For detrended, they employed an adaptive data decomposition method called empirical mode decomposition.[23] They preserved the first 4 components of the decomposed signals, which is equivalent to eliminating frequencies <0.07 Hz. For the detrended signals, the authors also calculated the standard deviation values. (The mean is approximately 0.)

The MSE method[24] quantifies the information content of a signal over multiple time scales. In practice, the algorithm comprises 2 steps: (1) a coarse-graining procedure that allows the authors to look at representations of the system's dynamics at different scales and (2) the quantification of the degree of irregularity of each coarse-grained time series, which can be accomplished using a measure-termed sample entropy.[25] The graphic output of the MSE method is the entropy of a signal plotted as a function of scale factor (Fig 2). The most complex