Approximate Entropy of Heart Rate as a Correlate of Postoperative Ventricular Dysfunction

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Background: Instantaneous changes in the heart rate, i.e., heart rate variation, traditionally have been quantified by the standard deviation of a series of intervals between successive heart beats. Approximate entropy provides another measure of variability by calculating the logarithmic likelihood that patterns that are similar remain similar on the next incremental comparison. Approximate entropy is a nonnegative number that will distinguish data sets by their amount of regularity, with larger numbers indicating more randomness. We hypothesized that a decrease in the approximate entropy of heart rate would be associated with postoperative ventricular dysfunction (e.g., myocardial infarction, unstable angina, congestive heart failure, prolonged inotropic support).

Methods: Twenty-three high-risk noncardiac patients were continuously monitored by ambulatory electrocardiographic recorders from the evening before surgery up to 80 h during the postoperative period; 9 demonstrated postoperative ventricular dysfunction, and 14 had an uncomplicated postoperative course. Hourly approximate entropy average values were calculated.

Results: Approximate entropy was high (>0.7) in all but two patients preoperatively. Postoperative approximate entropy <0.55 had a sensitivity of 88% and a specificity of 71% for being associated with postoperative ventricular dysfunction; preoperative approximate entropy values were not significantly different between the two groups.

Conclusions: These results suggest that changes in approximate entropy can distinguish between patients who sustained poor outcome and those who had an uncomplicated course. (Key words: Monitoring; heart rate variability. Outcome, postoperative; ventricular dysfunction.)

INSTANTANEOUS changes in the heart rate, i.e., heart rate variation, have been associated with cardiac health. In the term fetus, loss of this variation is an early indicator of fetal distress.1 In survivors of sudden cardiac death, those who demonstrate a reduced heart rate variation are at risk for future in-hospital death.2,4 Similarly, a low heart rate variation in patients who have sustained an acute myocardial infarction (MI) are at greater risk for short-term cardiac morbidity and mortality.3,5 Heart rate variation traditionally has been quantified by the standard deviation of a series of intervals between successive heart beats, i.e., R-R intervals, and has been called "variability." Another, distinct sense of variability is given by a measure of irregularity or unpredictability of the data. The development of a new statistical measure, termed approximate entropy (ApEn), provides such a measure of regularity.6 Approximate entropy is a model-independent statistic that can be applied to any time series, producing a nonnegative number that will distinguish among data sets, with larger numbers indicating more irregularity and randomness. Approximate entropy quantifies regularity in a manner consistent with intuition; it also quantifies subtler changes in regularity of data that may not be so perceptible to the observer. It is this latter property that holds a promise for new information in heart rate analysis.

A decrease in approximate entropy previously has been correlated with sickness in neonates, fetal acidosis, risk of sudden infant death syndrome, and aging.7,12 Findings associating greater heart rate regularity with compromised physiologic status also have been found with the Fourier analysis of heart rates with ventricular fibrillation, with spectral analysis on preterm infants, and with eventual sudden infant death syndrome victims.13-15 Although these latter findings have produced qualitatively interesting results, they lack a clear-cut statistic that summarizes the frequency spectra or underlying system behavior. Motivated by these results associating abnormal physiology with more regular, patterned heart rate tracings, we hypothesized that

Anesthesiology, V 78, No 4, Apr 1993
a decrease in approximate entropy of heart rate would be associated with postoperative ventricular dysfunction in high-risk noncardiac surgery patients. We therefore studied a cohort of high-risk noncardiac surgery patients to determine the perioperative changes observed in approximate entropy applied to heart rate.

Methods

Twenty-three patients were examined who were enrolled in our ongoing study of perioperative myocardial ischemia using ambulatory electrocardiogram (AECG) recordings. All were older than 18 yr (admitted prior to elective surgery to Yale-New Haven Hospital between June 1989 and June 1991), had documented coronary disease, were undergoing arterial vascular procedures, or had two or more of the following risk factors: hypertension (as determined by prior diagnosis and/or the use of antihypertensive medication), diabetes, hypercholesterolemia (serum cholesterol >240 mg/dl), age >70 yr, and smoking (>15 pack years). Two cohorts of patients were identified for study of heart rate variability on the basis of the presence or absence of perioperative cardiac morbidity. A cohort of nine patients were identified who had postoperative ventricular dysfunction as defined by the occurrence of an MI with new Q waves on the electrocardiogram (ECG), MI diagnosed by elevated total CK, and an MB isoenzyme fraction >5% associated with new ECG changes, ischemic pulmonary edema (as diagnosed by chest x-ray or elevated pulmonary artery wedge pressure with associated significant ST segment changes or T wave inversion on 2 leads of a 12-lead ECG), unstable angina (defined as a patient with new ST segment depression ≥1 mm or ST elevation ≥2 mm or T wave inversion on 2 leads of a 12-lead ECG with or without pain) and the need for prolonged inotropic support (>24 h) for maintenance of blood pressure and/or cardiac output. The second cohort of 14 patients had no evidence of cardiac morbidity or perioperative myocardial ischemia on AECG. Informed consent was obtained, as approved by the Yale University School of Medicine Human Investigation Committee.

A continuous AECG monitor was applied to each patient the evening before surgery. All patients were evaluated preoperatively by the anesthesia staff and found to be in their optimal medical condition by both the anesthesia and primary caregivers. No signs of congestive heart failure were exhibited by any patient before surgery. All patients had a preoperative standard 12-lead ECG some time during the 7 days prior to surgery. Each patient's routine dosage of anti-anginal medications, beta adrenergic antagonists, and calcium entry blockers was given the morning of surgery. Choice of premedication, intraoperative management, and postoperative monitoring and analgesia were at the discretion of the primary anesthesia and surgical teams. A 12-lead ECG was obtained the morning of each day on which the patient was monitored by the AECG, or more frequently if clinically indicated. Laboratory values including CK-MB levels were obtained according to the policy of the primary physicians. Interviews of the patients under study were conducted by a member of the research team on the first 3 postoperative days and again on the day of discharge.

Perioperative AECG Monitoring

Study patients were monitored by a calibrated amplitude-modulated AECG monitor (SpaceLabs AECG, model 90205, Redmond, WA) with modified bipolar lead V5 and modified bipolar lead V1 or V3. The AECG recordings were analyzed at the end of the monitoring period on lead V5 for ST segment changes on a computerized analysis system (SpaceLabs FT2000, Redmond, WA). The peak of the QRS was identified for each beat by a computer algorithm, and beat identification was confirmed by an investigator. The periods in which beat identification was poor were excluded from the analysis. Hour-long files containing successive R-R intervals were created.

Calculation of Approximate Entropy

Conceptually, the flow of the approximate entropy calculation, as it pertains here, is as follows. Start with a series of R-R intervals, denoting the i_th R-R interval as u(i). Next, preset a window length of m (e.g., m = 2 in the example below), form an associated vector time series, with vector x(i) consisting of the m u values commencing with u(i). For example, the first three vectors are x(1) = [u(1), u(2)], x(2) = [u(2), u(3)], and x(3) = [u(3), u(4)]. Each vector serves, in turn, as a template vector for comparison with all other vectors in the time series, toward the determination of a conditional probability associated with this vector. The conditional probability determines the percentage of instances in which vectors that are close to (within a preset tolerance r) the template vector have their subsequent point within the same tolerance r of the subsequent point following the template vector. Finally, approximate entropy aggregates these condi-

Anesthesiology, V 78, No 4, Apr 1993
tional probabilities into an ensemble measure of regularity.

Formally, given N data points \( u(1), u(2), \ldots, u(N) \), two input parameters, \( m \) and \( r \), must be fixed to compute approximate entropy, denoted precisely by approximate entropy \( (m,r,N) \). To define approximate entropy, first form vector-sequences \( x(1) \) through \( x(N-m+1) \) from the \{\( u(i) \)\}, defined by \( x(i) = [u(i), \ldots, u(i+m-1)] \). These vectors represent \( m \) consecutive \( u \) values, commencing with the \( i \)th point. Define the distance \( d[x(i),x(j)] \) between vectors \( x(i) \) and \( x(j) \) as the maximum difference in their respective scalar components. Use the sequence \( x(1), x(2), \ldots, x(N-m+1) \) to construct, for each \( i \leq N-m+1, C_i^m(r) = \frac{\text{number of } x(j) \text{ such that } d[x(i),x(j)] \leq r}{N-m+1} \). The \( C_i^m(r) \)'s measure within a tolerance \( r \) the regularity, or frequency, of patterns similar to a given pattern of window length \( m \). Next, define \( F_i^m(r) \) as the average value of \( \ln C_i^m(r) \), where \( \ln \) is the natural logarithm. We define approximate entropy by: approximate entropy \( (m,r,N) = F_i^m(r) - F_i^{m+1}(r) \). Approximate entropy measures the (logarithmic) likelihood that patterns that are close for \( m \) observations remain close on next incremental comparisons. Greater likelihood of remaining close, regularity, produces smaller approximate entropy values, and vice versa.

The value of \( N \) for approximate entropy computations is typically between 100 and 5,000. The value of \( m \) is usually 1, 2, or 3. Based on calculations that included both theoretical analysis and clinical applications, we have concluded that for \( m = 2 \) and \( N = 1,000 \), values of \( r \) between 0.1 and 0.25 standard deviations of the \( u(i) \) data produce reasonable statistical validity of approximate entropy \( (m,r,N) \). For smaller \( r \) values, one usually achieves poor conditional probability estimates; whereas for larger \( r \) values, too much detailed system information is lost.

When \( m = 2 \), as below, we interpret approximate entropy as a measure of the difference between the probability that runs of value of length 2 will recur within tolerance \( r \) and the probability that runs of length 3 will recur (to the same tolerance). A high degree of regularity in the data would imply that a given run of length 2 would often continue with nearly the same third value, producing a low value of approximate entropy.

For the study data, we calculated approximate entropy, with parameter values \( m = 2, r = 15\% \) of the average standard deviation, and \( N = 1,000 \), applied to the R-R time series. For such \( r \) values, we previously demonstrated the theoretical utility of approximate entropy \( (2,r,N) \) to distinguish data on the basis of regularity for both deterministic and stochastic processes and the clinical utility in the aforementioned applications to heart rate data. In choosing \( m = 2 \) and \( r = 10.0 \) ms for the present approximate entropy application, we conformed to this guideline.

Approximate entropy was calculated for 1,000 beat intervals using a Fortran algorithm run on a Macintosh computer as previously described. Average hourly approximate entropy values were subsequently calculated at 6-10-h intervals to obtain values at various times of day and night. Approximate entropy was not calculated during the intraoperative period because confounding effects of anesthetics and vasoactive drugs on heart rate would likely severely compromise a controlled environment for meaningful statistical calculations.

**Power Spectral Analysis**

The power spectral density for representative R-R interval series used to calculate approximate entropy was determined as follows: A series of 512 R-R intervals were reviewed visually for R wave determination and ectopic beats. Each series contained fewer than 5 ectopic beats. The intervals surrounding ectopic beats were removed, and the average R-R interval for the previous three beats was inserted to eliminate the effects of ectopy on the Fourier transformation. Frequency analysis of time series is preferably calculated based on evenly spaced times. Therefore, a plot of the R-R intervals was created and resampled at 4 Hz to obtain an evenly spaced series of instantaneous heart rates. The mean heart rate was then subtracted from the series, and a Daniellie smoothing filter was applied. The power spectral density plot was obtained by plotting the fast Fourier transformation of the resultant time series using S-Plus software (StatSci, Redmond, WA).

**Statistics**

Differences between the patients with good outcomes versus the patients with postoperative ventricular dysfunction were determined by Student's \( t \) test for continuous variables and chi-square or Fisher's exact test for dichotomous data with \( P < 0.05 \) as significant. Preoperative variables studied included age, sex, history of MI, hypertension, and use of beta-blockers. Intra- and postoperative variables studied included type of surgery, type of anesthesia, intraoperative time, estimated blood loss, and postoperative analgesia. A receiver operator characteristic curve was constructed to
determine the threshold approximate entropy that had the best sensitivity and specificity associated with morbidity cardiac events.

Results

Of the 23 high-risk patients studied, 9 (39%) demonstrated postoperative ventricular dysfunction, while 14 (61%) had an uncomplicated postoperative course and served as the control group. Of the nine patients with postoperative ventricular dysfunction, five sustained a postoperative MI, two developed unstable angina, and two required prolonged inotropic support.

The groups were not significantly different with respect to age, sex, history of MI, hypertension, preoperative use of beta-blockers, diabetes, vascular surgery, general anesthesia, intraoperative time, and postoperative analgesia (table 1).

Two patients who developed postoperative ventricular dysfunction also developed postoperative renal failure. One patient with a good outcome had preoperative renal failure. No other major organ dysfunction was noted.

Variability of Postoperative R-R intervals

Variability, quantified as the standard deviation of each subject's R-R interval during the period of the

Table 1. Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Postoperative Cardiac Dysfunction</th>
<th>Uncomplicated Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>76 ± 9</td>
<td>69 ± 10</td>
</tr>
<tr>
<td>Male gender</td>
<td>7/9 (77)</td>
<td>7/14 (50)</td>
</tr>
<tr>
<td>H/O myocardial infarction</td>
<td>3/9 (33)</td>
<td>3/14 (21)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5/9 (56)</td>
<td>10/14 (71)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5/9 (56)</td>
<td>4/14 (29)</td>
</tr>
<tr>
<td>Preoperative β-blocker</td>
<td>2/9 (22)</td>
<td>3/14 (21)</td>
</tr>
<tr>
<td>Vascular surgery</td>
<td>6/9 (67)</td>
<td>5/14 (36)</td>
</tr>
<tr>
<td>General anesthesia</td>
<td>6/9 (67)</td>
<td>10/14 (71)</td>
</tr>
<tr>
<td>Intraoperative time (min)</td>
<td>298 ± 149</td>
<td>232 ± 72</td>
</tr>
<tr>
<td>Intraoperative blood loss (ml)</td>
<td>514 ± 426</td>
<td>569 ± 697</td>
</tr>
<tr>
<td>Postoperative epidural analgesia</td>
<td>2/9 (22)</td>
<td>4/14 (29)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.

Table 2. Approximate Entropy (ApEn) Values

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative cardiac dysfunction (n = 9)</td>
<td>1.07 ± 0.27</td>
<td>0.40 ± 0.18*</td>
<td>0.67 ± 0.26†</td>
</tr>
<tr>
<td>Uncomplicated postoperative course (n = 14)</td>
<td>1.05 ± 0.22</td>
<td>0.74 ± 0.27*</td>
<td>0.31 ± 0.22†</td>
</tr>
</tbody>
</table>

* P = 0.003 for the lowest ApEn in patients with cardiac dysfunction vs patients with an uncomplicated course.
† P = 0.002 for the absolute difference in ApEn in patients with cardiac dysfunction vs the difference in patients with an uncomplicated course.

The lowest postoperative approximate entropy value, was not significantly different between the two groups (P = 0.09). During the postoperative period, it was 36 ± 17 ms for the group with postoperative ventricular dysfunction, and 53 ± 21 ms for the group with good outcomes.

Approximate Entropy Calculations

The average preoperative approximate entropy values were not significantly different between the two groups (table 2). The lowest approximate entropy value during the postoperative period was significantly lower in the group with ventricular dysfunction compared to the group with uncomplicated course. The absolute decrease from pre- to postoperative approximate entropy was significantly greater in the group with postoperative ventricular dysfunction. Table 3 indicates the type and timing of postoperative cardiac events in the nine patients, the preoperative approximate entropy values, and the approximate entropy value for the period immediately before the onset of morbidity. There is no

Table 3. Patients Who Sustained a Postoperative Event

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unstable angina</td>
<td>60</td>
<td>1.484</td>
<td>0.788</td>
</tr>
<tr>
<td>2</td>
<td>Unstable angina</td>
<td>76</td>
<td>0.664</td>
<td>0.415</td>
</tr>
<tr>
<td>3</td>
<td>Subendocardial myocardial infarction</td>
<td>36</td>
<td>1.257</td>
<td>0.117</td>
</tr>
<tr>
<td>4</td>
<td>Myocardial infarction/death</td>
<td>26</td>
<td>1.269</td>
<td>0.601</td>
</tr>
<tr>
<td>5</td>
<td>Subendocardial myocardial infarction</td>
<td>69</td>
<td>0.934</td>
<td>0.519</td>
</tr>
<tr>
<td>6</td>
<td>Unstable angina</td>
<td>21</td>
<td>0.725</td>
<td>0.358</td>
</tr>
<tr>
<td>7</td>
<td>Myocardial infarction</td>
<td>33</td>
<td>1.17</td>
<td>0.955</td>
</tr>
<tr>
<td>8</td>
<td>Low output state</td>
<td>Postoperative</td>
<td>0.986</td>
<td>0.469</td>
</tr>
<tr>
<td>9</td>
<td>Low output state</td>
<td>Postoperative</td>
<td>1.192</td>
<td>0.580</td>
</tr>
</tbody>
</table>
correlation between simultaneous measurements of approximate entropy and average heart rate ($R^2 = 0.018$). There was a weak correlation between approximate entropy and the more traditional measure of variability, standard deviation ($R^2 = 0.30$).

The perioperative approximate entropy values for each patient in the group who demonstrated postoperative ventricular dysfunction are depicted in figure 1, and for patients with good outcomes in figure 2. All but one of the patients in each group had a preoperative approximate entropy value of >0.7. Both of the patients with a low preoperative approximate entropy were older than 80 yr. All of the patients with postoperative ventricular dysfunction demonstrated a decrease in approximate entropy at some point during the postoperative period to below 0.7, and the patient with a low initial approximate entropy had the lowest subsequent approximate entropy value, less than 0.45. In the patients with good outcomes, 7 of 14 (50%) had at least one postoperative approximate entropy value <0.7.

Two distinct approaches to evaluate the relationship between approximate entropy and postoperative ventricular dysfunction were performed. Defining a low postoperative approximate entropy as <0.7, the sensitivity and specificity of the occurrence of two contiguous periods (8–10 h apart) of low values were calculated. For patients with good outcomes, only 3 of 14 (21%) had a sustained decrease in approximate entropy <0.7 for greater than one period studied. For patients with postoperative ventricular dysfunction, eight of nine (88%) had a sustained decrease in approximate entropy <0.7 for greater than one period studied. Therefore, two consecutive low approximate entropy values had a sensitivity of 88% and a specificity of 79% for being associated with ventricular dysfunction.

An alternative approach is to determine the single approximate entropy value that combines the best sensitivity and specificity. Using a receiver operator characteristic curve, an approximate entropy of below 0.55 gave the best combination of sensitivity (88%) and specificity (71%) for being associated with morbid cardiac events (fig. 5). Table 3 lists the nine patients who sustained postoperative ventricular dysfunction, with the corresponding type of morbidity and preoperative and pre-cardiac morbidity approximate entropy values. Using the decision analysis, with approximate entropy of <0.55 signifying morbidity, approximate entropy was predictive of morbidity in four of seven (57%) patients in whom the timing of the postoperative event was determinable. These results suggest that approximate entropy may be predictive of subsequent morbidity in a significant percentage of patients.

Figure 4 depicts the R-R interval trace for two patients, one during the period of postoperative ventricular dysfunction and the other, a patient with a good
Fig. 3. This receiver operator characteristic curve illustrates the relationship between sensitivity and 1-specificity at various approximate entropy levels and the association with ventricular dysfunction. Each point is labeled with the corresponding approximate entropy value.

outcome, during the postoperative period. Both patients demonstrated a similar variability (standard deviation of R-R intervals). The upper tracing has a smaller approximate entropy value than the lower tracing and demonstrates greater regularity, although classically recognizable patterns are not readily apparent. This illustrates the utility of approximate entropy as a complementary statistic to more classic variability measures.

Fig. 4. The R-R interval plots for 1,000 consecutive points in two patients during the postoperative period. (Top) Represents a patient with postoperative ventricular dysfunction; standard deviation of R-R interval = 54 ms; approximate entropy = 0.549. (Bottom) Represents a patient with a good outcome; standard deviation of R-R interval = 45 ms; approximate entropy = 0.887.

Fig. 5. The power spectral density plots of the two R-R interval plots in figure 4. Spectrum (in log ms²/Hz) is plotted against frequency (in Hz). (Top) Corresponds to the top graph in figure 4 of the patient with postoperative ventricular dysfunction. (Bottom) Corresponds to the bottom graph in figure 4 of the patient with a good outcome. The upper tracing has more total power concentrated in a narrow frequency band.
order differences between the two spectra in any particular frequency range.

Discussion

Approximate entropy is a statistic that quantifies a notion of regularity in a series of numeric values. This is distinguished from the measure of spread about a baseline average representing a measure of variability, such as standard deviation. Larger values of approximate entropy correspond to greater randomness and unpredictability, smaller values to more instances of recognizable patterns or features in the data. For example, a sine wave may have a large standard deviation but represent a very regular pattern with a low approximate entropy.

Significantly lower approximate entropy values were observed in our high-risk patients who demonstrated postoperative ventricular dysfunction compared with patients who had an uncomplicated postoperative course. A postoperative approximate entropy value of <0.7 at some point suggests postoperative ventricular dysfunction; however, it has a specificity of only 50%. To realize greater specificity for ventricular dysfunction, we can apply two distinct criteria, two consecutive (8 h apart) approximate entropy values below 0.7, specificity 79%, and a single approximate entropy value <0.55, specificity 71%. The association of low approximate entropy values with poor outcome quantifies the apparent reduced randomness and more recognizable features in the heart rate of patients who developed ventricular dysfunction. The low preoperative approximate entropy in the two patients older than 80 yr is consistent with previous studies. The results are consistent with other studies associating approximate entropy decrease with sickness and a greater risk of clinically significant developments. These results combined with the data in table 3 suggest the usefulness of approximate entropy is the early indication of ventricular dysfunction.

Although 88% of the patients with postoperative ventricular dysfunction demonstrated a low approximate entropy postoperatively, overall, approximate entropy was low in only 57% of the patients before ventricular dysfunction. This finding most likely reflects the fact that some of the events were acute in nature, without any predisposing conditions, and approximate entropy did not decrease until ventricular dysfunction occurred.

The algorithm for approximate entropy is somewhat similar in appearance to two algorithms to estimate the theoretical Kolmogorov-Sinai entropy, given by Eckmann and Ruelle and Grassberger and Procaccia. Approximate entropy has three technical advantages in comparison to Kolmogorov-Sinai entropy for statistical usage. Kolmogorov-Sinai entropy is badly compromised by steady, low levels of noise; generally requires a vast amount of input data to achieve convergence; and is usually infinite for stochastic processes. Approximate entropy is nearly unaffected by noise of magnitude below r, is robust to occasional very large or small artifacts, gives meaningful information with a reasonable number of data points, and is finite for both stochastic and deterministic processes. Therefore, approximate entropy has the capability to distinguish versions of stochastic processes, reasonable candidates for heart rate models, whereas Kolmogorov-Sinai entropy would be unable to do so.

The accurate modeling of heart rate appears to be a very difficult problem. The advantage of a model-independent statistic is that it can distinguish classes of systems for a wide variety of models. Mean, variability, and approximate entropy are all model-independent statistics, in that they can be applied to many classes of systems. In applying approximate entropy, we are not testing for a particular model form, such as deterministic chaos; we are attempting to distinguish among data sets of the basis of regularity. Such evolving regularity can be seen in both deterministic and random (stochastic) models.

Control of heart rate is complex and is related to the interaction of multiple systems. The parasympathetic and sympathetic nervous systems exert their effect through the vagus and cardioaccelerator nerves on the sinus node. Respiration also influences its effect on heart rate through the parasympathetic system, resulting in the "respiratory sinus arrhythmia." Additionally, circulating catecholamines can have profound effects on the sinus node. The renin-angiotensin system also is thought to exert its effect through hormonal mediators. Finally, local factors may exert some control over heart rate.

Several investigators have proposed using power spectral analysis in the study of heart rate variability. In a series of animal and human experiments, power (amplitude squared) in the frequency range of 0.15–0.40 Hz has been associated predominantly with parasympathetic tone, while power in the frequency range 0.05–0.15 Hz has been associated with sympathetic

Anesthesiology, V 78, No 4, Apr 1993
and, to a lesser extent, parasympathetic tone. Perturbations in any of these physiologic systems can result in a change in heart rate regularity as well as variability. Changes in autonomic function are known to have profound effects upon heart rate. Placental underperfusion is thought to lead to fetal nervous system anoxia and flattening of the fetal heart rate tracing. Patients with congestive heart failure demonstrate a chronic elevation of the sympathetic nervous system. This results in a predominance of the low-frequency component of heart rate variability.

Power spectral analysis of heart rate recently has been applied to the perioperative patient. Latson et al. have demonstrated that the power spectrum varies depending upon the anesthetic agent and surgical stimuli used, supporting the exclusion of intraoperative data from our analysis. Several investigators also have examined the power spectra in patients prior to undergoing coronary artery bypass grafting and demonstrated that baseline autonomic state varies and may influence the response to induction of anesthesia. However, the appropriate clinical interpretation of the power spectrum has not been resolved. Changes in autonomic tone have been expressed as changes in the absolute power, the ratio of the power or the percent power in each frequency band. Examination of the power spectra corresponding to the two tracings in figure 4, shown in figure 5, provides a partial understanding of a general relationship between spectral information and approximate entropy. Both spectra are very broad-banded and noisy for frequencies greater than 0.3 Hz. The upper tracing has more total power concentrated in a narrow frequency range (here the low frequency), whereas the lower tracing is broader-banded, with more power spread over a greater frequency range. Again, this interpretation implies greater regularity of the upper tracing from the patient with postoperative ventricular dysfunction: a spiked, narrowest-banded spectrum corresponds to a periodic function, e.g., a sinusoid.

In general, smaller approximate entropy and greater regularity correspond to more ensemble dependence in time series and process characterization. The two opposing extremes are (1) periodic and linear deterministic models, which produce very peaked, narrow-banded spectra, with low approximate entropy values, and (2) sequences of independent random variables for which time series yield intuitively highly erratic behavior and for which spectra are very broad-banded, with high approximate entropy values. Intermediate to these extremes are deterministic, nonlinear chaotic models and correlated stochastic processes, both of which can exhibit complicated spectral behavior. In some instances, the comparison in the spectral domain of healthy and diseased states may be crucial, when pronounced differences in a particular frequency band suggest underlying specific physiologic disorder. In other instances, such as in the comparison in figure 5, there is more of an ensemble difference between the time series, viewed both in the time domain and in the frequency domain, and the need remains to encapsulate the ensemble information into a single value, a replicable test statistic, to distinguish these data sets.

Patients who develop left ventricular failure also may lose their complex control over heart rate. Myocardial ischemia has been related to withdrawal of parasympathetic tone. Similarly, after an MI, patients demonstrate a reduction in heart rate variability and the high-frequency component associated with vagal tone. These losses, withdrawals, and reductions would typically result in a more regular heart rate, with a corresponding decrease in approximate entropy. Of note, our patient in figure 5 who demonstrated ventricular dysfunction exhibited less high-frequency band power than that noted in the patient with a good outcome.

The patients who developed left ventricular dysfunction exhibited lower complexity (greater regularity) in heart rate, visually manifested by more evident patterns in associated tracings. Although a small standard deviation of R-R intervals (variability) often is correlated with postoperative morbidity and a low approximate entropy, many "poor outcome" patients in this study demonstrated a regular pattern of high-amplitude fluctuations, statistically marked by a large standard deviation coupled with a low approximate entropy.

We have calculated approximate entropy at discrete intervals during the 4-day perioperative period. We therefore cannot exclude significant fluctuations between data periods; further studies refining the current findings would be useful. In several patients with good outcomes, approximate entropy decreased for one period; and it increased briefly in one patient with a poor outcome. However, these changes were transient.

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Approximate Entropy and Postoperative Dysfunction

For the majority of patients, the decrease in approximate entropy of heart rate occurs before ventricular dysfunction or coincident with it. A change in the inputs that control heart rate also may affect left ventricular dysfunction and cardiac morbidity or may be the result of damage to the cardiovascular system.

The application of a computationally intensive statistic, such as approximate entropy, to ECG data thus continues in the direction of increasing statistical and computerized analyses of these data. It is increasingly being recognized that more invasive and expensive procedures have not reduced morbidity and that information from the ECG is underutilized. 29 Computerized analysis of the ST segment of the ECG has revealed that the majority of episodes of myocardial ischemia go unrecognized by conventional analysis. 30 The addition of the computerized monitors have allowed earlier interventions. 31 Approximate entropy may complement information about myocardial ischemia derived from the ST segment and provide a noninvasive determination of functional status. Currently, approximate entropy indicates that there is a difference between good and poor left ventricular function, based on heart rate data, without indicating the cause of the difference.

This is the first indication that a suitable quantification of heart rate variation can provide a simply calculated noninvasive marker of outcome in noncardiac surgery patients. Further research into heart rate regularity may provide insight into the nature of perioperative cardiac dysfunction.

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Anesthesiology, V 78, No 4, Apr 1993

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