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The mixing rate of the arterial blood pressure waveform Markov chain is correlated with shock index during hemorrhage in anesthetized swine

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Abstract:

Identifying the need for interventions during hemorrhage is complicated due to physiological compensation mechanisms that can stabilize vital signs until a significant amount of blood loss. Physiological systems providing compensation during hemorrhage affect the arterial blood pressure waveform through changes in dynamics and waveform morphology. We investigated the use of Markov chain analysis of the arterial blood pressure waveform to monitor physiological systems changes during hemorrhage. Continuous arterial blood pressure recordings were made on anesthetized swine (N=7) during a 5 min baseline period and during a slow hemorrhage (10 ml/kg over 30 min). Markov chain analysis was applied to 20 sec arterial blood pressure waveform segments with a sliding window. 20 ranges of arterial blood pressure were defined as states and empirical transition probability matrices were determined for each 20 sec segment. The mixing rate (2nd largest eigenvalue of the transition probability matrix) was determined for all segments. A change in the mixing rate from baseline estimates was identified during hemorrhage for each animal (median time of 13 min, ~10% estimated blood volume, with minimum and maximum times of 2 and 33 min, respectively). The mixing rate was found to have an inverse correlation with shock index for all 7 animals (median correlation coefficient of -0.95 with minimum and maximum of -0.98 and -0.58, respectively). The Markov chain mixing rate of arterial blood pressure recordings is a novel potential biomarker for monitoring and understanding physiological systems during hemorrhage.

SECTION I. Introduction

Hemorrhage is a medical emergency frequently encountered by clinicians in situations as diverse as emergency and operating rooms, intensive care units or mass casualty incidents. A significant amount of blood loss due to hemorrhage can cause hemodynamic instability, inadequate tissue perfusion, hemorrhagic shock, and, if left untreated, eventual death [1]. Hemorrhage is the cause of 40% of deaths after a traumatic injury in the United States [2]. One of the limitations to treating hemorrhage is that vital signs can appear normal until a significant amount of blood has been lost. This delay in vital sign changes is due to the action of the sympathetic and parasympathetic control of blood pressure, which can effectively compensate until blood loss is significant. There is therefore much interest and value in identifying early and sensitive biomarkers of hemorrhage.

Heart rate variability is one method suggested in the literature to identify hemodynamic instability due to hemorrhage [3]. Although it has been shown that aggregate group mean values of heart rate

variability are correlated with stroke volume, heart rate variability is less reliable when tracking individual reductions in central volume during progressive lower body negative pressure or simulated hemorrhage [4]. It has been suggested that reductions in vagal activity assessed with heart rate variability or baroreflex sequences may represent identifiable early markers of hemorrhage [5]. Loss of blood volume triggers withdrawal of the parasympathetic nervous system and activation of the sympathetic nervous system, which tries to compensate for the drop in blood pressure. As a result, during the early stages of hemorrhage the mean arterial pressure may remain constant and when a significant change in blood pressure is eventually identified, the available medical interventions may be limited. Markov chain methods may describe changes in the compensating autonomic system dynamics related to hemodynamic instability prior to changes in traditional vital signs, potentially providing an early indicator of hemorrhage.

A Markov chain is defined as a system with different states where the transition probability from one state to the next depends only on the current state, the Markov assumption [5]. A discrete Markov chain can be described by a countable number of states (S) and a transition probability matrix **(P)** which describes the evolution of a sample path from one state to the other. Regular Markov chains have a limit distribution or steady state. The mixing rate of a Markov chain represents how fast the system is approaching the steady state. Empirical Markov chains can be constructed from sample time series data or first principles. Eigenvalues of Markov chains capture information about changes in system dynamics, which cannot otherwise be captured with nonlinear methods such as Poincare plots [6]. Properties of the transition matrix eigenvalues such as the presence of complex numbers, information content of the limit distribution, and the mixing rate (i.e. the second largest eigenvalue) can be examined to understand the underlying system.

The change in dynamics of the physiological systems that are represented in the arterial blood pressure (ABP) waveform as the body attempts to compensate for blood loss may be captured by the eigenvalues of the Markov chain. An empirical Markov chain can be constructed from ABP recordings. Each state of the Markov chain can be defined as a blood pressure range (e.g. 80 — 85 mmHg), and the steady state then represents the probability that the signal is at any one range. As the system dynamics and waveform morphology change, the system will approach steady state faster or slower and this can be observed through the mixing rate.

Here, we present a method to monitor the mixing rate of ABP waveforms. We hypothesized that a detectable change in the Markov chain mixing rate will occur prior to noticeable changes in traditional vital signs in an anesthetized swine model undergoing hemorrhage.

SECTION II. Methods

A. Experimental Protocol

Experiments were performed at University of Texas Medical Branch at Galveston. The protocol was approved by the University of Texas Medical Branch Institutional Animal Care and Use Committee (IACUC). Immature swine (N=7, female, 37.1 ± 15.1 kg (mean ± SD)) were propofol anesthetized and instrumented with bilateral catheters in femoral arteries and veins. An arterial pressure catheter was advanced 40 cm into the artery for proximal arterial readings. The carotid artery was catheterized for hemorrhages, a Foley catheter was inserted into the bladder, and a splenectomy was performed. The

animal was given a period of at least 30 minutes to recover upon the completion of surgery before data collection.

Data was collected during a continuous hemorrhage of 10 m1/kg over 30 min. Physiological monitoring began at least 5 min prior to the initiation of the hemorrhage and occurred throughout the experiment. ABP was recorded using a standard clinical pressure transducer at a sampling rate of 1,000 Hz.

B. Signal Processing

Heart rate and beat-by-beat blood pressures (systolic, diastolic, mean) were calculated from the ABP waveform using the publicly available code by Zong et al. [7] [8]. This algorithm uses a windowed and weighted slope sum function to identify ABP waveform features for each beat. ABP waveform data were down sampled to 125 Hz prior to feature identification. Shock index was calculated by dividing heart rate with systolic blood pressure [9].

C. Markov Chain Analysis

For computational efficiency, ABP waveforms were down sampled to 100 Hz for the Markov chain analysis. A moving average window (length 2000 samples) was subtracted from the ABP waveform to remove the effect of a change in the mean arterial pressure from the Markov model.

An empirical Markov chain was created from the ABP waveform by segmenting the range of pressure (minimum to maximum pressure recorded for each segment) over a specified window into a fixed number of 'states', each covering an equal range of blood pressure. Fig. 1a shows a sample ABP waveform filtered using a moving average filter with the same length for two seconds with three states for illustration. The range of blood pressure for each state is computed by dividing the difference of the maximum to the minimum of the blood pressure waveform by three. The empirical transition probability matrix represents the probability that blood pressure will enter any state given only the state that it is currently in. The entry at the i^{th} row and j^{th} column represents the probability with which blood pressure would change from the ith to jthstate. To compute the transition probability matrix, the state is defined for each sample by identifying the blood pressure range the sample lies in. Then, the matrix is filled by computing the number of instances a sample moves from state i(S^i) to state j(Sj) over all samples. Finally, the matrix is normalized by dividing each row with the sum of the row to have a probability distribution. These probabilities are shown by the arrow labels in the Markov chain in Fig. 1b which corresponds to the example ABP waveform in Fig. 1a.

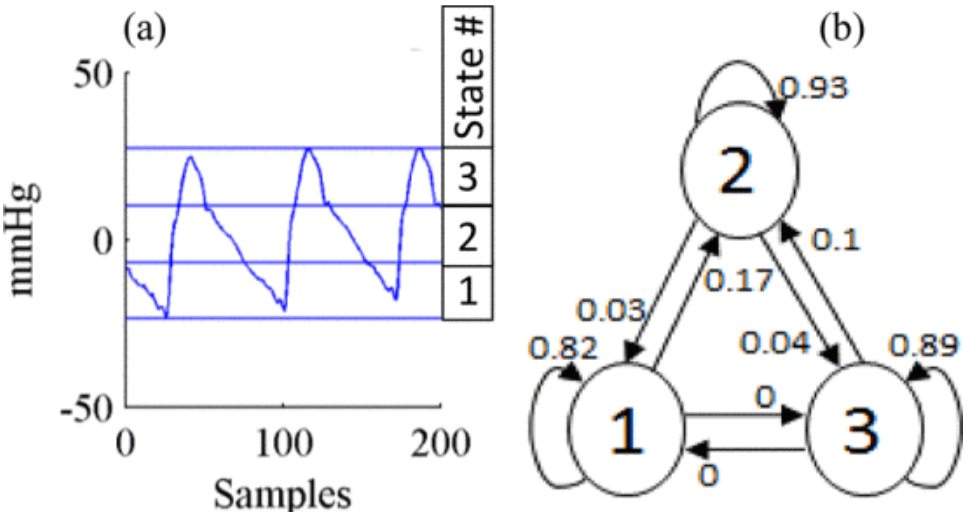

Figure 1. (a)An example of a 2 sec recording (sampled at 100 hz) of an arterial pressure waveform with 3 states. (b) Example markov chain and its transition probabilities for the three states from the arterial blood pressure wavefrom in (a).

The eigenvalues and the left eigenvectors are determined from the transpose of the transition probability matrix. For a regular Markov chain, all eigenvalues have magnitude less than or equal to 1. 1 is always an eigenvalue, and the eigenvalue with the second largest magnitude is defined as the mixing rate.

We tested a range of window sizes (5 to 30 seconds) and number of states (5 to 30) using the FDA Scientific Computing Laboratory Blue Meadow cluster with Octave parallel computing to identify the appropriate settings for observing changes in the mixing rate of the ABP waveform. The final window length and number of states used for the results reported here were selected as 20 sec and 20, respectively.

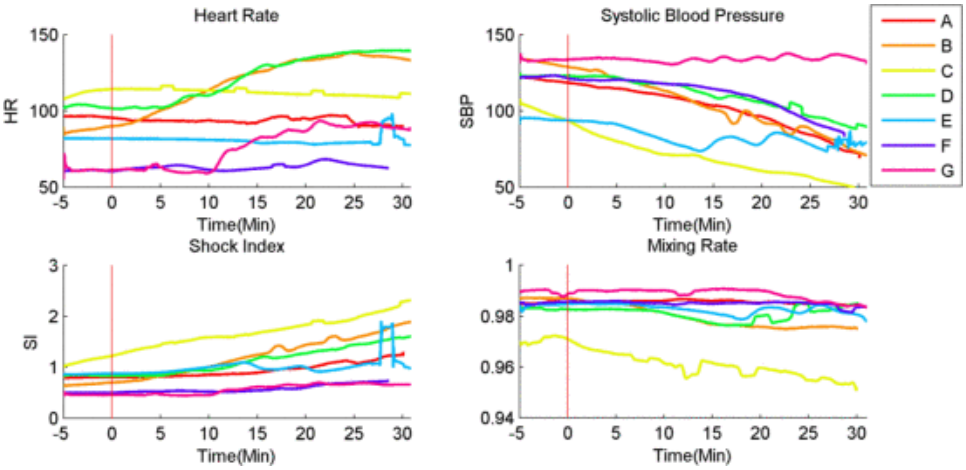

Figure 2. The vital signs (heart rate, systolic blood pressure, and shock index) for each animal along with the mixing rate during hemorrhage. Each color represents a different animal. The red vertical lines in each subplot indicate the start of hemorrhage.

D. Correlation Coefficient

Pearson correlation coefficients were determined between the mixing rate and each vital sign (heart rate, pulse pressure and systolic blood pressure). The mixing rate (determined at 100 Hz of ABP) was first interpolated using a cubic spline to match the sampling rate of the vital signs (determined at 125 Hz of ABP) that were computed using the Physionet code and all signals were then smoothed using a moving average filter (100 samples window) before computing the correlation coefficients.

E. Detection of Change in the Mixing Rate

A probabilistic approach was applied to detect a change in the mixing rate during hemorrhage. The distribution during the 5 min baseline period was considered and the 95% confidence interval was determined. A change in the mixing rate was considered at the first instance from the start of hemorrhage when 4 mixing rates (selected from a twelve point window, each of them three points apart) were outside of the 95% confidence interval in the same direction.

SECTION III. Results

Fig. 2 shows the vital signs and the mixing rate for each animal starting from 5 min before the start of hemorrhage through the 30 min hemorrhage. Hemorrhage was initiated at the red vertical line (0 min). There was significant inter-animal variability in the heart rate during the baseline period. The heart rate exhibited a heterogeneous response to hemorrhage between animals. Heart rate was almost constant in 4 animals while in 3 a dramatic rise in heart rate occurred. Differences in the heart rate response to hemorrhage between animals do not appear to be related to the baseline heart rate, Fig. 2. Most animals have a steady decline in blood pressure and pulse pressure. Shock index, which captures the changes in both heart rate and blood pressure rises for all animals. The mixing rate decreases during hemorrhage.

The correlation coefficients between the mixing rate and the vital signs quantify the relationship between the two, Table I. Overall, the mixing rate was inversely correlated with heart rate and positively correlated with blood pressure and pulse pressure, but these were not consistent across all animals. The mixing rate and shock index showed a strong inverse correlation for all animals.

Table I. Correlation coefficients between mixing rate and vital signs during hemorrhage

Animal	Heart Rate	Systolic Blood Pressure	Pulse Pressure	Shock Index
A	-0.10	0.47	0.56	-0.59
B	-0.99	0.94	0.98	-0.93
C	-0.09	0.96	0.93	-0.95
D	-0.99	0.98	0.93	-0.98
E	0.36	0.78	-0.31	- 0.82
F	-0.76	0.97	0.96	-0.98
G	-0.98	-0.66	-0.95	- 0.97
Group Statistics				
Median	-0.76	0.94	0.93	-0.95
Min	-0.99	-0.66	-0.95	-0.98
Max	0.36	0.98	0.98	-0.59

The first time that a statistically significant change in the mixing rate was identified for each animal is presented in Table II. There was significant variation between swine in the time that a change was detected, ranging from 2–33 min. The change in systolic blood pressure, heart rate, pulse pressure, and the shock index at the time a change in the mixing rate was detected is also presented in Table II. We see that the mixing rate change is identified for most swine prior to a significant change in the heart rate (median change of 5 BPM), pulse pressure (median change of 3 mmHg) or even shock index (median change of 0.19 BPM/mmHg). At the time a change in the mixing rate was detected, the systolic blood pressure had dropped by a median of 19 mmHg.

Table II. Timing of significant change in mixing rate and corresponding vital sign changes

Animal	Time till Mixing Rate change detected (min)	Δ from Baseline			
		SBP (mmHg)	*HR (BPM)*	*PP (mmHg)*	*SI (BPM/ mmHg)*
A	25	-38	0	-11	0.37
B	2	-7	5	-3	0.07
C	7	-23	6	-7	0.35
D	13	-17	21	-13	0.33
E	17	-19	-2	1	0.19
F	33	-19	4	10	0.14
G	12	-1	6	-2	0.04
Group Statistics					
Median	13	-19	5	-3	0.19
Min	2	-38	-2	-13	0.04
Max	33	-1	21	1	37

a. Time from the start of hemorrhage that a change was detected in the Mixing Rate using the approach outlined in II.E.

b. SBP: systolic blood pressure, HR: heart rate, PP: pulse pressure, SI: shock index

SECTION IV. Discussion

In an anesthetized pig model, the Markov chain mixing rate of the ABP waveform is strongly correlated with the vital signs. It has a correlation greater than 0.5 with systolic blood pressure (5 out of 7 animals) and inverse correlation greater than 0.5 with heart rate (4 out of 7 animals) and shock index (7 out of 7 animals).

The relationship between the mixing rate and the shock index indicates that this new variable might be an indicator of impending hemodynamic imbalance. Shock index is widely used in clinical scenarios for identifying patients that need immediate care. It has been shown that patients with an increasing or high shock index have a higher mortality likelihood [10]. The decreasing mixing rate may provide further information about the hemodynamic status of a patient. The shock index is computed from mean vital signs whereas the mixing rate is derived from the dynamics/waveform morphology. As a result, it is not necessary that they provide the same information. The resulting high correlation suggests that the Markov chain mixing rate is capturing changes in the system dynamics or waveform morphology that occur due to the same physiological system changes that affect the mean heart rate and/or blood pressure.

A decreasing mixing rate indicates one special kind of hemodynamic imbalance that occurs due to hemorrhage. Eigenvalues of Markov chains have previously been shown to be identifiers of changes in system dynamics [6]. The construction of the Markov chain from time series data indicates that a change

in waveform morphology or a change in system dynamics might cause a decreasing mixing rate. ABP waveform morphology has been shown to change during central hypovolemia [11]. In the present study, we did not determine if the effects of dynamic or morphological changes in the ABP waveform affect the mixing rate. We suspect that both contribute to the observed decrease in the mixing rate during hemorrhage. To identify if the changes in mixing rate are due to a specific change in waveform morphology, a comparative study of the timing of the changes in the ABP morphology and the timing of the change in mixing rate is needed.

The baseline heart rate and systolic blood pressure presented significant inter-animal variability. The source of the baseline inter-animal variability is unclear as all animals were prepared using the same procedure. The inverse correlation between the mixing rate and shock index occurred in all animals regardless of the baseline vital signs and response to hemorrhage.

The mixing rate change could be observed for a specific number of states (20) and specific window size (20 seconds). This suggests that the waveform morphology or system dynamics changes can be captured by this method with 20 sec waveform segments. This might be useful to understand the utility and the limitation of this method to identify hemorrhage or predicting impending hemodynamic imbalance. Further work is needed to determine the utility of the mixing rate in hemodynamic monitoring.

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