TOWARD NEW VITAL SIGNS: TOOLS AND METHODS FOR PHYSIOLOGIC DATA CAPTURE, ANALYSIS, AND DECISION SUPPORT IN CRITICAL CARE

By

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Dissertation

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in

Biomedical Engineering

May, 2006

Nashville, Tennessee

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To Marce and James

And those who helped them through tough times

ACKNOWLEDGEMENTS

Many individuals and organizations, through a variety of financial, professional, and personal contributions, made this work possible. Within Vanderbilt University, financial support was provided by the Medical Center Divisions of Trauma and Surgical Critical Care, Cardiology, Pediatrics, and Biomedical Informatics during various phases of this work. The Vanderbilt University Graduate School, through a dissertation enhancement award, funded equipment that enabled two additional beds to be equipped with the SIMON (Signal Interpretation and Monitoring) system. A Harold Sterling Vanderbilt Scholarship provided partial salary support during the early stages of this effort.

In terms of extramural financial support, the National Library of Medicine provided two years of salary support and equipment monies during early phases of this work through a pre-doctoral training grant (LM00053-01A1). Funds provided by the National Science Foundation supported early equipment purchases (CDA-9617519), and a contract from Suntory Pharmaceuticals funded expansion of SIMON to six additional ICU beds. Chris Darnell of Hewlett Packard Medical Systems (now Philips) provided in-kind support through no-cost equipment loans for interface testing and development.

Professional contributions include early work on the SIMON project by many people including Drs. Benoit Dawant, Eric Manders, Antoine Geisbuhler, Drew Gaffney, Bill Stead, Randy Miller, Dan Lindstrom and Karlkim Suwanmongkol. These efforts inspired a technical vision of an inexpensive, automated, reliable, physiologic data collection and management system for routine clinical and research use. While this

capability was beyond our grasp in those early years, the technical lessons learned and the clinical exposure to the neonatal and coronary intensive care units were invaluable.

The project began to thrive with support from the Vanderbilt Division of Trauma and Surgical Critical Care, driven by the vision and enthusiasm of its director, Dr. John Morris. Under his skilled clinical, research, and administrative leadership SIMON expanded to monitor an entire intensive care unit, enabling physiologic data from a large clinical population to be reliably captured and linked to an existing outcomes registry. Such an implementation, as well as the study of clinical alerts described in Chapter 3, could not have succeeded without the assistance of clinical nursing and administrative staff, led by Lenys Biga, Sarah Hutchinson, and Chris Kleymeer. Chris's ability to tackle both administrative responsibilities and technical development made solving many problems not only remarkably efficient, but also enjoyable. Dee Mewbourne and Carla Lasyone never failed to provide efficient and friendly help with any number of administrative needs.

The first research analyses on this rapidly growing physiologic database were guided by discussions with the Trauma and Surgical Critical Care faculty and fellows at Vanderbilt. In particular, Dr. Jeff Guy echoed a catchphrase of one of his former colleagues: "Railroad tracks vital signs" (i.e. parameters appeared as parallel lines, with minimal variability) upon seeing a critically ill patient's physiologic data graphs. This comment led to a number of subsequent discussions and analyses related to variability in the SIMON data. These early research efforts were helped a great deal by Judy Jenkins, who continues to lend her broad expertise in research administration and clinical medicine to this work. She has helped to obtain funding, managed IRB approvals,

answered endless clinical and operational questions, and co-written and edited manuscripts. Dr. Eric Grogan, then a surgical resident in the Veteran's Affairs Quality Scholars Program, also contributed a great deal to the early analyses and manuscripts studying heart rate in the trauma ICU population. These efforts jump-started our research in heart rate variability, leading to a number of fruitful collaborations with Vanderbilt experts in medical informatics, autonomic function, and health care quality research, including Drs. Renee Stiles, Dan France, Ted Speroff, Asli Ozdas, Russ Waitman, and Paul Harris.

A number of faculty and staff members from the Vanderbilt Department of Biomedical Engineering supported this work through technical and administrative expertise, advice, and encouragement. Drs. Paul King, Rich Shiavi, and Bob Roselli have been extremely helpful through their service on the dissertation committee, and for their advice over the years. Drs. Tom and Alene Harris's willingness to consistently share their insight, experience, and expertise about a wide range of topics, from science to education to faith, contributed to my personal and professional development immensely. Special thanks go to Dr. Stacy Klein for her friendship, persistent encouragement, and help in managing a number of tasks in the dissertation and defense process. The administrative support, encouragement, and occasional comic relief provided by Karen Fuller and Janiece Harrison throughout this work were indispensable.

Finally, I have been extremely fortunate to have the friendship, camaraderie, and unconditional support of family and friends throughout this effort. I am indebted to my early office mates at Vanderbilt - Kim Radford, Neal Sanders, Yuh-Show Tsai, and Ed Westberg – for sharing many professional and personal learning experiences, stimulating

conversations, and other fond memories. Similarly, friendships with other graduate students, including Linda Auther, Andy Bass, Hugh Barnaby, Tushar Desai, Lisa Faber, Adosh Mehta, Diane Muratore, Will Nau, Tom Rich, Kevin Seale, and Dan Shima contributed immeasurably to my personal growth and, in many cases, professional development over the course of this work. Most importantly, this work would not have begun without the caring, unconditional support my parents have provided in all my endeavors, and it would not have reached fruition without the love and patience of a truly special woman: Marcella Woods.

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CHAPTER I

INTRODUCTION

Objective

The overarching goal of this research is to improve the care of critically ill patients via novel physiologic data capture and decision support tools. *Dense physiologic data capture*, or the automated, reliable, second-by-second archiving of patient vital signs, provides amounts of data that greatly exceed that of traditional recording methods. Studying this data may yield new algorithms, or "vital signs", that predict patient outcome, clinical *trajectory* (improvement, stability, or deterioration) and stratify patients based on acuity, cost, or suitability for particular interventions. The corresponding research hypothesis is that these *new vital signs*, available through techniques of dense physiologic data capture and automated analysis, will inform medical decision-making in clinically significant, cost-effective ways.

Thus, this work seeks to bridge discovery of new algorithms based on dense physiologic data with their clinical application as new vital signs. The first prototype new vital sign presented is heart rate variability (HRV), and the domain of intracranial pressures (ICP) management is used to illustrate decision-support technology based on dense physiologic data. The following specific aims demonstrate how HRV and potentially other new measures can be discovered and implemented in a working intensive care unit (ICU).

Specific Aims

Specific Aim 1. *Design and implement an architecture for automated dense physiologic data capture, display, and decision support in a working ICU:* Commercial patient monitoring systems do not provide the long-term dense (i.e. second-by-second) data storage or custom signal processing capabilities required by this work. Assessing new algorithms requires data from clinical populations large enough to provide sufficient statistical power, and therefore requires information storage beyond the typical 48 to 72 hours provided by commercial systems. Providing effective decision support to clinicians based on new algorithms entails computations beyond the threshold and simple trend detection capabilities currently available on the market. Finally, data capture, storage, and processing must be automated, as a significant contribution of this work is to demonstrate feasibility in a working ICU. The first aim of this research is to develop and implement infrastructure for automated dense physiologic data capture, processing, and display.

Specific Aim 2. *Illustrate medical decision support based on dense physiologic data capture, and assess impact on patient care:* Information technology improves patient care to the extent it improves medical decision-making. Today's commercial systems provide limited clinical decision-support in terms of physiologic information display, event detection, or alerting. Because customizing these systems is expensive or impossible, novel tools will be needed to bring this information to the clinician once new algorithms based on patient physiology have been clinically validated. The second aim of this work is to demonstrate detailed, summary-level displays based on dense physiologic data, and to assess clinical alerts in the domain of ICP management.

Specific Aim 3. *Demonstrate new measurements derived from dense physiologic data that stratify patients by outcome, acuity, or adverse events:* Decades of research suggest that densely-sampled physiologic data will yield clinically significant information unavailable via conventional monitoring techniques. Such analysis will provide *new vital signs* that stratify patients into populations of clinical interest, predicting mortality or adverse events in time for introduction of new therapy. However, a number of barriers exist to validating research findings in large clinical populations. The final aim of this research is to illustrate the "proof of concept" that one new vital sign, HRV, can be applied to stratify patients by outcome and acuity in clinically significant, cost-effective ways.

Significance

Fundamental clinical approaches for assessing vital signs have changed little since 1903, when Cushing asserted the importance of periodically measuring a patient's heart rate and blood pressure[1]. While technology has improved sampling methods and added parameters to the milieu, interpreting patient physiology remains largely a manual, intermittent process. Ephemeral measurements of flows, pressures, and electrical activity within the body are dutifully recorded by nursing staff, but only in the most urgent circumstances is data recorded, or even reviewed, more than once per hour.

More frequent sampling and automated processing of physiologic data yields significant new information, as evidenced by a growing body of research. When coupled with electronic decision support tools, such information potentially improves quality and efficiency of medical care. In the intensive care unit, where acuity and costs are the

highest in the health care system, even modest improvements can yield significant savings.

Initiating these improvements requires overcoming technical, scientific, and cultural barriers. In the short-term, this work is significant in that it provides a road map to overcome these barriers, and consequently, contributes to the fields of medical informatics, physiology, and surgical critical care. A low-cost system for automated, continuous, dense physiologic data capture and decision support in a working ICU is described. The system has been in use continuously since 2000 on more than 3500 patients, and has been successfully deployed at a second clinical site. Additionally, a measurement of HRV has been developed, refined, and validated in a population of over 1000 patients. The result is not only a new predictor of mortality but also represents proof of concept that a working intensive care unit can serve as a rich, "automatic" source of data to discover new predictive patterns in patient physiology.

Ultimately, study of HRV and other "new vital signs" may correlate failure of the autonomic nervous system or other neural and hormonal communication pathways with specific injuries, diseases, or patient characteristics. These studies could, in turn, illuminate regulatory mechanisms uniting systems, organs, cells, proteins, and genes. Such knowledge provides a basis for additional basic science research, and informs design of the next generation of ICU decision support tools to improve quality and efficiency of heath care.

Background

ICU Decision Support Based on Physiologic Data

Many systems have been conceived to collect and process bedside medical device data with the ultimate goal of improving medical decision-making. Customized computer systems have been used to collect and manage physiologic data from critically ill patients as early as the mid-1960's[2], and continue to be reported in the literature[3-9]. Generic decision-support models and monitoring frameworks have been defined specifically with dense physiologic data in mind[10-14]. However, few systems employing complex, generic decision support models have reached routine clinical use. More successful implementations are restricted to specific problem domains such as ventilator[15-19] and drug infusion[20-21] management, even to the point of fully automatic "closed loop" control of these devices[22-23].

Other systems, without extensive decision support models, have successfully delivered clinical alerts beyond those available from commercial monitors[24-26], or captured dense physiologic data to support specific clinical research, i.e.[27-29], and documentation[30] needs. Physiologic data capture systems have been deployed to improve operational efficiency by making medical monitor data available remotely[31-32]. Gardner and colleagues demonstrated many of these advancements as early as the 1970's with the University of Utah's HELP system[33], and commercial solutions now offer significant capabilities.

However, most research or commercial systems that provide ICU decision support based on physiologic data do not archive data at high frequencies. Data is either

down-sampled prior to storage, or episodically archived at high density when resources and specific research needs align. Medical documentation requirements, as well as some decision support and clinical research needs, have been well-served by these systems. Other needs related to discovering and validating new physiologic measurements in large clinical populations remain largely unmet.

New Vital Signs

New vital signs are measurements based on densely-captured physiologic data that provide additional clinically significant, cost effective information for medical decision making. A large body of research suggests that these measurements exist and correlate with specific pathophysiology. For example: heart rate variability has been associated with onset of sepsis[26-27, 34-36], multiple organ dysfunction syndrome[37-38], myocardial infarction[39-41], and elevated intracranial pressure[29]; relationships between arterial and intracranial pressure may predict loss of cerebral autoregulation[42-43]; pulmonary emboli might be detected early based on characteristics of the pulmonary artery pressure waveform[44]; *pulsus paradoxus*, a phenomena observed by measuring the variation in blood pressure with respect to respiratory waveforms, is associated with a number of diseases[45]; and finally, other measurements relating blood pressure variability to respiration might be useful in assessing a patient's intravascular volume status[46-47].

However, these results are usually obtained in relatively small clinical populations using expensive, customized equipment and complex analytic tools. Proving that these measurements are indeed new vital signs, e.g. that they provide additional *clinically significant, cost-effective* information has been challenging. Measurements must be

scientifically validated in representative patient populations and incorporated into clinical workflows, but most commercial monitoring systems do not provide such measures, or even easy access to the underlying physiologic data needed to compute them. The need to build custom systems to collect and process data is a significant barrier to research and deployment, and has motivated development of shared repositories of data and processing tools[48]. While such repositories facilitate research, findings remain difficult to validate prospectively in clinical settings.

As such, even traditional vital signs and the relatively simple trend and threshold-based alerting algorithms available from modern ICU monitors remain largely unstudied in a rigorous scientific fashion. It is not surprising that more than half of alarms generated by commercial ICU systems are of dubious value[49-50], and that controversy occasionally arises over use of certain physiologic monitoring modalities such as pulmonary artery catheterization[51] and continuous fetal monitoring[52].

Physiologic Regulation in the Critically Ill

Potentially, new vital signs provide additional clinical information by reflecting the state of underlying physiologic regulatory mechanisms. Aberrations in communication pathways uniting systems, organs, cells, proteins, and genes may be signaled by new vital signs long before traditional measures show derangement. Critical illness may cause these effects directly, or expose pre-existing deficiencies in certain individuals as a result of additional physiologic stress.

For example, changes in heart rate variability (HRV) appear to be common in the critically ill[53-54], and are likely due to compromised neuroendocrine regulatory mechanisms, including the autonomic nervous system. Possible causes include the primary injury (i.e. head trauma[29,55]) as well as a number of secondary effects and complications listed above. Failure of regulatory mechanisms, either in the controlling "center", intermediate communication pathways, or affected organ, is a likely explanation for these effects. As organs become *uncoupled* in the critically ill, physiology changes.

Only recently has this uncoupling hypothesis been widely articulated and considered by intensivists as a unifying mechanism for understanding pathophysiology of the critically ill[56-57]. Clinical deterioration or improvement has been thought of as a continuous progression, and may appear as such when traditional vital signs are considered. However, it is becoming more and more likely that the body actually progresses through multiple physiologic states ("quanta") as individual, then multiple, organs become uncoupled or re-coupled. A potential role for new vital signs is to identify, characterize, and predict these "quantum" physiologic states in clinically significant, cost-effective ways.

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CHAPTER II

SIMON: REALIZING THE POTENTIAL OF DENSE PHYSIOLOGIC DATA IN CRITICAL CARE

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Abstract

SIMON (Signal Interpretation and MONitoring) continuously collects, permanently stores, and processes bedside medical device data. Since 1998 SIMON has monitored over 3500 trauma intensive care unit (TICU) patients, representing approximately 250,000 hours of continuous monitoring and two billion data points, and is currently operational on all 14 TICU beds at Vanderbilt University Medical Center. This repository of dense physiologic data (heart rate, arterial, pulmonary, central venous, intracranial, and cerebral perfusion pressures, arterial and venous oxygen saturations, and other parameters sampled second-by-second) supports research to identify "new vital signs" - features of patient physiology only observable through dense data capture and analysis - more predictive of patient status than current measures. SIMON's alerting and reporting capabilities, including web-based display, sentinel event notification via alphanumeric pagers, and daily summary reports of vital sign statistics, allow these discoveries to be rapidly tested and implemented in a working clinical environment. This

manuscript details SIMON's technology and corresponding design requirements to realize the value of dense physiologic data in critical care.

Introduction

Fundamental clinical approaches for assessing vital signs have changed little since 1903, when Cushing asserted the importance of periodically measuring a patient's heart rate and blood pressure[1]. While physiologic parameters have been added to the milieu, assessment remains largely a manual, periodic process.

A growing body of research suggests value in automated analysis of continuously sampled data. For example: Heart rate variability has been associated with onset of sepsis[2-6], multiple organ dysfunction syndrome[7-8], myocardial infarction[9-11], and elevated intracranial pressure[12]; Relationships between arterial and intracranial pressure may predict loss of cerebral autoregulation[13-14]; Pulmonary emboli might be detected early based on characteristics of the pulmonary artery pressure waveform[15]. Despite convincing research results from animal experiments and small clinical studies, these and similar observations remains largely unrealized in patient care.

Clinical adoption requires not only compelling scientific evidence from relevant patient populations, but also affordable solutions that can be practically implemented at the bedside. To date, technical, economic, and social barriers have made such advances difficult. Commercial monitoring systems do not adequately analyze physiologic signals, or store data for extended periods of time for off-line analysis without extensive customization. As such, even relatively simple trends in vital signs clearly requiring clinical attention may go unnoticed due to human inability to process information in busy

clinical settings[16], especially in the ICU where many automated alerts based on physiologic trends or thresholds are of dubious value[17].

A number of custom-built systems collect and process bedside medical device data with the ultimate goal of improving medical decision-making. Also, generic decision-support models and monitoring frameworks have been defined specifically with dense physiologic data in mind[18-22]. However, few systems employing complex, generic decision support models have reached routine clinical use. Other systems, without extensive decision support models, have successfully delivered clinical alerts beyond those available via bedside physiologic monitors[23-25], sampled and archived dense physiologic data to support clinical research[26-29], or made medical monitor data available remotely[30-31]. Gardner and colleagues demonstrated many of these advancements as early as 1972 with the University of Utah's HELP system[32], and commercial solutions are beginning to offer many of these capabilities.

Unfortunately, commercial solutions are not widely realized until years after technology becomes available for purchase, often decades after research first suggests clinical value. Regulatory requirements and market forces limit vendors' ability or willingness to rapidly provide new features. Fiscal as well as human-factors constraints prevent customers from adopting new monitoring technology as it becomes available. This delay, as Goldstein and colleagues note, means "a wealth of potentially valuable information that may affect clinical care remains largely an untapped resource"[26]. Clinicians and researchers wishing to leverage this resource are faced with building custom systems. Such systems have been technically described in the literature as noted

above, but few of these reports detail functional requirements needed to support clinical and/or research use of dense physiologic data.

Given ongoing changes in technology, these functional, as opposed to technical, details may be more relevant to those building or buying similar systems. This manuscript describes functional requirements encountered over the past ten years in our work on the SIMON project, solutions, and examples of how SIMON captures, stores, processes, and delivers data to meet those needs. These requirements provide a starting point for others to define needs based on specific goals and resources.

Design Considerations

A variety of clinical and research needs inform SIMON's design. The following functional requirements are correspondingly wide in scope but incomplete; SIMON continues to evolve as requirements expand and as new technology becomes available.

Data Capture

Acquiring physiologic data from bedside medical devices is the fundamental requirement of SIMON or similar systems. Ideally, data capture is *accurate, reliable,* and *complete*. Accuracy requires not only sampling correct values of physiologic parameters or waveforms, but also recording the time of each sample. In the case of multiple waveform data capture requiring calibration or high-frequency sampling (i.e. EKG waveform at 500 samples/second), these tasks can be non-trivial. Technically, high reliability requires robust data acquisition programming as well as system monitoring routines to detect unforeseen errors and alert technical staff. Finally, capturing all

parameters and waveforms simultaneously remains unrealistic for most applications. The scope, frequency, and duration of physiologic sampling are largely determined by specific needs.

Data Storage

Stored physiologic data must be *accessible* and *identifiable* by patient. The main design trade-offs in data storage involve size, speed of access, portability, and cost. For example, ASCII text files are simple to create, highly portable, and easy to access, but generally make inefficient use of disk space. Conversely, binary files or databases might make more efficient use of space, but require specialized, potentially expensive tools or knowledge to access.

Regardless of storage technology, data must be linked to individual patients. While the time and bed number of any data point can be determined automatically, identifying the bed occupant requires manual input. This can cause substantial difficulty; the patient's identity may not be entered promptly or accurately, or might not be changed as patients move in and out of beds, causing one patient's data to be recorded as another's.

Clinical Reports

Continuous data capture stores up to several hundred thousand data points from a single patient each day; effective summaries of this data are essential if continuous physiologic data is to be useful in patient care. Generally, a report should be *relevant* and *efficient*, presenting only information required to support decision-making in a way that is

easily accessed and interpreted. Dense physiologic data presents unique challenges since the optimal parameters, computed measurements, and most efficient display methods remain largely undefined. We are only beginning to rigorously study the value of measuring central tendency, statistical variation, and waveform characteristics of single vital signs in terms of their ability to predict outcome or adverse events in large clinical populations, not to mention more complex measures or interactions between multiple vital signs or the significance of changes in these measures over time. As such, while reports based on dense physiologic data must be relevant and efficient, they should also be adaptable to evolving research and clinical needs.

Clinical Alerts

Effectively detecting critical physiologic values and trends remains difficult. Most bedside monitors alert to short-term critical values via threshold settings, but longer-term trends, or abnormality characterized by trends in multiple variables or more complex measures, remain undetected by current technology. In addition, noise in certain signals may require substantial filtering. Systems like SIMON can provide advanced alerting capability to combat desensitization that may occur in observing long-term adverse trends, or due to the high false positive rate of bedside device alarms. Obviously such alerts should be sensitive and specific, but they must also be *customizable* and *efficient.* Customization by patient is required since it is unlikely that a physiologic alert based on universal characteristics of a single parameter will be sufficiently sensitive or specific over all patients, in all situations. A simple example of the need for customization is a patient who has end of life directives in place, and for

whom alerts are no longer clinically relevant. Efficiency is required since, unlike a report that is sought out by the care provider at his/her convenience, an alert requires immediate attention at the cost of interrupting existing workflow. Alerts can be made more efficient by grouping simultaneous alerts together for notification, or by alerting higher-level decision makers only after attempts to notify primary staff. Finally, as noted above alerts must be flexible since effective alerting algorithms based on dense physiologic data remain largely undefined.

Research Support

Data storage requirements, described above, provide much of the capability for research based on dense physiologic data. Additional requirements for research purposes include that the data be *linkable* by episode of care to other data sources, and easily *de-identified*. Research efforts typically link other sources of data to study effects of physiology on patient outcomes, for example, and patient confidentiality requires that identifiers be removed prior to analysis. In addition, on-line tools to analyze physiologic data are useful in discovering areas for further analysis, and for developing clinical alert definitions, i.e. determining how many alerts would be generated for a particular candidate event, and how the frequency of alerts changes as event parameters vary.

System Monitoring

Automated physiologic data collection systems must be regularly monitored to ensure reliable performance; both the technology and supporting human processes like patient identification and mobile device connection should be assessed. These

monitoring requirements are often overlooked, and are critical to fully realize the value of SIMON and similar automated, continuous physiologic data systems.

System Description

SIMON's current implementation represents one of many possible solutions to the needs described above, and has been implemented in a working trauma ICU since 1998. This section describes SIMON's current implementation and our use of the system to date.

System Architecture

Since the earliest UNIX-based versions of the system[33-34], modular design has been the hallmark of SIMON's architecture. Individual software components perform data capture, storage, analysis, and management functions. Modularity, combined with use of standard underlying communication protocols between components, enables: 1) Efficient distribution of system components over various computing platforms as the system grows; 2) Modification or addition of new components with minimal impact on existing functions; and 3) Robust operation, since failure of an individual component has minimal impact on other parts of the system. SIMON's current components, and their deployment over various computing systems, are shown in Figure 2.1. Detailed descriptions of architecture components follow.

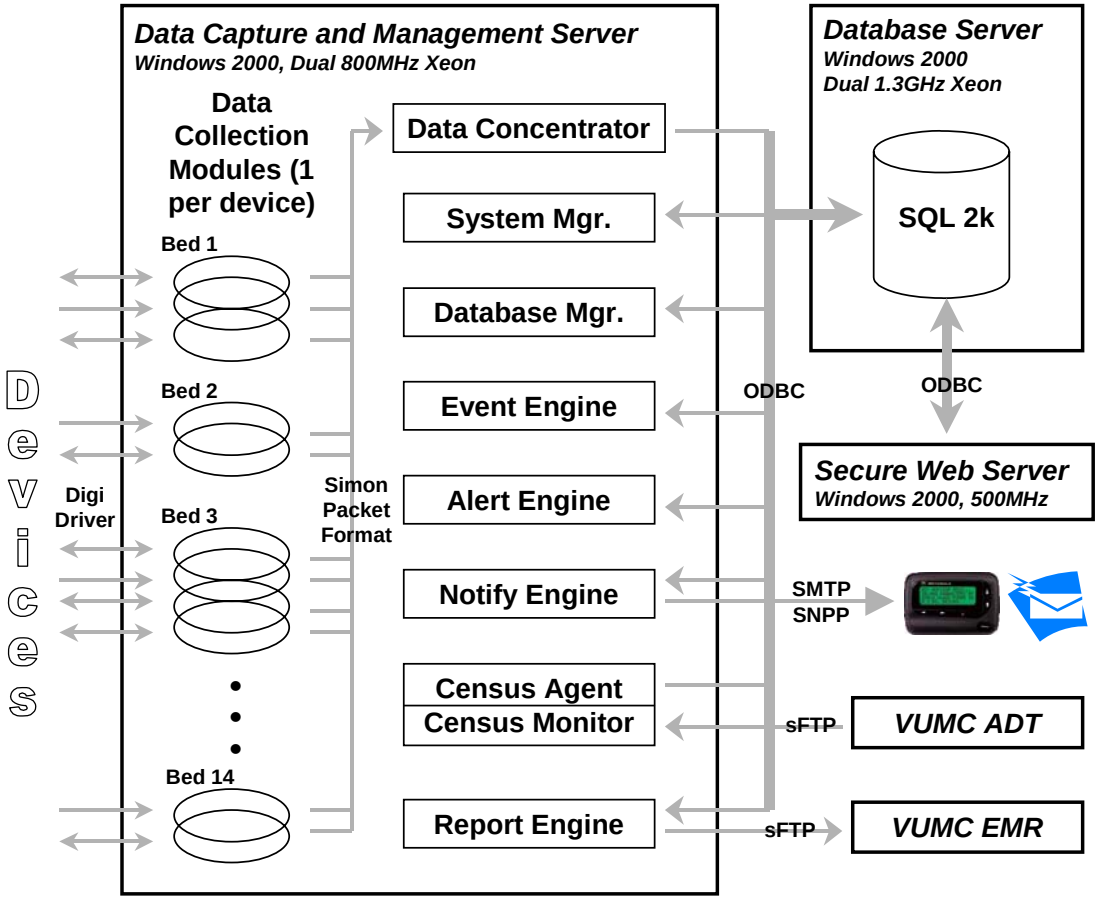


Figure 2.1: Current SIMON Components and Architecture. Grey arrows show communication paths between components. Bedside devices (left) interface to data collection modules via RS-232 over TCP/IP (Digi International, Minnetonka, MN). All data is routed from data collection components to the Data Concentrator via the SIMON Packet Format, a UDP-based protocol specifying time, bed number, parameter name, and value. The Data Concentrator stores all data to the SIMON Database via an Open Database Connectivity (ODBC) interface. Numerous other system components then access this data via ODBC to perform analysis and system management functions. Notifications are sent to alphanumeric pagers and email via Simple Network Paging Protocol (SNPP) and Simple Mail Transport Protocol (SMTP), respectively. Interfaces to the institution's admission-discharge-transfer (ADT) tracking system and electronic medical record (EMR) are implemented via secure file transport protocol (sFTP).

Data Capture

SIMON achieves accurate, reliable data capture through independent software modules running on a remote central server. Data capture is complete and fully automatic with respect to numeric parameters; waveform capture is possible, but requires manual intervention to select waveform channels and start and stop the acquisition process. Bedside equipment connections are made via the institution's local area network, using devices at each bed to translate medical device (RS-232) formats to network (Ethernet) formats. Every physiologic monitor on our trauma unit is permanently connected to SIMON. Nurses connect mobile devices using color-coded, connector-specific cables.

Data sampled through these connections is time-stamped by individual data collection modules, and then relayed to a central concentrator for relational database storage (see Figure 2.1). Individual data collection modules are continuously monitored by a "watchdog" program ("System Manager" in Figure 2.1); if a problem is detected the individual module is restarted without affecting data collection from other beds or devices. In this way, SIMON automatically and continuously captures all numeric parameters from bedside physiologic monitors and any portable cardiac monitors over 14 TICU beds. Table 2.1 lists all physiologic parameters routinely captured by SIMON.

Table 2.1: Parameters Captured by SIMON Second-by-Second.

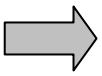
Bedside Physiologic Monitor (Hewlett-Packard/Philips) Parameters & Units	
Heart Rate	beats/min.
Respiration Rate	breaths/min.
Arterial Pressure: Systolic, Diastolic, Mean	mmHg
Pulmonary Arterial Pressure: Systolic, Diastolic, Mean	mmHg
Non-Invasive (cuff) Blood Pressure: Systolic, Diastolic, Mean	mmHg
Central Venous Pressure	mmHg
Intracranial Pressure	mmHg
Cerebral Perfusion Pressure	mmHg
Arterial Oxygen Saturation	%
Cardiac Monitor (Baxter Vigilance) Parameters & Units	
Continuous Cardiac Output (and Index)	l/min. (l/min./m^2)
End Diastolic Volume (and Index)	ml (ml/m^2)
End Systolic Volume (and Index)	ml (ml/m^2)
Venous Oxygen Saturation	%
Blood Temperature	degrees C
Heart Rate	beats/min.

Data Storage

Since December 2000 SIMON has stored all parametric data in a relational database (SQL Server, Microsoft), in tables corresponding to individual parameters. As shown in Figure 2.1, a single component, the Data Concentrator, receives data from multiple individual data collection modules, then formats and stores it in the database. The Data Concentrator adapts sampling rate in response to database load, so not every

sample is stored if the database system becomes busy with other tasks. Sampling period varies from one to four seconds, depending on bed occupancy and number of monitored parameters, with an average period of less than two seconds. Within the database, data is divided into two groups of tables to allow for rapid access to very recent data while maintaining space efficiency for long-term storage. Recent data is stored in tables with a single record corresponding to each sample, allowing easier access for tasks including event detection and graphical displays. Periodically, the Database Manager automatically groups data from these tables into five-minute intervals. All data from the interval is encoded and stored in a single record along with basic statistics over that interval, providing more efficient long-term storage. The two record formats are shown in Figure 2.2.

RECENT RECORD FORMAT	
Field	**Type**
utcTimeValid	datetime
Bed	varchar
Value	integer or numeric



LONG-TERM RECORD FORMAT	
Field	**Type**
utcIntervalStart	datetime
bed	varchar
value	integer or numeric
min	integer or numeric
max	integer or numeric
median	integer or numeric
mean	float
stDev	float
numPoints	integer
rawData	varchar

Figure 2.2: Format of Single-Valued SIMON Physiologic Database Records. Periodically, data in "recent" format tables (one record per data point) is analyzed and grouped into "long-term" tables (one record per 5 minutes of data). Separate tables are maintained for each parameter. All original data is maintained. Multi-valued parameters (i.e. pressures with systolic, diastolic, and mean components) are stored in similar tables with additional fields.

Additional database tables associate individual patients with particular beds. SIMON accurately determines bed occupancy by monitoring census information from the hospital's admission-discharge-transfer (ADT) system, with manual verification by unit staff whenever data resumes from a particular bed following an interruption in data (indicating a possible change in bed occupancy). A dedicated laptop displays bed occupancy at the nursing station (Figure 2.3), and prompts for confirmation when needed. Once identity is validated all data since the interruption is associated with that patient.

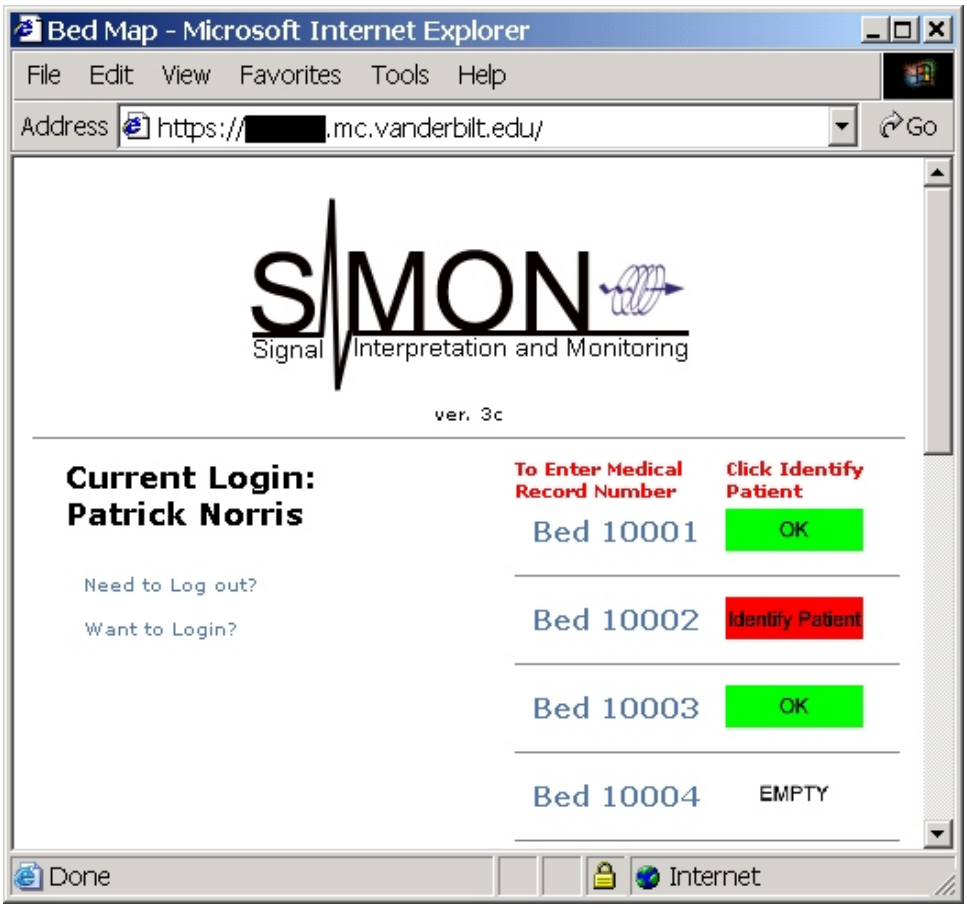


Figure 2.3: Portion of SIMON Patient Identification Interface (4/14 Beds Shown). In this example the patient in bed 10002 needs to be identified, which is accomplished by clicking on the red square and entering the patient's medical record number.

Clinical Reports

SIMON reports physiologic data in both graphical and text formats. Graphs of select parameters are accessible via a secure web site, and can be viewed from remote locations. Graphs are refreshed minute by minute to reflect the most recent data from each patient, and can be viewed at several resolutions ranging from a full day to a one-hour period. Figure 2.4 shows data graphs for a single patient over a 24-hour period.

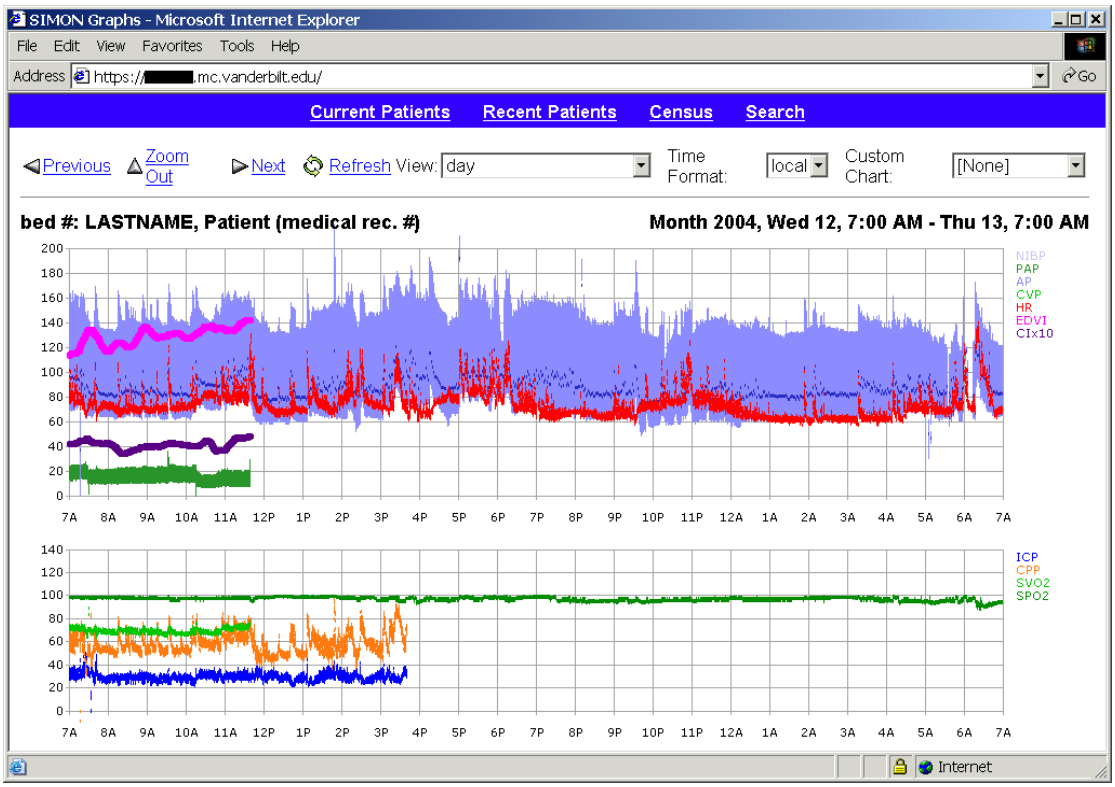


Figure 2.4: SIMON Data Graphs Over 24 Hours. Parameters shown on upper graph: heart rate (red), systolic arterial pressure (blue, with mean in dark blue), pulmonary arterial pressure (green), end diastolic volume index (magenta), cardiac index (scaled x10, purple). Parameters shown on lower graph: arterial O_2 saturation (dark green), venous O_2 saturation (light green), intracranial pressure (blue), cerebral perfusion pressure (orange).

In addition to the on-demand graphs of patient physiologic data, text reports are automatically generated at predefined intervals based on flexible templates stored in the database. These text reports contain a variety of summary statistics for one or more patients, formatted appropriately, as shown in Figures 2.5 and 2.6. Templates reference *database stored procedures*, small programs contained within SIMON's database, to generate individual numbers within the reports, such as mean heart rate for a patient during the reporting period. Certain text reports are regularly sent to the institutional electronic patient record, which can also be viewed remotely via secure web interfaces.

The content or format of SIMON text reports can be changed by modifying the template or corresponding stored procedures, and new reports can be created by adding templates and new stored procedures if needed. All text reports are generated based on events, which might be specified as the same time each day, i.e. for reports used in morning rounds, or a specific change in patient physiology, and are stored in the SIMON database.

			Vital Signs								Cardiac						Intracranial				
			HR		CVRD	BP			SpO2		SvO2		CI		EDVI		ICP			CPP	
		Mon. hrs.	mean bpm	% >120	%SD5 <0.5	mean SYS mmHg	% SYS <90	% SYS >180	mean %	% <90	mean %	% <65	mean l/min/m2	% <2.5	mean ml/m2	% <100	mean mmHg	% >20	% >30	mean mmHg	% <60
10001	[MRN] [NAME]	22	88	2%	0%	152	0%	1%	99	0%	no data		no data		no data		(13)	(7%)	(1%)	(91)	(0%)
10002	[MRN] [NAME]	13	107	**33%**	**28%**	122	**16%**	0%	100	0%	no data		no data		no data		**38**	**83%**	**64%**	62	**65%**
10002	[MRN] [NAME]	10	104	**14%**	**42%**	151	1%	1%	100	0%	no data		no data		no data		**85**	**100%**	**100%**	**37**	**92%**
10003	[MRN] [NAME]	24	67	0%	4%	142	0%	1%	97	0%	**64**	**57%**	4.2	0%	153	0%	no data			no data	
10004	[MRN] [NAME]	19	84	0%	**30%**	114	3%	0%	96	0%	73	0%	3	2%	108	**12%**	no data			no data	
10005	[MRN] [NAME]	23	**132**	**97%**	0%	112	4%	0%	100	0%	no data		no data		no data		no data			no data	
10006	[MRN] [NAME]	17	95	5%	0%	119	2%	1%	99	1%	no data		no data		no data		no data			no data	
10007	[MRN] [NAME]	21	92	0%	0%	125	0%	0%	99	0%	no data		no data		no data		no data			no data	
10008	[MRN] [NAME]	20	**145**	**100%**	**11%**	134	0%	1%	96	0%	**64**	**63%**	5.4	0%	110	**14%**	no data			no data	

Figure 2.5: Portion of SIMON Daily Unit Summary Report (8/14 beds shown). Bold indicates critical value, parentheses denote statistics computed based on data covering less than half of total monitored hours ("Mon. hrs.") shown.

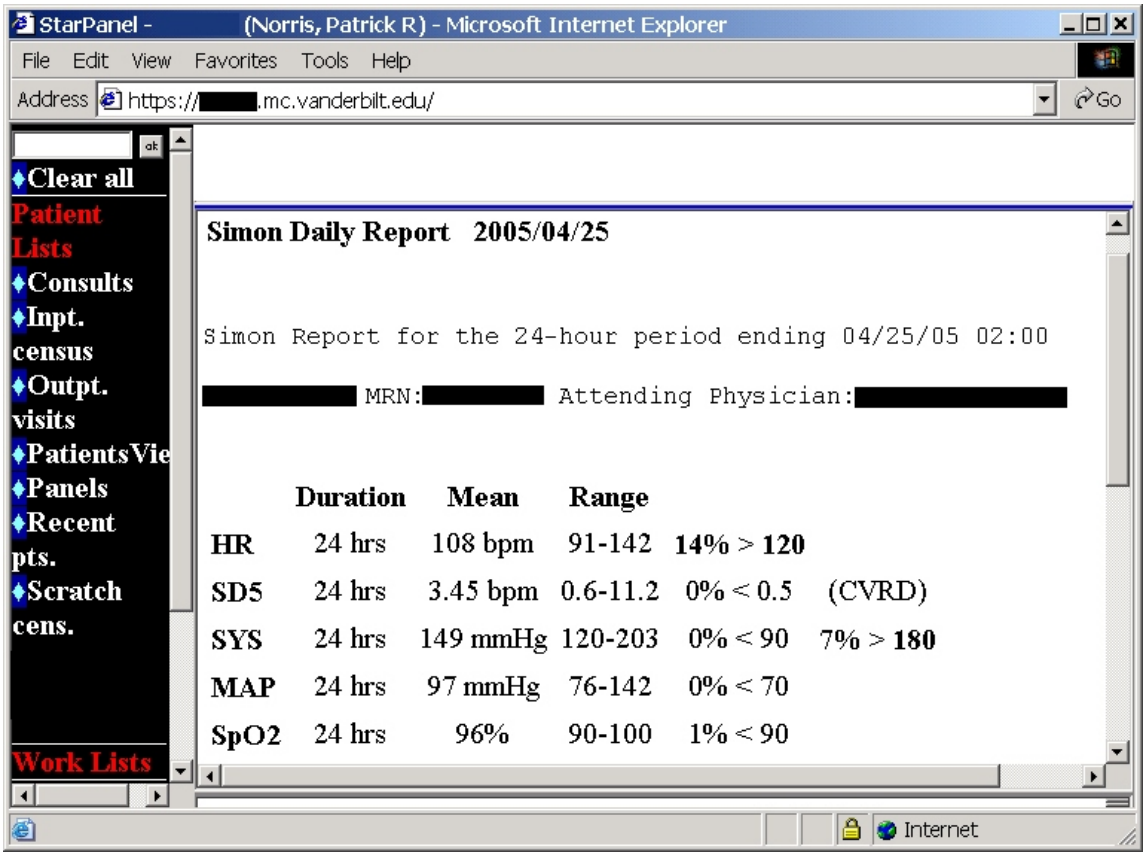


Figure 2.6: Portion of Individual Patient Daily SIMON Report in Institutional Electronic Medical Record (EMR) System. Details of EMR interface not shown. Range denotes the interval in which 98% of data is contained.

Clinical Alerts

SIMON uses a combination of *event*, *alert*, and *notification* templates stored in the database to realize flexible, efficient alerting. Event templates specify a combination of one or more algorithms, implemented as database stored procedures, that define a potential alert condition, i.e. “Intracranial pressure above 25 AND cerebral perfusion pressure below 60”. For each event, one or more alert templates define the duration that the event must occur before sending an alert, and the text of the alert message, i.e. “ICP > 25 and CPP < 60 for MRN 123123 at bed 10001”. Finally, for each alert, one or more

notification templates define the recipients of the alerts by alphanumeric pager number or other communication channels. Figure 2.7 shows one such notification on an alphanumeric pager.

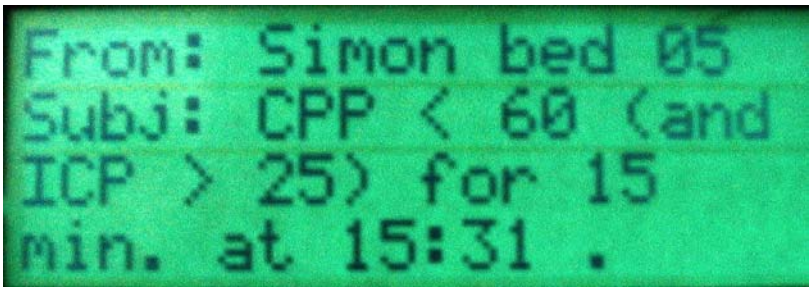


Figure 2.7: SIMON Alphanumeric Pager Notification.

Individual alerts can be specifically disabled or enabled for one or more patients, and each communication channel can be disabled for any period of time. Finally, each communication channel can be set to group all alerts in a certain time period into a single notification, i.e. send an alphanumeric page for all alerts in a five minute period. Individual alerts can be configured to override this “batch” delivery, to ensure timely notification of short-term and/or potentially highly critical alerts. All instances of events, alerts, and notifications are stored in the database. Figure 2.8 illustrates how a single event might trigger multiple alerts, which, in turn, may result in multiple notifications.

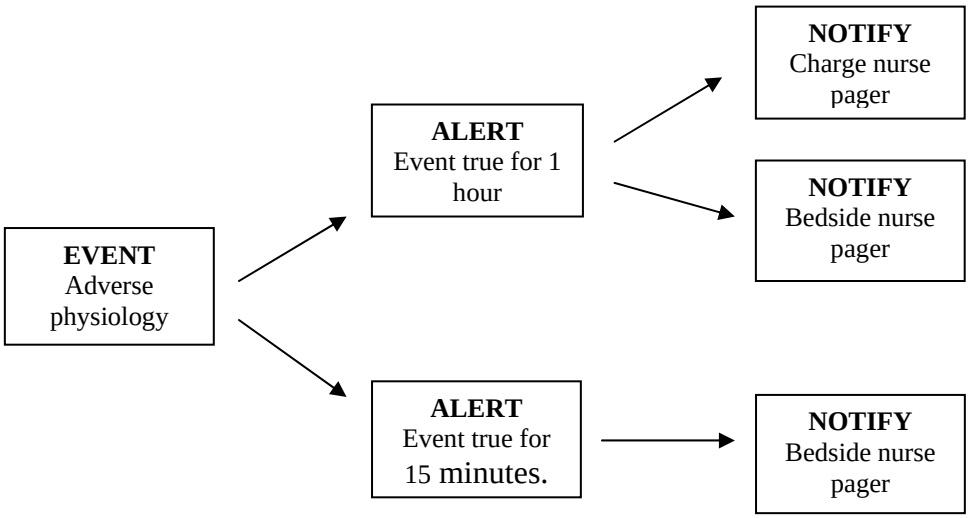


Figure 2.8: Sample Event, Alert, and Notification Configuration.

Research Analysis

SIMON identifies individual patients by medical record number, and episode of care by the time data was collected as well as institutional case number. These identifiers are stored in tables separate from physiologic data (linked by time and bed number) facilitating de-identification for research purposes. Furthermore, every SIMON alert or report can be generated with all patient identifiers removed, for delivery to authorized research personnel not directly involved in patient care. SIMON does not have on-line tools for extensive retrospective filtering or other research analyses; intensive queries can substantially reduce system performance, so data is extracted from the database to separate systems for analysis. Efforts have begun to build a separate, de-identified database to facilitate on-line analysis without impacting performance of the clinical system.

System Monitoring

SIMON provides a number of automated alerts and reports to ensure reliable operation. Network, database, institutional data links, and server status are constantly monitored, with redundant paging systems to alert technical staff to problems. Human processes, such as patient identification and mobile device connections are similarly monitored (lack of a connected bedside cardiac monitor can be automatically detected since a pulmonary pressure signal is present from the physiologic monitor, and in our institution all such patients receive additional cardiac monitoring) with corresponding alerts sent directly to unit staff. Each week a number of reports are generated for review, including statistics of system and network uptime, total number of patients monitored, and bed occupancy and data collection rates. Staff performance is also reported for patient identification and mobile device connections, including any related alerts and the time until corrective action was taken. Table 2.2 lists representative values for many of the parameters monitored and reported to technical and administrative staff on a weekly basis.

Table 2.2: Select System Parameters Automatically Monitored on a Weekly Basis.

Parameter	Representative Value
Percent network uptime	99.88 %
Percent system uptime	99.95 %
Number of patients monitored	36
Total continuous monitored time (all 14 beds)	1856.4 hours
Average monitored time per bed, per day	18.9 hours
Total number of heart rate data points collected	5.25 million
Average sampling period of heart rate data	1.27 seconds
Bed occupancy percentage, according to monitor data	79.6 %
Bed occupancy percentage, according to validated patient identity	78.9 %
Percent of data reliably identified (via manual confirmation)	99.14 %
Number of manual identification entries (confirmations) by shift and individual user	1-11 entries (per shift)
Number of reports generated and successfully delivered to individuals and institutional electronic medical record	108/108
Number of clinical administrative alerts (device connections, patient transfers) generated and successfully delivered	26/26
Number (and list) of individual recipients of all alerts and reports	18

Current Status

SIMON is currently implemented on all 14 trauma ICU beds at Vanderbilt University Medical Center. This section describes the current status of the SIMON database, use of decision support tools, and ongoing research initiatives. Costs in terms of equipment and system maintenance are also detailed.

The SIMON Database

As of May 2005, SIMON's database contains data from more than 3500 trauma ICU patients, representing approximately three billion physiologic data points and 281,000 patient-hours of continuous monitoring. The database occupies 23 GB of disk space. Waveform data is not currently stored in the database, but streamed directly to files as needed for particular studies. Roughly 70 patients are added to SIMON's database each month, representing 50 million data points, 5500 patient-hours of monitoring, and 0.5 GB of database storage. Data accrues automatically, with manual interaction required only to confirm patient identify and to connect portable bedside devices to the system. Table 2.3 show statistics for select parameters in SIMON's database, aggregated over all trauma patients in a recent 8 month period.

Table 2.3: Statistics for Select SIMON Physiologic Parameters, 7/1/04 – 2/28/05. PAP = Pulmonary artery pressure, NIBP = Non-invasive blood pressure, AP = Arterial pressure. Patient-hours represents the total duration of data for that parameter, over all patients.

Parameter	Mean ± SD	Patient-hours
Systolic PAP	36.1 ± 15.0 mmHg	9429
Mean PAP	26.3 ± 12.6 mmHg	9429
Diastolic PAP	20.0 ± 11.9 mmHg	9429
Systolic NIBP	124.5 ± 19.8 mmHg	35309
Mean NIBP	80.5 ± 14.7 mmHg	35309
Diastolic NIBP	59.1 ± 14.8 mmHg	35309
Systolic AP	130.3 ± 25.7 mmHg	45004
Mean AP	88.9 ± 18.0 mmHg	45004
Diastolic AP	69.2 ± 16.4 mmHg	45004
Heart Rate	99.8 ± 20.7 bpm	64620
Pulse Oximetry	97.2 ± 3.6 %	64692
Cardiac Output	9.1 ± 2.7 l/min.	7334

Decision Support

SIMON's daily vital sign summaries are the most frequently used decision support tools. The attending physicians, ICU medical director, and nurse managers use the unit summary report (Figure 2.5) regularly to provide a picture of overall patient acuity. In most cases, these numbers confirm observations made in the course of daily care. Occasionally, unexpected derangements in individual patient physiology are noted prompting closer review of the patient, sometimes resulting in additional therapy or diagnostic procedures. The daily reports act as a "safety net" to bring attention to the individual patient, in the event that unexpected deterioration over 24 hours is missed. In addition, care providers on other services sometimes use the single patient summary

reports (Figure 2.6) to evaluate a patient's physiology prior to transfer or operative procedures.

Providing effective "safety net" functionality on a time scale shorter than the daily reports has proved challenging. Currently, SIMON's ability to send alerts to alphanumeric pagers (Figure 2.7) is no longer used on a regular basis. Given our current ICU work processes, lack of pagers for individual bedside nurses, skilled providers, and existing monitoring systems, the benefit of alerting based solely on existing measures of patient physiology has been marginal. Reasons for this are discussed more fully below in "Lessons Learned".

SIMON's data graphs (Figure 2.4) are occasionally used to support clinical decision making, but have proven more useful in their support of clinical research. Many studies have physiologic criteria for patient enrollment, and our research staff views these graphs remotely to ascertain patient eligibility for particular studies. This has reduced the need for research staff to communicate with care providers or travel to the ICU to evaluate patients.

SIMON also enhances administrative decision-making. For example, SIMON provides the most accurate measures of bed occupancy available in our institution, as a patient effectively always has EKG and pulse oximetry monitoring while in a bed. From the data in table 2.3, we can determine that our ICU beds were occupied 79.2% of the time. Infrequently, serious adverse patient events are reviewed retrospectively using SIMON's data graphs.

Research Applications

New measurements of patient physiology available from densely captured data will define future monitoring strategies, decision support algorithms, and clinical processes. We have only begun to explore how these "new vital signs" might efficiently stratify groups of patients by acuity, outcome, and need for particular therapy, or identify clinical deterioration or improvement in the individual patient. Our work has described the relationship to patient outcome of heart rate and blood pressure mean, ranges, and variability over the ICU stay[35]. We have begun to investigate short-term heart rate variability (HRV), derived from integer heart rate. Within the first 24 hours, HRV predicts trauma patient death occurring a median of 5 days after admission, with a sensitivity of 70% and specificity of 80%[36]. Patient triage, in both civilian and military environments, is one application of this and other new measurements based on dense physiologic data[37].

Heart rate represents one of many parameters available for study, simple statistics are but one method of analysis, and effective triage represents a single application in a multitude of clinical decision support needs. Our current analyses are early steps to bringing new vital signs, based on a continuum of patient physiology, to the bedside. Developing new decisions support tools based on dense physiologic data will require: 1) New methods of representing data, information, and knowledge; 2) Provider training and new clinical workflows to optimize utility; and 3) Rigorous evaluation of costs and benefits of clinical deployment. To date, we only informally explored these medical informatics research opportunities[38].

Cost

SIMON's equipment and maintenance costs are relatively low. A single bed can be instrumented for roughly $3000, as shown in table 2.4.

Table 2.4: Single-Bed SIMON Equipment Costs.

Item	Approx. Cost
RS-232 monitor interface option	$1500 ($600 in new models)
Ethernet network port installation	$600
Ethernet to RS-232 translator (terminal server)	$800
Cables, UPS, etc.	$100
TOTAL	$3000

One or more servers are required to capture and store data, and to provide decision support functionality. As of May 2005, a single standard Intel server sufficient to fully implement SIMON on 14 beds costs approximately $7000. This cost includes database server and operating system licenses, at academic discount prices. Overall, SIMON adds approximately 10% to the cost of the standard ICU monitoring infrastructure, or an additional cost of approximately $1.20 per day per bed over an eight year life cycle. Particular skills required to install SIMON include: 1) Familiarity with the Windows operating system and an ODBC-compliant database package; and 2) Ability to manufacture RS-232 cable from inexpensive, commonly available components (although custom pre-manufactured cables can be purchased from a variety of sources). An important component of installation is training nursing staff to connect mobile

devices, and clerical assistants to maintain the bed occupancy information (Figure 2.3). While these tasks take negligible time, a well-trained staff that can complete these duties reliably is an important component of a successful installation.

Routine technical maintenance can be done by someone familiar with Windows server operation. It requires making backup copies of data, installing operating system patches, and other general procedures to ensure system security and reliability. SIMON requires some special maintenance to maintain high reliability of data capture from mobile devices (Baxter Vigilance Monitors). Cables need to be repaired or replaced every few years on average, due to both breakage (connector left on floor and stepped on, or handled roughly) and corrosion from occasional fluid spills (connector left on floor and affected by subsequent spill). We have also found that, from time to time, cables are connected to the wrong port on devices or the terminal servers. In addition, Baxter Vigilance monitors need to be checked semi-regularly to ensure proper data output configuration. Firmware upgrades to these devices, or turnover between devices on our unit and other areas of the hospital, seem to be the main cause of mis-configuration. Finally, several times per year one of the terminal servers (RS-232 to Ethernet translators) somehow loses its network connection, and must be power-cycled. SIMON employs a number of automated mechanisms to notify technical staff of potential problems, and overall maintenance requirements for our 14-bed installation average about 5 hours per month.

Lessons Learned

Our experience designing, building, and maintaining SIMON over the past decade carries a number of valuable lessons. The following have been selected for their significance in constructing and using a reliable, automated, physiologic data capture and analysis system.

Build Modular Systems

G. Octo Barnett and his colleagues detailed the benefits of modular design in clinical information systems nearly four decades ago[39]. We have realized a number of these advantages in SIMON's component-based architecture. Flexibility in modifying, fixing, or augmenting functionality has been paramount, as some of the components shown in Figure 2.1 have undergone more than 30 revisions since their initial implementation. SIMON's modular design allows individual components to be developed, debugged, and tested on separate systems, then deployed with minimal interruption to other functionality. This relative ease of modification allowed SIMON to grow from a simple data collection tool storing physiologic parameters in text files, to a physiologic data management solution supporting diverse clinical and research applications.

Reliability is also enhanced by SIMON's modular architecture. Individual component failures are rapidly detected and, in most cases, automatically fixed by restarting the failing module. Automatic component restart allows SIMON to promptly resume operation following network or power failures. The most notable of these rare incidents was failure of our institution's network for 12 hours as a result of the "SQL

Slammer" worm in January, 2003. Individual SIMON components resumed operation as network connectivity was restored, without manual intervention. SIMON's modular design also enhances reliability in that components can be rapidly moved between systems in the event of failure. During the most severe internal failure in SIMON's history, where an operating system patch temporarily disabled the Data Collection and Management Server (Figure 2.1), essential components were migrated to a spare system and core functionality was restored within two hours.

Finally, SIMON's scalability results, in large part, from modular design. The system has grown from two beds in September, 1998, running on a single 300Mhz Pentium-II system, to 14 beds running on two dual-processor servers without significant change in architecture. New components are easily added to capture data from additional beds, or to implement new functionality. However, scalability and reliability do not arise from modular design alone. The following section describes our strategy for building individual components to fully realize these and other benefits of modular design.

Use Simple, Observable, Portable Components

Modularity affords little advantage if the system's individual components are complex "black boxes" tied to specific computing hardware. Components should be as simple as possible in terms of functionality, configuration, internal design, and operation. We found state flow diagrams to be a useful way to assess complexity of system components. A component's functionality is diagramed to a level of detail sufficient to represent individual subroutines. If the state flow diagram cannot be easily represented

without crossing lines on a single page, the component is considered for redesign, perhaps by dividing into sub-components.

Component operation should also be observable, to allow monitoring and troubleshooting as the system runs. Each component should, at a minimum, periodically report that it is operating normally. Ideally, internal state, history of operation and error conditions can be queried as well. All SIMON components periodically write a "lifetick" file, in addition to logging events and errors to text files. Select components store additional state information, updated in real-time, in a database. An automated watchdog process periodically monitors all operating components (currently 39 instances), restarting components if needed.

Finally, components should be portable, allowing for distribution across physical systems, perhaps even running different operating systems. SIMON achieves a degree of portability by using a single database for storing all persistent system information, and by using common protocols for communication between components. These protocols (ODBC, TCP/IP) are widely supported across operating systems and programming languages, allowing a great deal of flexibility in choosing development and implementation technology.

Develop Work Processes Alongside Technology

SIMON's successful operation, even though highly automated, requires human involvement. On a day-to-day basis, people must monitor the system to ensure proper operation. Patient identity must be confirmed, and portable bedside devices must be connected promptly to avoid loss of data. Occasional maintenance must be completed, as

described above. Initially, we underestimated the difficulty in getting staff to perform these tasks reliably as part of their existing duties, and to maintain a high level of reliability over time. These issues were addressed by defining administrative processes by which: 1. Staff feedback is sought during periods of change (even relatively small change); 2. Performance is regularly evaluated, sometimes with the aid of automated reports; and 3. Positive and negative incentives are used if performance wanes. Most of these processes were defined and implemented not by technical staff, but by the trauma unit assistant nurse manager.

Continued success requires a greater degree of strategic planning. The cost/benefit of SIMON and similar endeavors should be regularly evaluated. In the long-term either external research funding must be secured, or the work must be funded as part of operational costs. We have only begun to formalize work processes to assess SIMON's cost and benefit on a regular basis, and to organize our efforts to seek collaborators, secure external funding, and otherwise leverage SIMON's value over the long-term.

Project Champions Are Crucial

SIMON and similar efforts span disciplines, potentially involving many individuals with diverse skills, interests, and commitments. Project champions are important to bridge cultural barriers, secure resources, establish vision and long-term goals, and to keep team members or support staff motivated, especially thorough short-term setbacks. Ideally, project champions are well-respected both within and outside

their disciplines of expertise, have substantial time and energy to devote to the project, and have access to resources needed to "seed" new research or development efforts.

Future Plans

SIMON's expansion can be considered along four dimensions: implementation environments, parameters captured, research analyses, and applications. The next twelve months should see our work advance along each of these axes. In terms of implementation environment, SIMON will be expanded to Vanderbilt's air medical transport helicopters, to capture data closer to time of injury. SIMON may also expand to capture data from trauma step down beds as well as other surgical intensive care units, to acquire data across a more diverse population.

SIMON will also grow in terms of the number and type of physiologic parameters captured. We hope to begin continuous, routine capture of EKG and other physiologic waveforms to augment and validate some of our integer-based measurements. Institutional efforts to acquire data from other bedside devices, including ventilators, should provide SIMON with data feeds to those parameters as well.

A number of additional research analyses are possible, using data from new sources as well as existing ones. We have only begun to examine physiologic parameters other than heart rate. Our existing analytic methods are small steps compared to the variety of data mining, signal processing, and other algorithms that might be applied to this vast physiologic data store. Linking patient physiology to other clinical information, including laboratory, pharmacy, physician order, and beside chart data provides still more opportunities for analysis. We anticipate the need for more robust artifact rejection as we

examine signals containing more noise than heart rate, such as blood pressure and/or pulse oximetry.

Finally, we envision a number of new applications supporting both research and clinical use of dense physiologic data. A formal data repository for research purposes will be constructed to routinely merge and de-identify data from SIMON and other clinical information systems. Such a repository facilitates making data available to other researchers both within and outside our institution. As we discover new algorithms to stratify patients based on acuity, mortality, and/or type of injury, we expect to deliver this information using our existing reporting and alerting mechanisms, as appropriate. In the long-term, controlled clinical trials will be needed to assess the value of new physiologic measurements and the decision-support tools used to bring them to the clinical bedside. Results from those trials, and the foundational work we and our colleagues are now undertaking, will define future patient monitoring strategies and establish the value of dense physiologic data capture, analysis, and decision support in caring for the critically ill.

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CHAPTER III

CLOSING THE LOOP IN ICU DECISION SUPPORT: PHYSIOLOGIC EVENT DETECTION, ALERTS, AND DOCUMENTATION

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Abstract

Automated physiologic event detection and alerting is a challenging task in the ICU. Ideally care providers should be alerted only when events are clinically significant and there is an opportunity for corrective action. However, the concepts of clinical significance and opportunity are difficult to define in automated systems, and effectiveness of alerting algorithms is difficult to measure. This paper describes recent efforts on the Simon project to capture information from ICU care providers about patient state and therapy as alerts occurred, in order to assess the value of event definitions and progressively refine alerting algorithms. Event definitions for intracranial pressure and cerebral perfusion pressure were studied by implementing a reliable system to automatically deliver alerts to clinical users' alphanumeric pagers, and to capture associated documentation about patient state and therapy when the alerts occurred. During a 6-month test period in the trauma ICU at Vanderbilt University Medical Center, 530 alerts were detected in 2280 hours of data spanning 14 patients. Clinical users electronically documented 81% of these alerts as they occurred. Retrospectively

classifying documentation based on therapeutic actions taken, or reasons why actions were not taken, provided useful information about ways to potentially improve event definitions and enhance system utility.

Introduction

Effective medical care processes typically embody a feedback loop, in which care providers continually assess patient condition and take action to improve it. Physiologic data from bedside monitors is one indicator of patient condition, and is a factor in 13-22% of clinical decisions made during ICU rounds[1]. Computerized decision support systems have been developed to monitor physiologic data and alert care providers when events of possible clinical significance occur. However, these systems generally reflect only the information delivery portion of the "loop", in that alerts are delivered but there is no facility for capturing information about related actions or relevance of the alert. Information about patient state and related therapeutic actions at the time of alerts is invaluable if event definitions and are to be progressively improved in a scientific way.

Without such refinement, current systems for physiologic event detection and clinical alerting remain inadequate. One study in 1997 found that only about 23% of physiologic alerts based on heart rate threshold alarms from physiologic monitors were clinically relevant[2]. While ICU monitoring technology is relatively advanced in terms of technical architecture, information display, variety of sensors, and interfaces to other bedside devices, alert definitions remain primarily restricted to specifying high or low limits of individual monitor parameters, independent of time. Given the substantial variability in patients and clinical environments, providers are faced with a difficult

tradeoff in setting these limits: either set the acceptable range of values wide to minimize false alarms, potentially at the expense of timely notification, or set the range narrow to receive earlier notification, at the expense of considerable false-positive alerts. While a variety of event-detection solutions have been proposed including multi-state filters[3], template recognition[4], and fuzzy logic process models[5], these and other advancements are typically not assessed in terms of the relevance of individual alerts generated during actual patient care. Notable exceptions include work by Tate et. al. to examine effectiveness of alphanumeric pager alerts based on critical lab values[6], and by Shabot and colleagues to study alerts delivered to wireless devices based on physiologic and laboratory data[7]. This paper describes recent work on the Simon (Signal Interpretation and Monitoring) project to provide physiologic event detection, alert notification, and documentation capabilities in a working ICU information system, and to study how data entered by clinical users in response to alerts can be used to assess and improve system performance.

Methods

Since the main purpose was to deliver alerts to care providers over the course of patient care and to capture feedback as alerts occurred, the first step was to implement an architecture that could support progressive development of event detection and alerting mechanisms, while maintaining a level of reliability sufficient for routine clinical use. Existing architectural components[8,9] were deployed, and several new components were added. A schematic of this architecture is shown below in Figure 3.1.

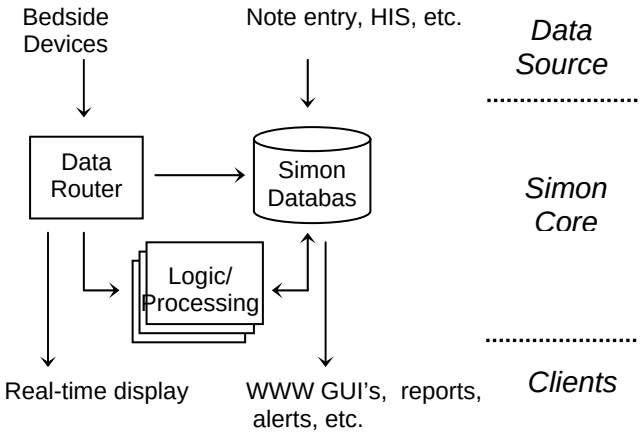

Figure 3.1: Simon Architecture.

For performance reasons, the architecture separates high bandwidth data streams generated by bedside devices from other data channels such as user notes and hospital information system (HIS) data. The central point of access for all bedside device data is a *data router*, which relies on a publish-subscribe mechanism implemented over TCP/IP sockets to rapidly relay data from bedside medical device interfaces ("publishers") to processing modules and other "subscribers" requiring immediate, continuous access to bedside device data, sampled every few seconds. All other data access is accomplished through open database connectivity (ODBC) connections to a relational database on a separate machine, implemented using Microsoft SQL Server. Components developed as part of this work included:

1. A database archive module to store all physiologic data to the database in "batches";

2. Processing/logic modules to compress these data for long term storage, associate data with patients based on hospital census information, monitor and manage system components, notify the researcher if system problems occurred, and deliver alerts to care providers via email and/or alphanumeric pager;
3. A java-based note application for entering free text notes in response to alerts, modified from existing code developed at VUMC;
4. Clients for WWW display of current data, alphanumeric pager alerting, and recently generated alerts.

During the test period, the implementation of this architecture supported data collection and processing from up to six different medical devices on each of four trauma ICU beds, and a variety of other sources and clients. Since then, six additional beds have been added, as of July, 2001.

After implementing the basic architecture, an attending trauma surgeon with over 20 years of critical care experience was asked to define a set of physiologic events for testing that he thought might have clinical significance. He choose to generally express events in the form of threshold conditions over time, for example *intracranial pressure > 25 mmHg for 15 minutes*. Some events did not have a duration requirement, such as *cardiac index < 2.5 l/min/m*^{2}. An event detector was developed by another member of the project team[9], and tested off-line on actual data. Several factors became apparent during initial testing, that influenced the event detection algorithms as well as the choice of events to study: 1) Some parameters were not always available, due to device configuration requirements that unit staff were trained to do; 2) Noise and artifacts would

require more advanced processing than simply monitoring current values in the data streams; and 3) False positive alerts would likely be present even with better processing, due to external variables that could not be sensed by the system, including lab data and patient status (organ donor, DNR).

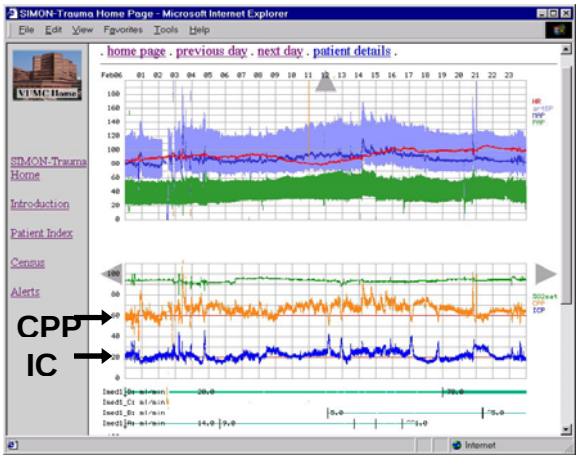

Figure 3.2: Portion of Simon WWW GUI.

As a result, initial efforts focused on detecting events in intracranial pressure (ICP) and cerebral perfusion pressure (CPP), two parameters the system could reliably acquire at all times. The corresponding event definitions were:

ICP > 25 mmHg for 15 minutes

CPP < 60 mmHg for 15 minutes

Typical ICP and CPP signals are noted above in Figure 3.2, which shows a full day of data for a single patient. Each arrow points to the respective threshold value. In addition,

a multi-state detection algorithm was defined to improve performance in the presence of noise, short data dropouts, and other artifacts.

While the event detector was being tested, a note-entry application was implemented that allowed users to enter free-text notes in response to alerts. It was important to be able to link this application with existing information sources, and to be able to easily deploy it on three bedside laptops dedicated to the project. An existing template-based note entry application, written in java at VUMC, was adapted to run via a web browser, and to directly interface with the Simon database via Java Database Connectivity (JDBC). Four nurses initially tested this application over a period of six weeks, and performance issues were addressed by adding additional memory to the three bedside laptops dedicated to the project.

Finally, mechanisms were needed to notify care providers of alerts and to tie event, alert, and note data together. Database tables were defined to store events, alerts, and notes, as well as configuration data such as who should receive alerts for a particular bed. When an event is detected and added to the database, a notification engine looks up any number of email or alphanumeric pager recipients for the particular bed, delivers alerts appropriately, and logs the delivery in the database. A pager display of an actual clinical alert is shown in Figure 3.3.

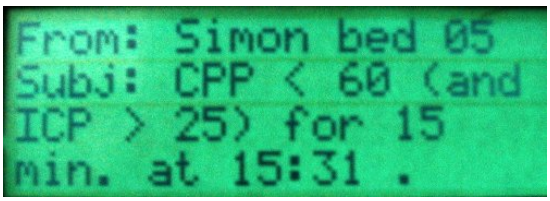

Figure 3.3: Clinical Alert on Alphanumeric Pager

A WWW page (Figure 3.4) lists all alerts generated over the past 12 hours, and if notes have been entered for each alert. Clicking on the alert hyperlink brings up the note entry application with patient demographics, timestamps, and alert information automatically entered.

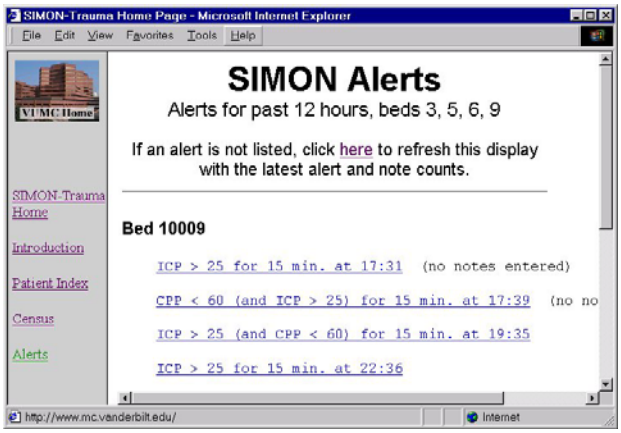

Figure 3.4: Alert Status GUI.

After all components were developed and tested, a group of clinical users was identified who would enter documentation in response to each alert. The VUMC Division of Trauma staffs a clinical nurse supervisor (CNS) position with a licensed nurse practitioner at all times, and this was an ideal test group for several reasons. First, they are generally aware of the state of the most critically ill patients in the trauma unit. Second, their duties permit them to review alerts for any patient, assess the situation, and enter documentation in a timely manner. Most important, they generally have significant clinical experience and interest in the project, and were willing to act as “filters” between the system and the other members of the care team.

In July 2000, users attended a brief presentation and demonstration of the system, and the CNS on duty began receiving alerts via alphanumeric pager. After only a few days, they suggested an important refinement to the alert definitions. While users wanted to receive ICP alerts at all times, they only felt CPP alerts were significant in the presence of increased intracranial pressure, so the system was modified accordingly. Data from August 8, 2000 through Jan. 18, 2001 were reviewed, and data corresponding to patients that arrived in a Simon bed before the start of this interval, or left after the end, were not considered. For each patient with ICP or CPP alerts, the total monitored time was computed as the duration of ICP monitoring less data gaps greater than five minutes. Since an important aspect of the work was in assessing the feedback side of the process, documentation for each alert was subjectively classified into one of five areas according to the type of clinical action, or reason why no action was taken, in relation to the alert.

Results

Over the study period, 530 ICP and/or CPP alerts were detected in 14 different patients, corresponding to about 2280 total hours of ICP data. Four additional patients had ICP/CPP monitoring for a significant time (> 30 minutes), but no alerts were detected. Figure 3.5 shows the incidence of ICP and CPP alerts by patients who had at least one alert.

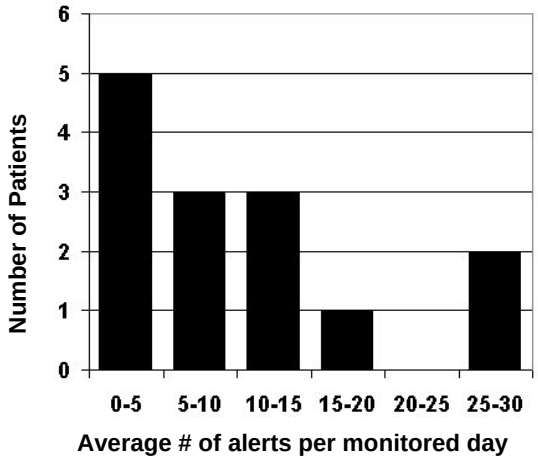

Figure 3.5: Frequency of ICP and CPP Alerts in Four Trauma ICU Beds. 8/00-1/01.

Figure 3.6 shows the breakdown of documentation types entered in response to alerts during the study period.

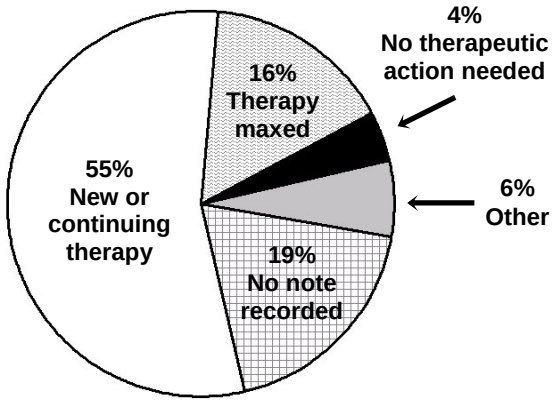

Figure 3.6: Types of Documentation Entered in Response to 530 Alerts.

While users were not given specific instructions about what type of information to include in notes, almost all documentation referenced new or continuing therapy related to the alert condition, or gave reasons why therapeutic actions were not taken. Such reasons included: 1) Medical therapy maxed – no additional medical treatment options were available due to patient lab values, or 2) No therapeutic action was needed because the condition spontaneously resolved, or a determination was made to discontinue treatment for ICP/CPP, as in the case of patients with do not resuscitate (DNR) orders. Six percent of notes could not be classified into these groups, and included a wide variety of information such as the patient being under care of another service, to technical feedback and suggestions. A few in this category were reports of disbelief by the bedside nurse that the alert condition occurred, when asked by the CNS who received the alphanumeric page. No notes were recorded for 19% of alerts, although almost all of these were for a single patient over a four-day period, indicating a short-lived technical or user issue that went undetected.

Technically, the system generally performed well during the test period. There was one known period of extended outage, of 5 days duration starting on 11/23/00. Outages were otherwise limited to a few hours per month on average, usually due to network and/or power glitches. Subjective user feedback was fairly positive, although users expressed dismay in a few cases where alerts continued after DNR orders were in place, as the system had no way of sensing this situation. Finally, successive notes included substantial repetition, discussed in more detail below.

Discussion

Overall, the system was effective at providing clinical alerts to users, as well as capturing data about how alerts were related to clinical therapy or lack thereof. Users were remarkably good at ensuring a note was entered for each alert. If the one period mentioned above is omitted (where notes for one patient were not entered over a 4-day period) more than 95% of all alerts were documented. Factors that contributed to this high response rate likely included a simple, easy-to-use interface for documentation, as well as substantial enthusiasm for the project from the trauma division director. From a technical standpoint, alerts were reliably detected for ICP and CPP because of fully automatic operation with no special connection or configuration requirements. Reliably detecting events in other signals, such as those from portable bedside devices that must be physically connected to the system each time or specifically programmed to send data, might be more difficult and require substantial user training.

Also, success in detecting alerts and eliciting documentation from users does not necessarily imply clinical usefulness. Subjective review of note content indicated that users probably considered many of the alerts redundant, due to substantial numbers of notes reading “ditto”, “see previous entry”, or similar. This effect is in part due to the close coupling of ICP and CPP. CPP is the difference between mean arterial pressure and ICP, so an increase in ICP is usually accompanied by a decrease in CPP. In many cases this would trigger two alerts within a few minutes of each other, with similar user documentation. While it is difficult to assess utility given the fact that supervisors entered all data and were not specifically asked to rate usefulness in any controlled way,

the presence of duplicate notes and the short time interval between the corresponding alerts implies some unnecessary redundancy in alert delivery.

However, note type and content may be used to prioritize system improvements to reduce this redundancy, making the system more suitable for routine use by bedside nurses. Note content was very important during initial testing, in terms of deciding to only deliver CPP events in the presence of an increased ICP event. During the study period, the types of alerts entered suggest additional enhancements. Since 16% of notes indicated that therapy was maximized based on clinical lab values, only notifying care providers when therapy could be resumed based on lab data, or by not sending alerts in cases where no therapy could be provided, might improve usefulness. In addition, a facility to tell the system not to send alerts for patients with DNR orders would be helpful. Notes referencing corresponding therapy were most prevalent, suggesting that a mechanism to incorporate information about drug administration and other therapies might be most beneficial. In this case, the system would not generate alerts if appropriate therapy was being administered. Defining "appropriate therapy" in terms of computational algorithms may be challenging, requiring higher-level knowledge than the fairly simple event definitions described here. However, by "closing the loop" and evaluating not only alerts generated to care providers but also related therapeutic actions, such modifications can be progressively implemented and evaluated to improve performance.

Acknowledgements

Support for portions this work was provided by the VUMC Division of Trauma, and National Library of Medicine Training Grant LM00053-01A1. The authors would like to thank John A. Morris, Jr., MD, for providing event definitions, and the nursing staff of the Vanderbilt University Trauma Unit for their participation in system evaluation.

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CHAPTER IV

VOLATILITY: A NEW VITAL SIGN IDENTIFIED USING A NOVEL BEDSIDE MONITORING STRATEGY

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Abstract

Background: SIMON (Signal Interpretation and Monitoring) monitors and archives continuous physiologic data in the ICU (HR, BP, CPP, ICP, CI, EDVI, S_VO_2, S_PO_2, SVRI, PAP, and CVP). We hypothesized: heart rate (HR) volatility predicts outcome better than measures of central tendency (mean and median). **Methods:** Over 600 million physiologic data points were archived from 923 patients over two years in a level one trauma center. Data were collected every 1 to 4 seconds, stored in a MS-SQL 7.0 relational database, linked to TRACS, and de-identified. Age, gender, race, Injury Severity Score (ISS), and HR statistics were analyzed with respect to outcome (death and ventilator days) using logistic and Poisson regression. **Results:** We analyzed 85 million HR data points, which represent over 71,000 hours of continuous data capture. Mean HR varied by age, gender and ISS, but did not correlate with death or ventilator days.

Measures of volatility (standard deviation, % HR > 120) correlated with death and prolonged ventilation. **Conclusions:** 1) Volatility predicts death better than measures of central tendency. 2) Volatility is a new vital sign that we will apply to other physiologic parameters, and that can only be fully explored using techniques of dense data capture like SIMON. 3) Densely sampled aggregated physiologic data may identify sub-groups of patients requiring new treatment strategies.

Introduction

Fundamental approaches to assessing vital signs in the critically ill have changed little since the early 1900's when Cushing asserted the importance of periodic recording of blood pressure and other vital signs.[1] While technical advancements and clinical research have expanded the number of physiologic parameters, treatment options, and management protocols available to the intensive care unit (ICU) physician,[2] interpreting physiologic data remains largely a manual process utilizing only a small fraction of data potentially available.[3] A growing body of evidence suggests that automated analysis of densely-sampled physiologic data can provide information about ICU patient outcome[4-8] or adverse events.[7, 9-11] The SIMON (Signal Interpretation and MONitoring) project began in 1998 with the aim of continuously capturing physiologic data from trauma ICU patients.[12] Clinical impressions led us to believe that patients with wide swings in heart rate had poor outcomes. We hypothesized that heart rate volatility predicts inpatient hospital mortality better than the patients' mean or median heart rate (measures of central tendency).

Methods

Setting

Vanderbilt University Medical Center (VUMC) is the only level one trauma center serving a 65,000 square-mile area. There are approximately 3200 annual trauma admissions and over 1800 of these patients are admitted to a 31-bed dedicated trauma unit. Fourteen of the 31 beds are ICU beds, serving 600-700 admissions per year. Ten ICU beds are equipped with the SIMON data capture system.

Data Sources

SIMON: The SIMON (Signal Interpretation and MONitoring) project is an ongoing collaborative effort between the Vanderbilt Division of Trauma and School of Engineering. Since December 2000, physiologic data from bedside medical devices have been continuously captured and stored from 4 trauma ICU beds[13]. SIMON was expanded to 10 beds in June 2001. Physiologic parameters include heart rate (HR), invasive and non-invasive blood pressures, intracranial and cerebral perfusion pressures, arterial and venous oxygen saturations, blood temperature, pulmonary and central venous pressures, cardiac index, and end diastolic volume index. As of November 2003, data had been collected for approximately 2150 patients for their entire length of ICU stay in a SIMON monitored bed, representing more than 150,000 total hours of continuous monitoring and over 1.5 billion data points. Data are automatically sampled every 1-4 seconds depending on system load and stored in an SQL Server (Microsoft Corp., Redmond, WA) relational database. SIMON does not average or filter the data; the monitor applies short-

term smoothing and other artifact rejection before sending data to SIMON. In the case of heart rate, the monitor reports heart rate in beats per minute rounded to the nearest integer, and averaged over approximately the past three seconds. For clinical use, patient specific data are displayed on a secure website (Figure 4.1) and daily aggregated summary reports are generated and placed in each patient's electronic medical record. In addition, daily unit summaries for all patients on SIMON are sent to the ICU medical director and nurse manager prior to rounds (Figure 4.2).

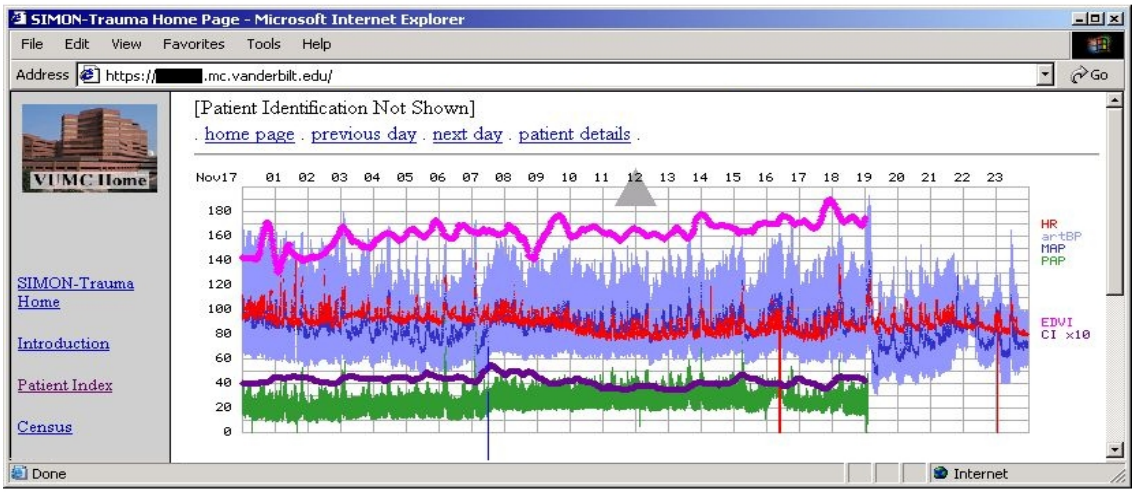

Figure 4.1: SIMON Physiologic Parameter Web Display.

SIMON Unit Summary Data
for the 24-hour period ending 02:00

			Vital Signs						
			HR		BP			SpO2	
		Monitored for	mean bpm	% >120	mean SYS mmHg	% SYS <90	% SYS >180	mean %	% <90
10001	[Pt. name and MRN not shown]	24 hrs 0 min	85	**9%**	112	**12%**	0%	95	0%
10002	[Pt. name and MRN not shown]	23 hrs 0 min	**140**	**83%**	105	**36%**	1%	98	1%
10003	[Pt. name and MRN not shown]	15 hrs 0 min	60	0%	123	1%	0%	92	2%
10004	[Pt. name and MRN not shown]	24 hrs 0 min	99	**7%**	125	1%	1%	96	0%
10005	[Pt. name and MRN not shown]	13 hrs 40 min	79	1%	**81**	**76%**	1%	98	0%

Figure 4.2: Daily SIMON Summary Report of ICU (Only the first five beds are shown).

***TRACS**:* The VUMC Division of Trauma has participated in the Trauma Registry of the American College of Surgeons (TRACS) since 1986. All patients admitted to Vanderbilt University Medical Center with trauma or burns are entered into this database. Data are maintained locally and shared quarterly with the national repository after de-identification. Currently more than 300 parameters are captured via retrospective chart review, including patient demographics, injuries, diseases, operative procedures, hospital disposition, complications, length of stay at various levels of care, costs, and resource utilization. For this study, data from SIMON and TRACS were linked via medical record number and de-identified for analysis after IRB approval.

Inclusion Criteria

The sample included 923 patients that 1) were admitted to Vanderbilt University Medical Center's Trauma ICU between December 15, 2000 and December 31, 2002, as identified by TRACS and 2) had 12 to 240 hours of stored SIMON heart rate data (Figure 4.3). Patients with less than 12 hours or > 240 hours of SIMON data were excluded patients who had early death or transfer and prolonged SIMON recorded ICU stay. These two excluded groups represent a separate future analysis.

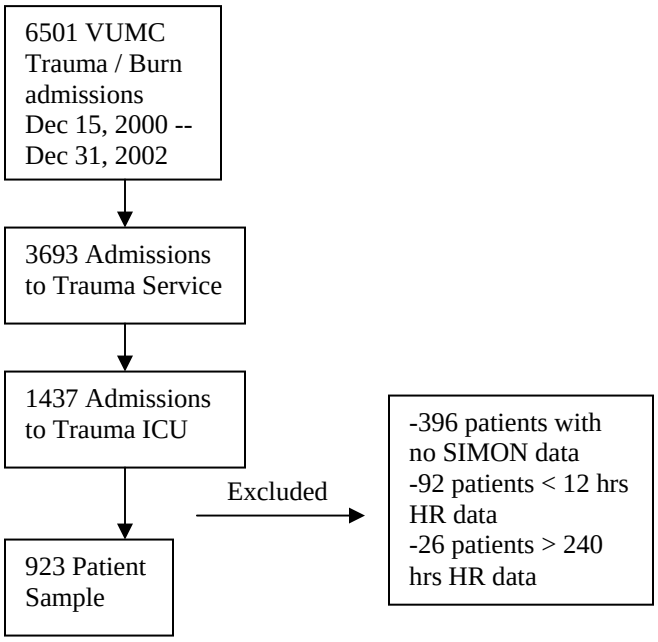

Figure 4.3: Patient Inclusion Criteria.

Measurements

Over 85 million heart rate data points representing 71,334 hours of data capture were stored in the 923 patient sample. Demographics were obtained from TRACS and included age, gender, race, Injury Severity Score (ISS) and discharge status (home, rehab, skilled nursing facility, and death). Heart rate statistics (independent variables) were computed for each patient over all available data from that patient's stay, and included mean, median, standard deviation, skewness and kurtosis (measures of how well data fit a normal distribution), percent of data points above 120bpm, and percent of data points below 60bpm. Measures of central tendency were defined as the mean and median for each patient's set of heart rate data. Statistical variability was given the term "volatility" and included standard deviation, percent of data points above 120, and percent of data points below 60. Our outcomes of interest (dependent variables) included death and ventilator days.

Statistical Analysis

Statistical analysis was performed using STATA v. 7 (College Station, TX). T-test and ANOVA were used to detect mean heart rate differences based on age, gender, race, ISS, and survival status. Logistic regression was used to measure the predictive value of heart rate statistics for death. Poisson regression was used to assess the relationship of these measures with ventilator days. Multivariate analysis was performed controlling for age, gender and ISS. For the logistic and Poisson regressions, ISS was treated as a continuous variable. Age was divided into five binary categorical variables

representing 20-year intervals to control for the curvilinear relation of age and death, with age <20 years serving as the reference category.

Results

Demographics and Heart Rate Statistics

The patient characteristics (n=923) are listed in Table 4.1. The mean age was 38.5 +/- 18.7 years and mean ISS was 28.1 +/- 12.3. There were 99 deaths (10.7%), the median length of stay was seven days, and the majority of the group was male (69.6%). The mean heart rate for the patient sample was 98.6bpm +/- 16.4 and the distribution is shown in Figure 4.4. This graph represents 71,334 hours of stored heart rate data and the distribution of heart rate in a large segment of the ICU population over a two-year period (67% of ICU admissions). Table 4.2 compares the heart rate statistics by age. ANOVA analysis revealed a statistical difference in these groups with the mean heart rate decreasing with age. There was a statistical difference in mean heart rate comparing males to females, but this had doubtful clinical relevance (Table 4.3). No difference existed when comparing the mean heart rate by ethnic group. Patients with an ISS $\geq$ 25 had a higher mean heart rate (99.9) when compared to those with an ISS<25 (96.6). This small difference is probably is not clinically relevant. No statistical difference existed when comparing the mean heart rate by survival status.

Table 4.1: Patient Characteristics (n=923). ISS =Injury Severity Score. LOS=Length of Stay. Vent=Ventilator.

	Mean	Median	Standard Deviation	Min	Max
Age (years)	38.5	35.6	18.7	12	98
ISS	28.1	27.0	12.3	1	75
LOS (days)	10.8	7.0	11.2	1	172
ICU Days	5.4	3.0	6.5	1	67
Vent Days	5.2	3.0	8.6	0	172

Table 4.2: Mean Heart Rate Statistics by Age. *P* value determined for mean heart rate across age groups using ANOVA. Heart rate in beats per minute (bpm). $P < 0.001$.

	N	Mean	Median	Min	Max	Standard Deviation
All Patients	923	98.6	99.0	56.4	148.2	16.4
Age Group						
<20	165	102.5	103.2	56.3	143.7	18.4
20-39	380	100.1	100.4	56.7	148.2	16.9
40-59	241	97.9	99.7	57.4	133.9	14.5
60-79	107	92.3	94.6	61.9	117.6	13.2
80-100	30	86.9	88.2	61.3	108.2	12.1

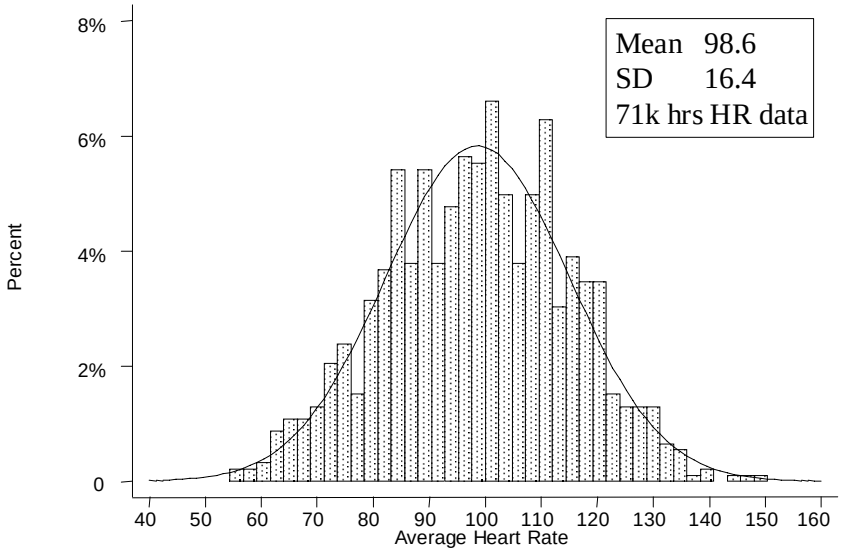

Figure 4.4: Distribution of Patients' Average Heart Rate (n=923).

Table 4.3: Heart Rate Statistics Over Entire SIMON Bed Stay. *P* value determined for mean heart rate in gender and groups using t-test. ANOVA used for ethnic comparison. Heart rate is in beats per minute (bpm).

	N	Mean	Median	Min	Max	Standard Deviation	*P* value (mean)
Gender							
Male	642	97.5	98.2	56.3	148.2	16.3	
Female	281	101.2	101.1	60.0	143.7	16.5	0.001
Race							
White	757	98.4	98.7	56.3	148.2	16.3	
Black	103	100.1	100.0	62.4	137.8	17.5	
Hispanic	58	100.1	103.6	64.4	126.2	16.5	
Other	5	93.0	90.4	81.9	113.0	12	0.56
ISS							
<25	347	96.6	96.7	56.3	140.1	15.9	
>=25	576	99.9	100.7	56.7	147.2	16.6	0.003
Hospital Disposition							
Alive	824	98.6	98.5	56.3	143.7	16.1	
Dead	99	98.9	99.4	65.8	148.2	18.8	0.85

Regression Analysis: Results of the regression analysis after controlling for age, gender, and ISS are shown in Table 4.4. Measures of central tendency (mean and median) did not predict a poor outcome. Measures of volatility (standard deviation, % of data points > 120bpm, % of data points <60bpm) were predictive of death and prolonged ventilation. Measures of normal distribution (skewness and kurtosis) were not statistically significant predictors of outcome (not shown).

Table 4.4: Regression Analysis for Heart Rate Statistics. OR and IRR signify the relationship between the independent heart rate variables and outcome (death and vent days). Multivariate logistic and Poisson regression analysis used, controlling for age, gender, and ISS. Confidence intervals are reported as 95%. OR = Odds Ratio. IRR = Incidence Rate Ratio.

Heart Rate Measure	Death			Ventilator Days		
	OR	***P* value**	**Confidence Interval**	**IRR**	***P* value**	**Confidence Interval**
Mean	1.01	0.47	(0.99-1.02)	1.00	0.32	(0.999-1.00)
Median	1.00	0.54	(0.99-1.02)	1.00	0.22	(0.999-1.00)
Std Dev	1.12	<0.001	(1.07-1.17)	1.03	<0.001	(1.02-1.03)
% Data > 120	4.13	0.005	(1.54-11.0)	1.48	<0.001	(1.30-1.69)
% Data < 60	8.28	0.045	(1.05-65.4)	3.38	<0.001	(2.60-4.39)

Discussion

This study explores the clinical value of dense physiologic data capture in the ICU. We hypothesized that dense data capture of multiple physiologic variables, over time, will identify a sub-group of patients at risk for adverse events and, from that, decision support tools can be developed for early intervention. In this manuscript, we take a first step in investigating that hypothesis using a single physiologic parameter: heart rate. We have defined the distribution of heart rate across multiple demographic groups. We have shown, in the case of heart rate, measures of volatility, rather than measures of central tendency (mean and median), are predictive of hospital mortality and number of ventilator days. Most importantly, we demonstrated that dense data capture can be utilized in a working ICU. While others have demonstrated similar technology[14-16] or analysis of periodically sampled dense data in a similar population[4, 7, 17], our work overcomes implementation barriers associated with identification, reliability, storage, and

analysis. Further, we demonstrated that dense data capture in a large trauma population can be linked with outcomes to identify new risk factors for death and prolonged ventilation.

Summary of Important Findings

We analyzed 85 million HR data points, which represent over 71,334 hours of continuous data capture. Measures of volatility (standard deviation, % HR >120bpm, and %HR<60bpm) were predictive of death and prolonged ventilation. Measures of central tendency (mean, median) were not predictive (Table 4.4). The odds ratio for standard deviation was 1.12 (1.07-1.17) and incidence rate ratio was 1.03 (1.02-1.03) for death and ventilator days, respectively. Analysis of the percent of data points > 120bpm gave an odds ratio of 4.13 (1.54-11.0) and incidence rate ratio of 1.48 (1.30-1.69) for death and ventilator days, respectively. This was also true when controlling for the mean heart rate in the regression model. Similar results were found for % HR <60bpm. The mean heart rate decreased with age as expected and there was no difference in gender. Statistically significant differences in the mean HR existed when grouped by gender and ISS score (< 25). While these differences are probably not clinically relevant, we chose to control for these covariates in the multivariate regression.

Strengths and Limitations

The strengths of this study include the use of population of patients from a large demographic area over a 2-year period, the large data set, and 67% capture of all ICU admissions. Continuous, automatic data capture across 10 ICU beds provided reliable

data for nearly 1000 patients. This large data set allows us to search for patterns of physiologic response across a wide range of injuries and make new observations. Finally, we are defining a path whereby in the ICU, patient specific physiologic data are collected and stored in an electronic repository, distilled to only provide relevant information, and distributed in real-time to clinicians both at the bedside and in remote[13, 17-19] locations. In addition to providing a useful clinical tool, the data are readily accessible for research.

We expect that dense physiologic data capture will be an important tool in the ICU. However, for that to occur, limitations present in this study must be addressed. In the first year of the study period, when SIMON only existed for 2-4 beds, sample bias may have occurred by placing the sickest patients in the SIMON beds. In the second year of the study, all admission beds in the ICU had the SIMON data capture system. We plan to expand SIMON to all trauma beds allowing data capture for the entire hospital stay. This will allow us to detect potentially unique physiologic patterns at different time points in the patient's hospital course. Additionally, our statistical analysis on aggregate data represents a preliminary step in exploring the clinical significance of continuous physiologic data in the ICU. Future refinements will involve time series analysis and segmentation into shorter critical periods of observation as predictors of outcomes. These analyses are ongoing.

Our methods and underlying data used to describe "volatility" are distinct from those traditionally used to characterize HR variability. Most work in HR variability relies on waveform-derived measures of heart beat timing that are more precise than integer HR data. This precision enables analyses that are difficult or impossible to apply to integer

data, but requires orders of magnitude more computational storage and/or processing capacity than our methods. As we shorten our interval of analysis below the entire ICU stay, we will begin to compare traditional methods of waveform analysis with our concept of volatility. Finally, we will need to investigate the time-course of volatility. We do not yet know whether volatility is a more important predictor early in the injury process, suggesting inadequate resuscitation, or late in the disease process, suggesting initiation of a hyper-inflammatory/septic state.

Implications and Future Directions

This manuscript establishes a framework for our analysis henceforth. First, we will look at individual physiologic parameters and determine whether variation of central tendency or volatility appear most predictive of outcome. Once defined, we will examine interactions between multiple physiologic parameters to determine if that enhances predictability.

We have begun to utilize these tools clinically with continuous web-based display of physiologic parameters, individual patient summary reports placed in the electronic medical record, and daily SIMON unit summaries. From this study, we know the heart rate statistics for the unit and therefore when a patient falls outside of the normal distribution. These patients require justification for their deviation. It is exciting to contemplate new tools for decision support such as automated physiologic alerts[13, 22, 23] and reports, but this work is in its infancy. We will need to refine and validate these measures as predictors of adverse events. In addition, we must create an environment that supports process change as well as integration of technical and educational principles

to optimize the opportunity presented by analysis of dense data. The expense of data processing, management, and storage mandates that we define the optimal rate of capture for each physiologic parameter and determine the sensitivity and specificity of deviation from the expected values.

We must understand for each physiologic parameter the influence of patient demographics such as age, gender, and race. Decision support tools can then be created that will allow us to analyze data in real-time, display it graphically at the bedside, and define patient specific alert criteria when these parameters exceed certain predetermined thresholds. In addition, we will need to learn the specific predictive physiologic patterns associated with different types of death. Finally, we must adequately describe these dense data capture technologies and analysis techniques, prove their clinical value, and determine their cost-effectiveness.

In summary, volatility in HR over the entire ICU course identifies a sub-group of patients at increased risk of dying. The SIMON system captures these data in real-time and will serve as both a research and decision support tool for enhancing patient care.

Conclusions

1. In the Trauma ICU, volatility in heart rate predicts death better than measures of central tendency, when looking at the statistics over the entire SIMON monitored ICU stay.
2. Volatility is a new vital sign that can only be fully explored using techniques of dense data capture.

3. Novel computer analysis of dense physiologic data capture may be able to detect early predictors of death.

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CHAPTER V

REDUCED HEART RATE VOLATILITY: AN EARLY PREDICTOR OF DEATH IN TRAUMA PATIENTS

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Mini Abstract

New techniques to capture dense physiologic data in the ICU have identified reduced heart rate volatility as a new vital sign. Aberrations of this vital sign in the first 24 hours following injury predict patient death with 70% sensitivity and 80% specificity after incorporating age and injury severity score.

Abstract

OBJECTIVE: To determine if using dense data capture to measure heart rate volatility (standard deviation) measured in five-minute intervals predicts death. BACKGROUND: Fundamental approaches to assessing vital signs in the critically ill have changed little since the early 1900's. Our prior work in this area has demonstrated the utility of densely sampled data, and in particular, heart rate volatility over the entire patient stay, for predicting death and prolonged ventilation. METHODS: ~120 million

HR data points were prospectively collected and archived from 1316 trauma ICU patients over 30 months. Data were sampled every 1-4 seconds, stored in a relational database, linked to outcome data, and de-identified. HR standard deviation was continuously computed over 5-minute intervals (CRVD-Cardiac Related Volatility Dysfunction). Logistic regression models incorporating age and injury severity score were developed on a test set of patients (N=923), and prospectively analyzed in a distinct validation set (N=393) for the first 24 hours of ICU data. RESULTS: Distribution of CRVD varied by survival in the test set. Prospective evaluation of the model in the validation set gave an area in the ROC curve of 0.81 with a sensitivity and specificity of 70.1 and 80.0, respectively. CRVD predict death as early as 24 hours in the validation set. CONCLUSIONS: 1. CRVD identifies a subgroup of patients with a high probability of dying. 2. Death is predicted within first 24 hours of stay. 3. We hypothesize Cardiac Related Volatility Dysfunction (CRVD) is a surrogate for autonomic nervous system dysfunction.

Introduction

Fundamental approaches to assessing vital signs in the critically ill have changed little since the early 1900's when Cushing asserted the importance of periodically recording blood pressure and other vital signs.[1] While technical advancements and clinical research have expanded the number of physiologic parameters, treatment options, and management protocols available to the intensive care unit (ICU) physician,[2] interpreting physiologic data remains largely a manual process that utilizes only a small fraction of potentially available data.[3] A growing body of evidence suggests that real-

time automated analysis of densely-sampled physiologic data can provide information about ICU patient outcome[4-8] or adverse events[7, 9-11] that is far superior to that generated via conventional processes. The SIMON (Signal Interpretation and MONitoring) project began at Vanderbilt in 1998 with the aim of continuously capturing physiologic data from Trauma ICU patients.[12]

Our prior work in this area has demonstrated the utility of densely sampled data, and in particular, heart rate volatility over the entire patient stay, for predicting morbidity and mortality.[13] This study extends the practical value of our previous work for real-time patient management by hypothesizing that heart rate (HR) volatility (standard deviation) over a 5-minute interval in patients admitted to the trauma intensive care unit predicts death. Our approach is conceptually distinct from, yet complementary to, studies that have used spectral analysis of EKG waveforms to determine heart rate variability and then demonstrate that loss of autonomic function suggests a poor prognosis in many disease processes.[14-17]

Methods

Setting

Vanderbilt University Medical Center (VUMC) is the only level one trauma center serving a 65,000 square-mile area. Of the facility's approximately 3,200 annual trauma admissions, over 1800 are admitted to a 31-bed dedicated trauma unit. The fourteen trauma unit beds classified as ICU beds accommodate 600-700 admissions per year. At present, ten of the ICU beds are equipped with the SIMON data capture system.

Data Sources

SIMON: The SIMON (Signal Interpretation and MONitoring) project is an ongoing collaborative effort between VUMC's Division of Trauma and the University's School of Engineering. Physiologic data from bedside medical devices have been continuously captured and stored from 4 trauma ICU beds[18] since December 2000, with an expansion to 10 beds occurring in June 2001. The physiologic parameters monitored include heart rate (HR), invasive and non-invasive blood pressures, intracranial and cerebral perfusion pressures, arterial and venous oxygen saturations, blood temperature, pulmonary and central venous pressures, cardiac index, and end diastolic volume index.

As of February 2004, data had been collected for over 2200 patients for their entire length of ICU stay in a SIMON monitored bed, representing more than 170,000 total hours of continuous monitoring and over 1.5 billion data points. Data are automatically sampled every 1-4 seconds (depending on system load) and stored in an SQL Server relational database (Microsoft Corp., Redmond, WA). For clinical use, patient-specific data are displayed on a secure website (Figure 5.1) with daily aggregate summary reports generated and placed in each patient's electronic medical record. In addition, daily physiologic data summaries for all patients on SIMON are sent to the ICU medical director, chief residents, and nurse manager prior to rounds (Figure 5.2).

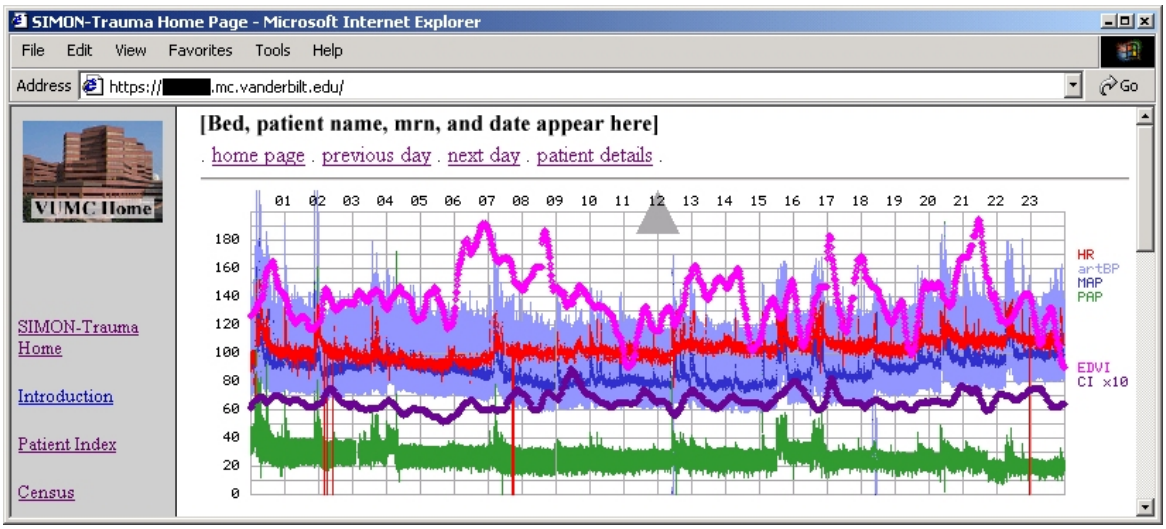

Figure 5.1: SIMON Physiologic Parameter Web Display (24 hours).

SIMON Unit Summary
Data for the 24-hour period ending 03:00

			Vital Signs								
			HR		HRV		BP			SpO2	
		Monitored for	mean bpm	% >120	HRsd5 mean	% <0.5	mean SYS mmHg	% SYS <90	% SYS >180	mean %	% <90
10001	[Pt. id not shown]	11 hrs 15 min	**121**	**53%**	**1.9**	0%	142	0%	0%	99	0%
10002	[Pt. id not shown]	21 hrs 0 min	**133**	**87%**	**1.47**	**11%**	140	0%	1%	97	**7%**
10003	[Pt. id not shown]	7 hrs 45 min	91	**8%**	7.29	0%	145	0%	0%	100	0%
10004	[Pt. id not shown]	21 hrs 55 min	94	5%	4	0%	(**195**)	(0%)	(**77%**)	97	3%
10005	[Pt. id not shown]	24 hrs 0 min	97	3%	4.37	0%	145	0%	2%	97	1%

Figure 5.2: Daily SIMON ICU Unit Summary Report (5/14 beds shown) sent to ICU Director, Nurse Manager, and Chief Resident.

TRACS: The VUMC Division of Trauma has participated in the Trauma Registry of the American College of Surgeons (TRACS) since 1986. Demographic, clinical, and injury-related data on all patients admitted to VUMC for trauma or burns are entered into the database, which is maintained locally and shared quarterly with the National Trauma Data Bank (NTDB) after de-identification. Among the more than 300 parameters currently captured via retrospective chart review are patient demographics, injuries, diseases, operative procedures, hospital disposition, complications, length of stay at various levels of care, costs, and resource utilization. For this IRB-approved study, data from SIMON and TRACS were linked via medical record number and de-identified prior to analysis.

Inclusion Criteria

The test set included data from 923 patients who 1) were admitted to Vanderbilt University Medical Center's Trauma ICU between December 15, 2000 and December 15, 2002, as identified by TRACS and 2) had 12 to 240 hours of stored SIMON heart rate data. Patients who had fewer than 12 or more than 240 hours of SIMON data were excluded. These patients had early death, were transferred, or experienced a prolonged SIMON recorded ICU stay. Data from patients in the exclusion groups were retained for use in a separate future analysis. The validation set consisted of data from 393 patients admitted from December 16, 2002 until July 31, 2003 with the same criteria as the test set (Figure 5.3).

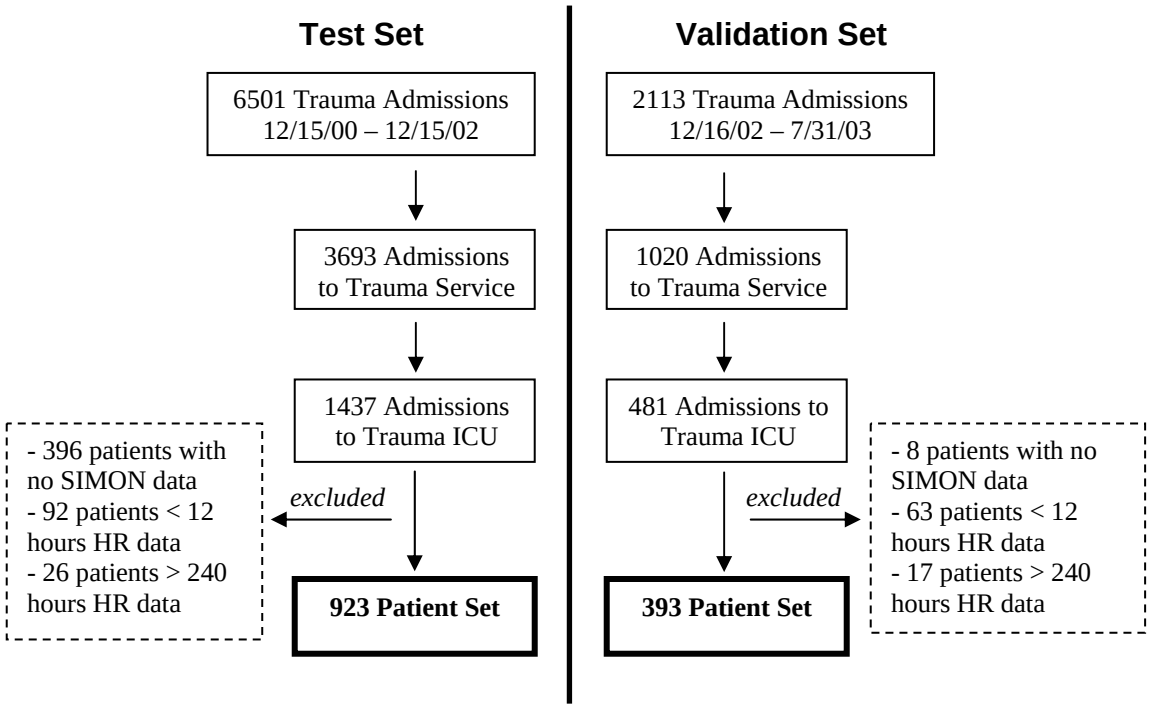

Figure 5.3: Patient Inclusion Criteria for Test and Validation Sets.

Measurements

Over 120 million heart rate data points, representing approximately 100,000 patient-hours of data capture, were stored in the combined 1316 patient sample. Demographic data obtained from TRACS included age, gender, race, discharge status (home, rehabilitation facility, skilled nursing facility, and death), and Injury Severity Score (ISS), an index of anatomic injury severity that correlates with survival in blunt trauma patients.[19, 20]

Our parameter of interest, short-term heart rate volatility, is computed for a given patient once every five minutes by calculating the standard deviation of all heart rate samples collected during that time interval. Duration (five minutes) and intensity

(standard deviation) of volatility are reflected in this measure. The five-minute time interval follows established practices for collecting data for heart rate variability analysis.[21] However, our data differ from that used in traditional heart rate variability analysis in that precise instantaneous heart rate is not acquired at every beat. The SIMON system samples heart rate from a standard monitor (Phillips Viridia) at an average rate of once every two-three seconds. Thus, a typical five-minute interval will contain between 100 and 150 heart rate data samples for a single patient. The standard deviation of these points is our basic parameter of short-term volatility.

We further characterize short-term volatility according to an *observation window* and a *distribution range,* and from these derive a measure of *cardiac volatility related dysfunction* (CVRD). The *observation window* defines the length of time over which short-term volatility is observed, in this case, arbitrarily, the first 24 hours of ICU stay. Therefore the maximum number of volatility measurements in the first 24 hours is 288 (i.e., one measurement every five minutes, 12 five-minute intervals per hour x 24 hours). Figure 5.4 demonstrates patient mortality by distribution of short-term volatility.

The *distribution range* is that portion of the distribution where the measure optimally predicts the dependent variable, death. We chose a *distribution range* of 0 – 0.5, noting the substantial difference in mortality associated with this range (Figure 5.4), as well as substantial prior research by others suggesting reduced variability is associated with poor outcome.

Finally, we define *cardiac volatility related dysfunction* (CVRD) as the percent of time during the observation window (in this case, the first 24 hours in the ICU) that a patient's short-term heart rate volatility fell within the distribution range (i.e., 0-0.5).

Thus, a patient whose short-term volatility readings were evenly distributed between zero and two during the first 24 hours would be assigned a CVRD value of 25%.

Our primary outcome of interest (dependent variable) was death as documented in TRACS, and defined as any inpatient death from any cause during the index hospital admission.

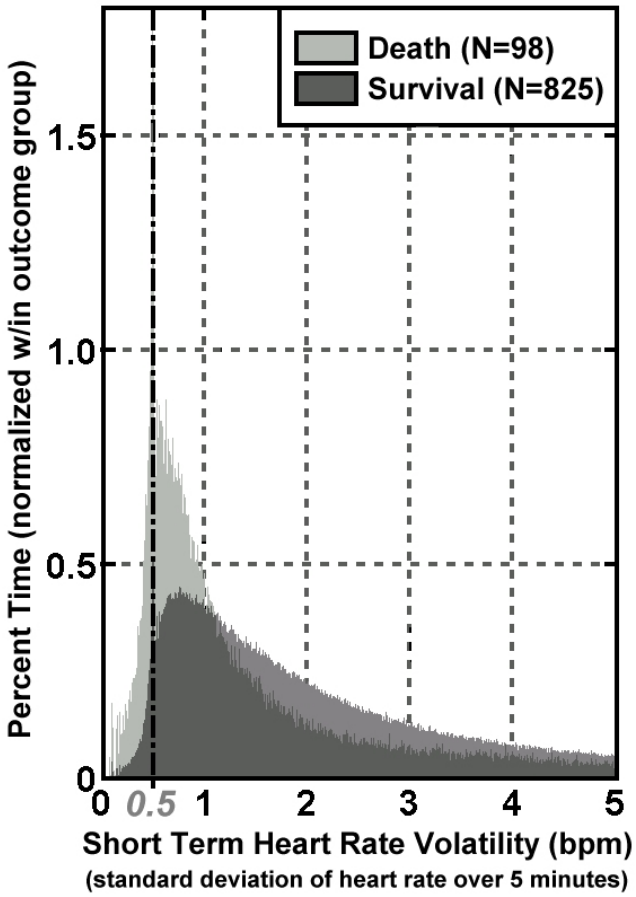

Figure 5.4: Distribution of Short-term Heart RateVolatility Over ICU Stay by Mortality in the 923 Patient Test Set. Percent < 0.5 was used to define Cardiac Volatility Related Dysfunction (CVRD) measurement. Bin size = 0.01.

Statistical Analysis

Statistical analyses were performed using STATA v. 7 (College Station, TX) and SPSS v. 12.0 (Chicago, IL). To assess the equivalency of the test and validation sets, we used T-tests and Mann-Whitney U tests to compare continuous variables pertaining to patients (age) and clinical episodes (LOS, ISS, ventilator days). Contingency tables and the chi-square statistic were used to compare categorical variables (gender, race, and mechanism of injury).

We performed logistic regression to measure cardiac volatility related dysfunction's (CVRD) value for predicting death. Univariate analyses were performed to identify variables that should be included in the multivariable analyses. Multivariable model development and verification was performed on the test set. We used logistic regression to construct multivariate models incorporating age and ISS. To control for the curvilinear relation of age and death, we divided age into five binary categorical variables representing 20-year intervals, with age <20 years serving as the reference category. Using the regression equation developed on the test set, we evaluated the performance of the model on the validation set. Finally, we computed receiver operator curves (ROC) to compare the resulting models.

Results

The demographics of the test and validation sets were sufficiently comparable (Table 5.1) to enable combining both groups for additional characterization and analysis. Stratifying *Cardiac Volatility Related Dysfunction* (CVRD) by gender and race across the combined data sets (Table 5.2) revealed no differences over the first 24 hours of SIMON

data, although significant differences were observed when stratifying by outcome and mechanism of injury. The difference in mechanism of injury was likely due to a higher ISS in the blunt trauma patients. CVRD increased as age and ISS increased (Figure 5.5). Morbidity, defined as number of ventilator days and units of blood transfused, also increased with CVRD (Figure 5.5).

Table 5.1: Comparison of Test Set and Validation Set Demographics.

	Test Set	**Validation Set**	**P value**
Number	923	393	
Age	38.7 ± 19.5	39.6 ± 18.1	0.17
Gender			0.10
Male	642 (69.6%)	291 (74.0%)	
Female	281 (30.4%)	102 (26.0%)	
Race			0.06
White	752 (81.5%)	295 (75.1%)	
Black	103 (11.2%)	68 (17.3%)	
Hispanic	58 (6.3%)	24 (6.1%)	
Other	10 (1.1%)	6 (1.5%)	
Death	98 (10.6%)	37 (10.4%)	0.51
ISS	28.1 ± 12.4	25.7 ± 11.9	0.001
CVRD (% < 0.5)	3.6 ± 9.0	3.3 ± 8.3	0.73

Table 5.2: Characteristics of Cardiac Volatility Related Dysfunction (CVRD).

	N	Mean	P value
Discharge Status			<0.001
Alive	1181	2.45	
Dead	135	10.9	
Gender			0.69
Female	383	3.16	
Male	933	3.39	
Race			0.19
White	1047	3.6	
Black	171	2.29	
Hispanic	82	2.16	
Other	16	5.41	
Mechanism			0.02
Blunt	1116	3.56	
Penetrating	194	1.92	

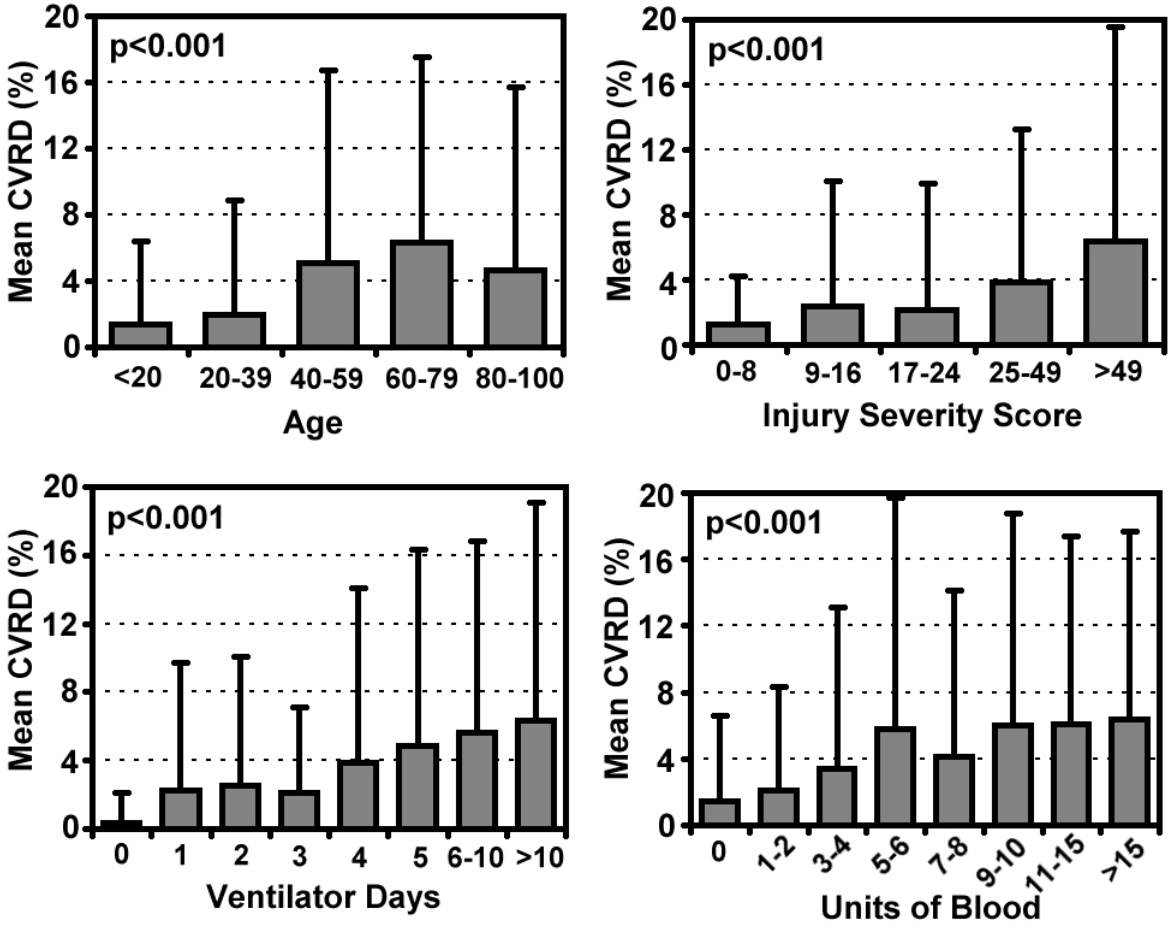

Figure 5.5: Mean CVRD In First 24 Hours of ICU Stay vs. Age, Injury Severity Score, Ventilator Days, and Units of Blood Transfused. Combined dataset (N=1316). P-values using ANOVA.

Without incorporating age or ISS, we also stratified patient deaths in the combined data set by CVRD and found a 3.8% mortality rate in patients without CVRD. Conversely, patients with *any* abnormality in CVRD had a 21% mortality rate. The mortality rate increased as CVRD increased (Figure 5.6).

Having identified the key covariates (age and ISS) that contribute with CVRD to death, we developed a regression model incorporating both elements. The covariates that were significant in both the test and validation set were age > 80 and ISS (Table 5.3).

The formula using the regression equation generated a score ranging from 0-1. The cutoff value, which maximized sensitivity and specificity in the test set, was found to be 0.1. This same model was then prospectively evaluated for predictive accuracy in the validation set. The receiver-operator curves (ROC) for both the test and validation sets (Figure 5.7) show no statistical difference. The ROC area for the validation set was 0.816 and the sensitivity and specificity were 70.1% and 80.0% respectively (Table 5.4). To further evaluate the effectiveness of the model, we compared the true positives and false negatives to the days to death (Figure 5.8). This demonstrated that the regression equation above remains effective for predicting death beyond the first several days.

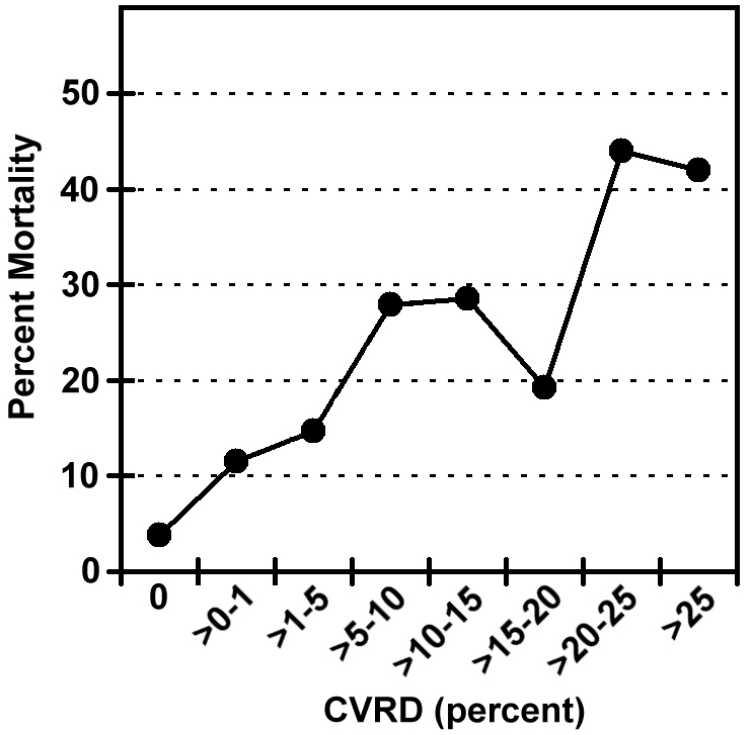

Figure 5.6: Percent Mortality vs. Cardiac Volatility Related Dysfunction (CVRD) in the First 24 Hours of ICU Stay. Age and ISS not incorporated. Data for test and validation set (N=1316).

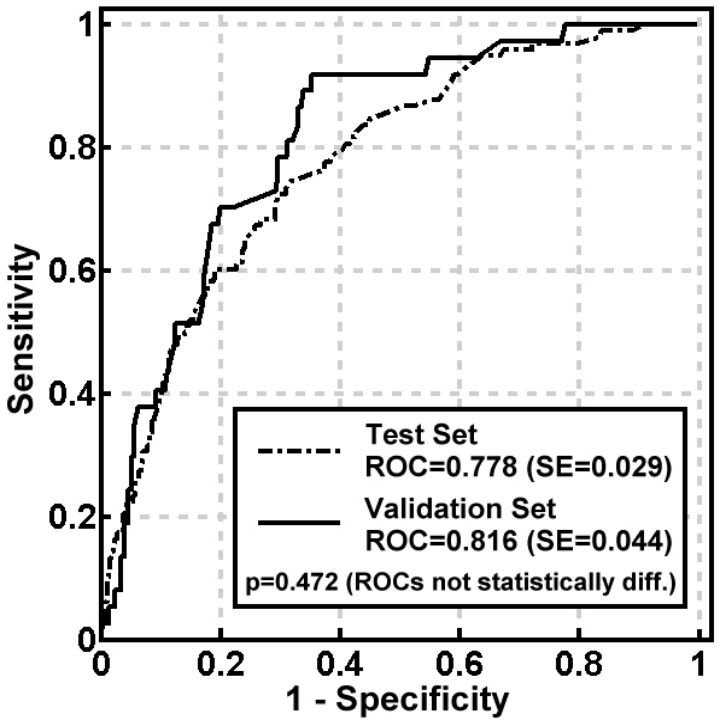

Figure 5.7: Logistic Regression Model ROC Curves for Test and Validation Sets. P-value shown is comparing test and validation set curves. P-value for both curves <0.0001.

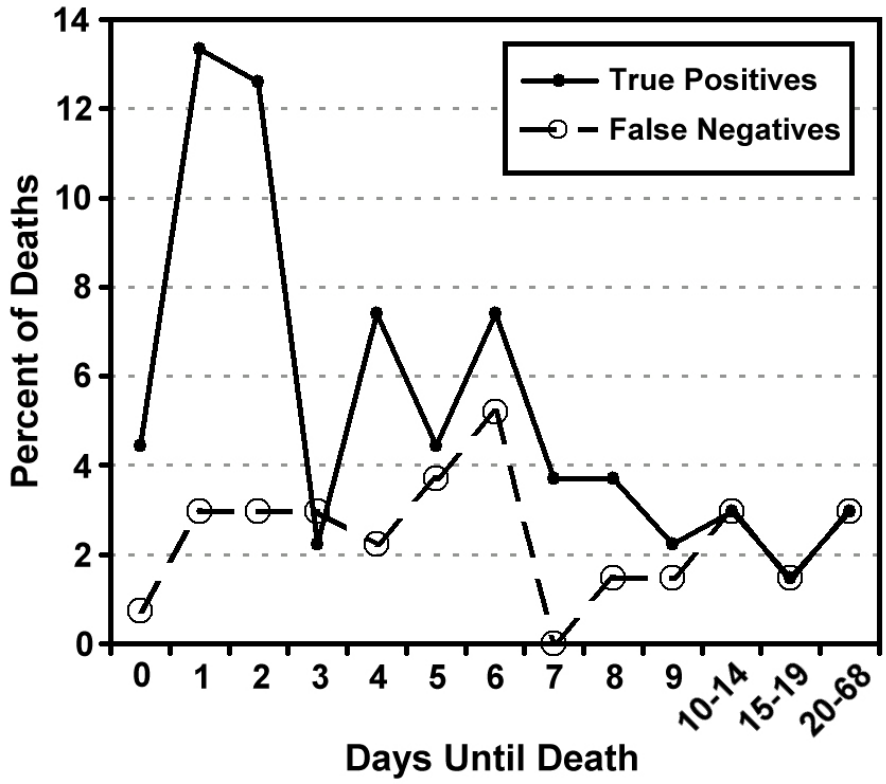

Figure 5.8: True Positive (patients predicted to die who die) and False Negative (patients predicted to live who die) Rates vs. Days to Death. Combined test and validation sets (N=1316).

Table 5.3: Logistic Regression Model Parameters. (Developed on Test Set, N=923).

Parameter	Coefficient	95% Confidence Interval
[constant]	-4.114	N/A
ISS	0.053	1.035-1.074
If age > 80	1.254	1.273-9.645
CVRD	0.050	1.033-1.071

Table 5.4: Receiver Operator Curve Statistics. The model described in table 5.3 was applied to the validation sample (N=393).

Time interval	Sensitivity	Specificity	ROC	P value
1st 24 hours	70.1%	80.0%	0.816	<0.0001

Discussion

This study explores the clinical value of dense physiologic data, captured in the ICU and automatically stored in a relational database. It is our global hypothesis that the SIMON project's automated dense data capture and systematic analysis of multiple physiologic variables, will, over time, facilitate both the identification of patients at risk for adverse events and development of decision support tools useful for early intervention. Our previous work demonstrated that measures of long term heart rate volatility (standard deviation, percent of time in extremes during the entire hospital course) were better predictors of survival in a population of trauma patients than were measures of central tendency (mean, median).[13]

This study extends that effort by investigating whether patterns of short-term volatility in five-minute intervals (CVRD) aggregated over the initial 24-hours of ICU stay have predictive value during a patient's entire hospital course. We chose the five-minute interval to maximize comparability with previously described heart rate variability analyses, which also measures heart rate changes over five-minute intervals.

In this manuscript we use raw data to demonstrate that cardiac volatility related dysfunction in the first 24 hours of ICU stay is an independent predictor of death. This measure also predicts morbidity (ventilator days and transfusion).

CVRD varies with age, injury severity score, and mechanism of injury. We use regression data incorporating age and ISS in an independent validation set to demonstrate the sensitivity and specificity of this measure in predicting death. Using the ROC, we show that 82% of variation is accounted for by our model. However, we do not advocate that CVRD be used in isolation to predict individual patient mortality.

The practical and operational evidence that dense data capture can occur in a working ICU enhances the clinical significance of our findings. While others have demonstrated similar technology[22-24] or analysis of periodically sampled dense data in a similar population,[4, 7, 25] our work demonstrates the value of overcoming barriers associated with patient identification, reliability, storage, and analysis of dense physiologic data. Further, we demonstrate that linking dense data captured in a large trauma population to clinical outcomes facilitates identification of new risk factors for death and morbidity.

Strengths and Limitations

Strengths: The strengths of this study include use of: 1.) a diverse population of patients with a wide range of injuries spanning a 3 year period, 2.) a large, prospectively-collected test data set (N = 923), 3.) an independent, prospectively-collected validation set (N = 393).

Clinicians were blinded to these data during the course of care, therefore the results are independent of clinician intervention; this de facto, blinding also serves to establish our institution's baseline practice pattern against which future interventions designed to highlight CVRD can be benchmarked.

Finally, this study defines a methodology for ICUs to collect, store, distill, and distribute electronically patient-specific physiologic data in real-time to clinicians both at the bedside and in remote locations.[18, 25-27] In addition to their clinical value, the data are readily accessible for research and operational applications.

Limitations: We expect that dense physiologic data capture will become an increasingly important tool in the ICU, but for that to occur limitations of our study must be addressed. In the first year of the study period, when SIMON only existed for 2-4 beds, sample bias may have occurred if clinicians tended to allocate the SIMON beds, a scarce resource, to the sickest patients. If this occurred, the problem would have resolved by the second year of the study, when all admission beds in the ICU were equipped with the SIMON data capture system. Further expansion of SIMON to all 31 beds on the trauma unit will allow dense data capture to continue throughout a patient's entire hospitalization, facilitating detection of potentially unique physiologic patterns occurring at different time points in the patient's hospital course. In addition, the absence of pharmacology data rendered us unable to determine whether beta-blockade or administration of other drugs explains the increasing loss of volatility associated with age, injury severity, or mortality.

With regard to the regression model, loss of 30-day mortality data on cases discharged to long-term care facilities may have had the effect of understating true positives, and

failure to include mechanism of injury despite its positive association with mortality may have diminished the model's predictive power. Finally, construction of chronologically distinct (serial) test and validation sets renders the analysis vulnerable to variations occurring over time. The fact that our model performed better in the validation set could be due to such variations. We will address these issues in future analyses by means of bootstrapping, time series analysis, segmentation into shorter critical periods of observation as predictors of outcomes, and other appropriate techniques. These analyses are ongoing.

Future Work

This work represents a series of compromises between the rigor of the laboratory and the realities of delivering bedside care. Previous work in heart rate variability has been largely based on waveform analyses[15, 21] that assess autonomic function via precise R-R interval computation from EKG waveforms. The increase in precision obtained via this methodology comes at a cost—waveform analysis requires several orders of magnitude more storage and processing capacity than the methods presented here. We have begun to compare the methods of waveform analysis with CVRD to determine if the loss of short-term volatility represented by CVRD is a measure of autonomic dysfunction. While we hypothesize CVRD is an indicator of autonomic dysfunction, it is possible that we are measuring intrinsic cardiac dysfunction, failure of resuscitation, physiologic exhaustion, patient's genetic ability to respond to injury, global hypoperfusion, or a parameter specific for neurologic dysfunction.

Continued refinement of our measure will help to identify the time interval of standard deviation, the standard deviation distribution range, and the observation window that optimizes the ROC curve. Since our data are prospectively collected and stored indefinitely, we can use test / validation and bootstrapping methodologies to find the most powerful measurement tool and model to predict outcome in our ICU.

We must also continue to investigate the time-course of this measure. While the model predicts reliably death occurring within 5-10 days based on the first 24 hours of data, accuracy decreases as the patient's stay lengthens. If CVRD predicts death equally well later in a patient's disease process, it may herald the onset of the hyper-inflammatory/septic state. Aggregation of data into 24-hour blocks reported here is a preliminary step in a wider exploration of the clinical significance of continuous physiologic data in the ICU. Analysis of short-term volatility in finer observation windows such as one, six, and 12-hour blocks is also necessary for CVRD to evolve into a powerful real-time bedside tool.

Each physiologic parameter (blood pressure, oxygen saturation, intracranial pressure, pulmonary artery pressure, cardiac index, pulmonary capillary wedge pressures, SVO_2 and others) stored by SIMON must also be explored and described in the context of at least three types of measures: 1) volatility, 2) central tendency and 3) waveform analysis. We must define each parameter and determine if it is best characterized by measures of central tendency or statistical variation, and begin waveform analysis to analyze the potential of each to predict outcome. Once these individual physiologic parameters are defined, we will analyze the interactive effects of the parameters and determine the best overall and organ system specific indicators of patient status. Only by

employing rigorous scientific process, can we create data-driven alarm systems for individual patients to predict deterioration or poor outcome. Finally, we must replicate the system in other clinical contexts to determine if patterns of physiologic response observed thus far are applicable to other populations of hospitalized patients.

Conclusions

In conclusion, cardiac volatility related dysfunction (CVRD) is potentially the first new vital sign born from the concept of dense physiologic data capture in the Intensive Care Unit. CVRD predicts death in the first 24 hours of ICU stay with 70% sensitivity and 80% specificity when incorporating age and injury severity score. We hypothesize CVRD is a measure of autonomic dysfunction and have demonstrated that patients who lose short-term volatility are at higher risk for death. Further studies are underway to more robustly define CVRD and assess its clinical utility. Dense physiologic data capture may be a powerful new tool for defining subgroups of patients with poor outcome.

Acknowledgements

Financial support for the SIMON project comes from the Division of Trauma, Vanderbilt University. No conflicts of interest exist.

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CHAPTER VI

HEART RATE VARIABILITY PREDICTS TRAUMA PATIENT OUTCOME AS EARLY AS 12 HOURS: IMPLICATIONS FOR MILITARY AND CIVILIAN TRIAGE

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Abstract

Background: Our previous work demonstrated dense physiologic data capture in the intensive care unit (ICU), defined a new vital sign Cardiac Volatility Related Dysfunction (CVRD) reflecting reduced heart rate variability**,** and demonstrated CVRD predicts death during the hospital stay adjusting for age and injury severity score (ISS). We hypothesized a more precise definition of variability in integer heart rate improves predictive power earlier in ICU stay, without adjusting for covariates.

Methods: ~120 million integer heart rate (HR) data points were prospectively collected and archived from 1316 trauma ICU patients, linked to outcome data, and de-identified. HR standard deviation was computed in each 5-minute interval (HR_{SD5}). HR_{SD5} logistic regression identified ranges predictive of death. The study group was randomly divided. Integer heart rate variability (% time HR_{SD5} in predictive distribution ranges) models were developed on the first set (N=658) at 1, 2, 4, 6, 8, 12, and 24 hours following ICU admission, and validated on the second set (N=658).

Results: HR_{SD5} is bimodal, predicts death at low (0.1 - 0.9 bpm) and survival at high (1.8-2.6 bpm) ranges. HRV predicts death as early as 12 hours (ROC = 0.67). HRV in a moving 1-hour window is a simple graphic display technique.

Conclusions: Dense physiologic data capture allows calculation of HRV, which: 1) Independently predicts hospital death in trauma patients at 12 hours; 2) Shows early differences by mortality in groups of patients when viewed in a moving window; and 3) May have implications for military and civilian triage.

Introduction

The response to and outcome of injury in trauma patients has long been a topic of interest for study, but an efficient method of dense data collection and interpretation has been unavailable. SIMON (Signal Interpretation and Monitoring) is an information management tool that captures, stores, analyzes, and displays physiologic and other patient information from the patient's bedside[1,2]. The goal of this multi-year project is to determine the utility of densely captured data in a manner that informs and supports clinical decision-making. Using SIMON, dense data capture and the sampling and storage of multiple patient parameters on a second by second basis is now incorporated into our standard ICU workflow. Our goal is to link this large physiologic data set with other clinical data sets (such as host factors, demographics, outcome, pharmacy and laboratory) and ultimately research data sets (i.e. proteomics and genomics) to better characterize the response and outcome to injury.

We expect the first products of this effort to be the development of "new vital signs" defined by the data gathered by SIMON. Integer heart rate variability (HRV) is

the first of these potential new vital signs[3]. Previously, we have shown that integer HRV in the first 24 hours of ICU stay is associated with increasing probability of morbidity and mortality[4]. Additionally, our work suggests that integer HRV is similar to spectral (waveform) measures of HRV[5]. We postulate that HRV is a reflection of failure of autonomic control of not only the heart, but of multiple organ systems as well.

In this manuscript, we refine the definition of distribution ranges for integer HRV and articulate its basic characteristics. Specifically, we demonstrate:

1) The bimodal significance of integer HRV distribution for predicting death and the critical distribution ranges for both increased mortality and an as yet undefined "protective effect".

2) As the observation window of integer HRV increases over 24 hours the association with death increases, but the bimodal pattern and critical distribution ranges remain consistent.

3) The concept of the rolling percentage of integer HRV to display this new vital sign in real time at the bedside.

Methods

Setting

Vanderbilt University Medical Center (VUMC) is the only level one trauma center serving a 65,000 square-mile area. Of the facility's approximately 3200 annual trauma admissions, over 1800 are admitted to a 31-bed dedicated trauma unit. The fourteen trauma unit beds classified as ICU beds accommodate 700-800 admissions per

year, all of which are currently equipped with the SIMON data capture system. During the study period, SIMON was expanded from four to fourteen ICU beds.

Data Sources

SIMON: The SIMON (Signal Interpretation and MONitoring) project is an ongoing collaborative effort between VUMC's Division of Trauma and the University's School of Engineering. Physiologic data from bedside medical devices have been continuously captured and stored from four trauma ICU beds since December 2000, with an expansion to 10 beds occurring in June 2001. The physiologic parameters monitored include heart rate (HR), invasive and non-invasive blood pressures, intracranial and cerebral perfusion pressures, arterial and venous oxygen saturations, blood temperature, pulmonary and central venous pressures, cardiac index, and end diastolic volume index.

As of December 2004, data has been collected for over 3000 patients for their entire length of ICU stay in a SIMON monitored bed, representing more than 240,000 total hours of continuous monitoring and over two billion data points. Data are automatically sampled once every 3-4 seconds (depending on system load) and stored in an SQL Server relational database (Microsoft Corp., Redmond, WA). For clinical use, patient-specific data are displayed on a secure website with daily aggregate summary reports generated and placed in each patient's electronic medical record. In addition, daily physiologic data summaries for all patients on SIMON are sent to the ICU medical director, chief residents, and nurse manager prior to rounds.

TRACS: The VUMC Division of Trauma has participated in the Trauma Registry of the American College of Surgeons (TRACS) since 1986. Demographic, clinical, and

injury-related data on all patients admitted to VUMC for trauma or burns are entered into the database, which is maintained locally and shared quarterly with the National Trauma Data Bank (NTDB) after de-identification. Among the more than 300 parameters currently captured via retrospective chart review are patient demographics, injuries, diseases, operative procedures, hospital disposition, complications, and length of stay at various levels of care, costs, and resource utilization. For this IRB-approved study, data from SIMON and TRACS were linked via medical record number and de-identified prior to analysis.

Study Population

The study population included data from 1316 patients who 1) were admitted to Vanderbilt University Medical Center's Trauma ICU between December 15, 2000 and July 31, 2003, as identified by TRACS and 2) had 12 to 240 hours of stored SIMON heart rate data. Patients with fewer than 12 or more than 240 hours of SIMON data were excluded. These patients had early death, were transferred, or experienced a prolonged SIMON recorded ICU stay. Data from patients in the exclusion groups were retained for use in a separate future analysis. The population was randomly divided into two equally sized test and validation sets (Figure 6.1).

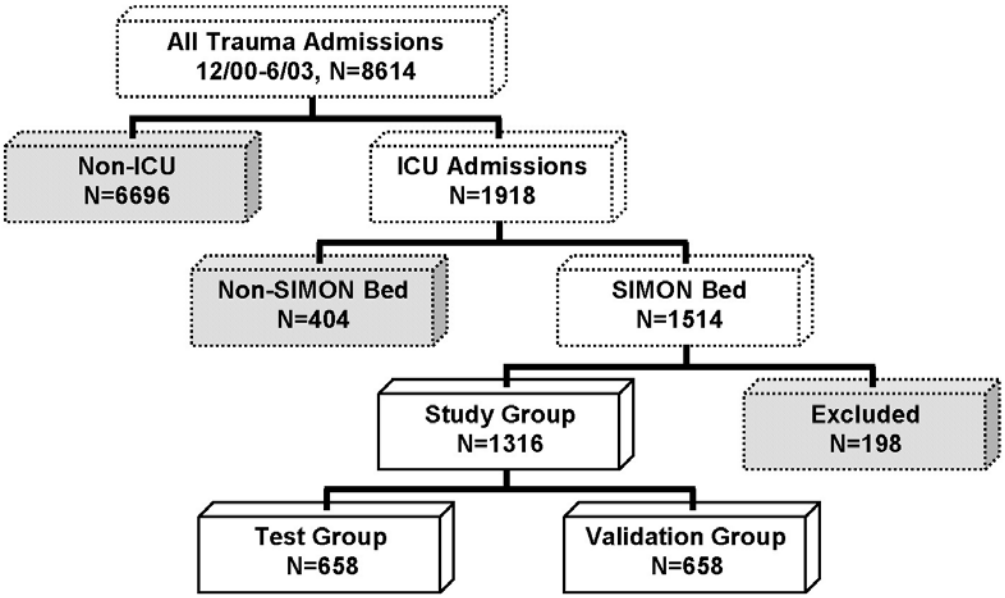

Figure 6.1: Study Population. Patients in the study group were randomly divided into two equally sized test and validation groups.

Measurements

Over 120 million heart rate data points, representing approximately 100,000 patient-hours of data capture, were stored in the combined 1316 patient sample. Demographic data obtained from TRACS included age, gender, race, discharge status (home, rehabilitation facility, skilled nursing facility, and death), and Injury Severity Score (ISS), an index of anatomic injury severity that correlates with survival in blunt trauma patients.

Our parameter of interest, short-term heart rate variability (HR_{SD5}), is computed for a given patient once every five minutes by calculating the standard deviation of all heart rate samples collected during that time interval. Duration (five minutes) and intensity (standard deviation) of variability are reflected in this measure. The five-minute time interval follows established practices for collecting data for HRV analysis, and our

analysis of heart rate standard deviation in collections of these intervals resembles time-series techniques for assessing HRV (i.e. SDANN)[6]. However, our data differ from that used in traditional HRV analysis in that precise instantaneous heart rate is not acquired at every beat. The SIMON system samples heart rate from a standard monitor (Phillips Viridia) at an average rate of once every one to four seconds. Thus, a typical five-minute interval will contain between 75 and 300 heart rate data samples for a single patient. The standard deviation of these points is our basic parameter of short-term HRV, and the units of this measure are beats per minute (bpm).

We further characterize short-term variability according to percentage, as defined by an observation window and a distribution range. The observation window defines the length of time over which short-term variability is studied, and the distribution range defines the range of values of interest. Our principle measure of heart rate variability is the percent of time short-term HRV measurements fall within a particular distribution range during a given observation window. For example, if the observation window is the first 24 hours of ICU stay, and a patient's short-term HRV measurements were evenly distributed between 0 and 4 bpm during this time, their HRV was 100% for the distribution range 0-5 bpm, 25% for the distribution range 1-2 (and 0-1, 2-3, 3-4 bpm), 50% for the distribution range 2-4 bpm, etc.

In this study we considered eight observation windows, corresponding to the first 1, 2, 4, 8, 6, 12, 18, and 24 hours of a patient's ICU stay. 100 different HRV distribution ranges were formed by dividing the range 0-10 bpm into tenths. Variability percentages

were computed for each subject over every observation window and distribution range, for a total of 800 measurements on each subject[1].

Our outcome of interest (dependent variable) was death as documented in TRACS, and defined as inpatient death from any cause during the index hospital admission.

Statistical Analysis

Statistical analyses were performed using STATA v. 7 (Stata Corp., College Station, TX) and MATLAB v. 6.5 (Mathworks Inc., Natick, MA). To assess the equivalency of the test and validation sets, we used T-tests to compare continuous variables pertaining to patients (age) and clinical episodes (injury severity score, short-term HRV in first 24 hours). Contingency tables and the chi-square statistic were used to compare categorical variables (gender, ethnicity, and death).

Univariate logistic regression was used to assess each variability distribution range's association with death, in each of the eight observation windows, in the entire population (800 models). Within each observation window, logistic regression models for predicting death based on multiple distribution ranges were constructed and evaluated as follows: Multivariate models were developed on the test set, by adding variability distribution ranges (in order of significance from univariate results) to the model until performance did not improve. Each of the resulting eight multivariate model equations

[1] Within a particular observation window, patients with data captured less than 50% of the time were discarded for that window only. Any observation window contained a minimum of 1018 patients.

was then applied to the validation set, and evaluated in terms of resulting area under the receiver operator curve.

To examine evolving patterns of reduced HRV during the first 24 hours, and how these patterns might differ by patient outcome, "rolling percentages" were compared between survivors (N=1181) and non-survivors (N=135) in the entire population. At each time relative to ICU admission in the first 24 hours, the mean and standard deviation of percent low HRV over the past hour were computed within the two outcome groups. Percent low HRV was defined as the percent of time integer HRV fell between 0.3 and 0.6 bpm. The Mann-Whitney test was used to assess whether the two groups were statistically different at each time point, at a significance level of 0.05.

Results

1,316 patients admitted to our trauma ICU form the study group and were assessed for integer HRV in the first 24 hours following admission. 135 patients (10.3%) died and 1,181 patients (89.7%) survived to discharge from the hospital.

Figure 6.2 shows statistical significance of each of 100 univariate logistic regression models for determining outcome, based on the percent time short-term HRV fell within the respective distribution tenth over the first 24 hours of ICU stay. The curve demonstrates the bimodal significance of the distribution ranges, with both low (0.1 – 0.9 bpm) and high (1.8 –2.6 bpm) distributions associated with outcome. This analysis was repeated using discrete observation windows corresponding 1, 2, 4, 6, 8, 12, and 18 hours following ICU admission. The summary results are shown in Figure 6.3. It demonstrates

the emerging bimodal pattern of significance as observation window time increases, and the relative constancy of critical distribution ranges.

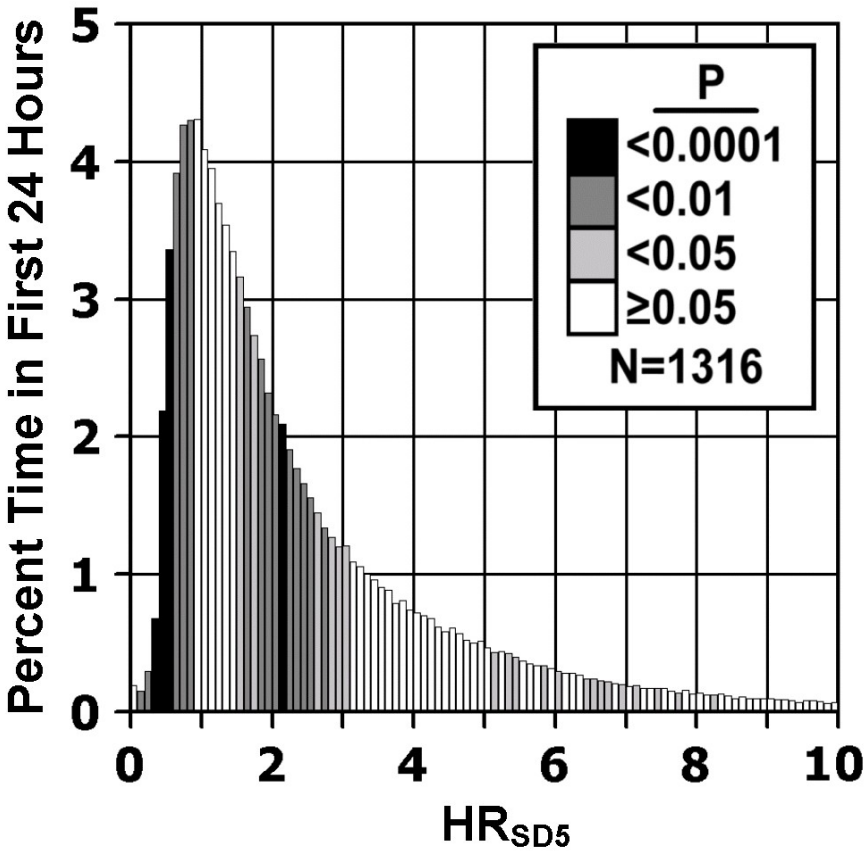

Figure 6.2: Relationship of HRV Distribution Ranges in First 24 Hours to Outcome. Each bar represents a one-tenth range of short-term integer heart rate variability (HR_{SD5}), i.e. 0.3-0.4 bpm. The height of each bar corresponds to the percent of time all patients' HR_{SD5} fell within that range within the first 24 hours of ICU stay. The color of each bar represents statistical significance of a logistic regression model using the percent time within that range as the only input variable and death as the outcome.

This analysis was repeated using discrete observation windows corresponding 1, 2, 4, 6, 8, 12, and 18 hours following ICU admission. The summary results are shown in

Figure 6.3. It demonstrates the emerging bimodal pattern of significance as observation window time increases, and the relative constancy of critical distribution ranges.

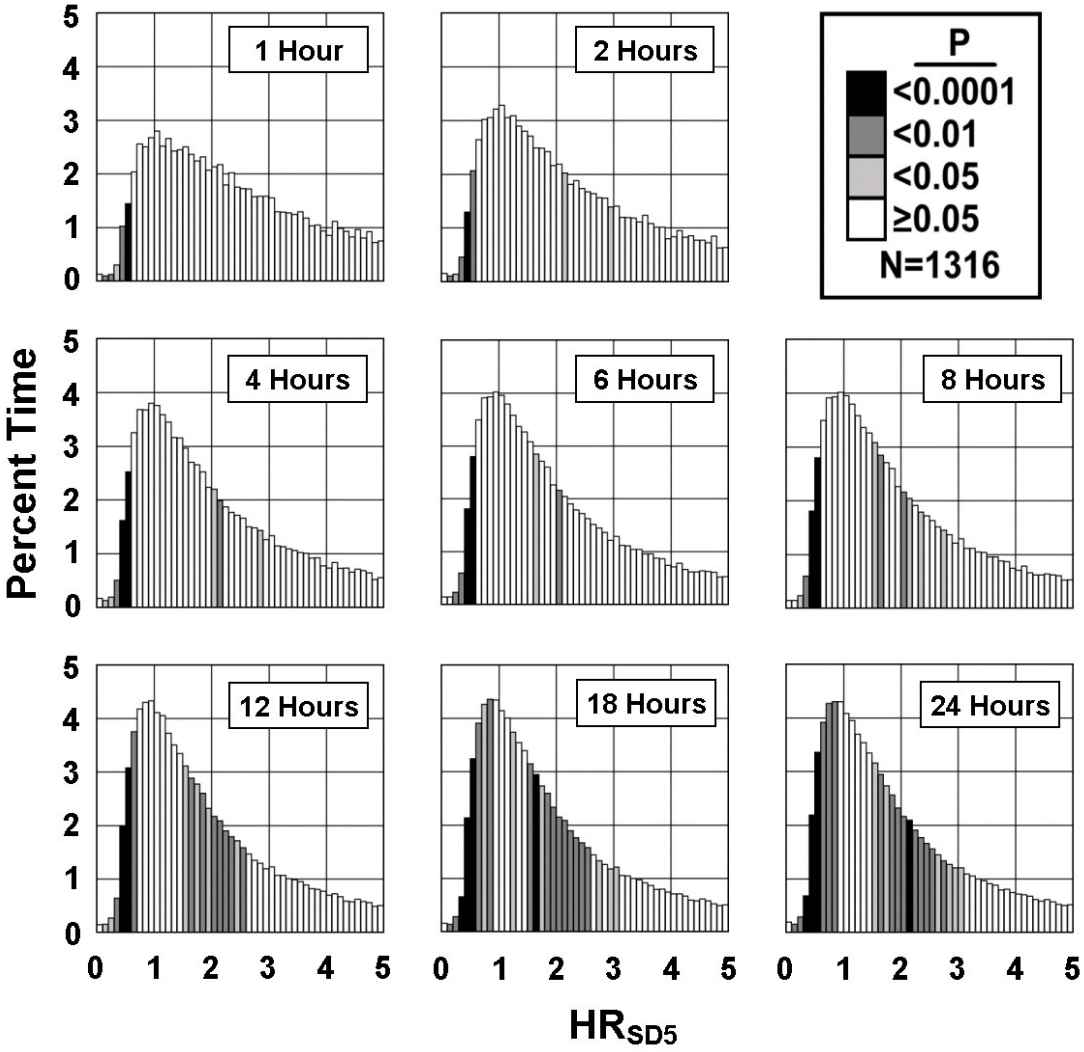

Figure 6.3: Relationship of HRV Distribution Ranges in Various Observation Windows to Outcome. See Figure 6.2 description. Not shown: Distribution ranges above 5 bpm were not statistically significant ($P < 0.05$) except in the 24 hour observation window (see Figure 6.2), and from 5.8 – 5.9 bpm in 6, 8, 12, and 18 hour windows.

The 1,316 patients were then divided randomly into test and validation sets of 658 patients each. There were no statistical differences in age, gender, ethnicity, injury

severity score, short-term HRV within the first 24 hours, or mortality between the two groups (Table 6.1).

Table 6.1: Comparison of Test and Validation Sets. ISS = Injury Severity Score. HR_{SD5} = Short term integer heart rate variability.

	Test Set	**Validation Set**	***P* value**
Number	658	658	
Age	38.9 ± 19.7	39.1 ± 18.7	0.87
Gender			
Male	453 (68.8%)	480 (72.9%)	0.10
Female	205 (31.2%)	178 (27.1%)	0.10
Race			
White	525 (79.8%)	522 (79.3%)	0.83
Black	80 (12.2%)	91 (13.8%)	0.36
Hispanic	46 (7.0%)	36 (5.5%)	0.25
Other	7 (1.1%)	9 (1.4%)	0.61
Death	63 (9.6%)	72 (10.9%)	0.41
ISS	27.3 ± 12.2	26.9 ± 12.9	0.50
HR_{SD5}, 1^{st} 24 hours	2.60 ± 1.43	2.64 ± 1.41	0.55

Eight multivariate models, one for each observation window, were constructed using the test set and evaluated in the validation set. The results are summarized in Figure 6.4, which shows the area under the receiver operator curve for the validation set at various observation windows. This demonstrates that the predictive power of the model increases over the first 24 hours of ICU admission.

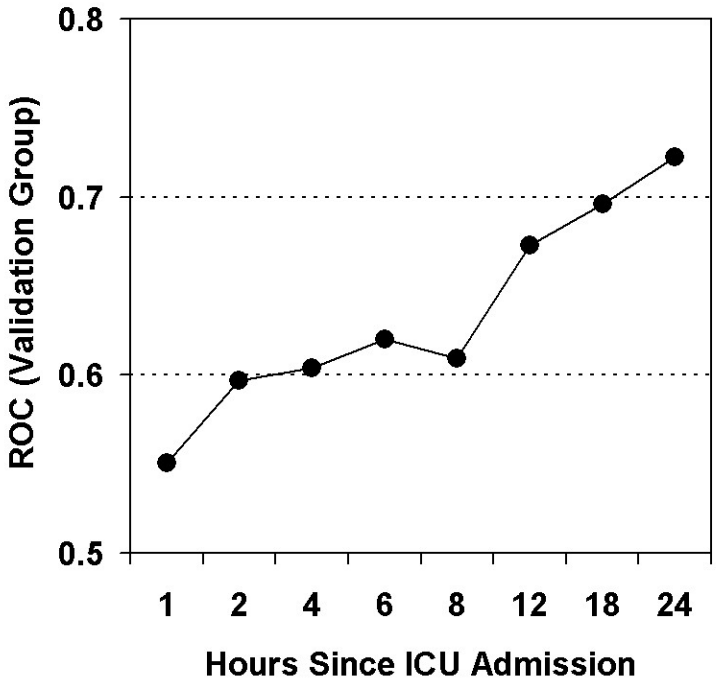

Figure 6.4: Accuracy of Heart Rate Variability in Predicting Death Versus Observation Window. Eight multivariate logistic regression models were constructed to predict death based only on integer HRV data within the first 1, 2, 4, 6, 8, 12, 18, and 24 hours of ICU stay, using a test set of 658 patients. Inputs were the percent of time patients' short-term HRV fell within critical distribution ranges. Each point represents the area under the receiver operator curve when the model was applied to a distinct validation set of 658 patients.

Figure 6.5 demonstrates the rolling percentage of integer HRV over the first 24 hours for two groups: 135 patients who died and 1,181 survivors. While the two populations appear discrete throughout the entire observation window and are statistically different at each time point, there is in fact great variation in the data as shown by the frustratingly large standard deviations (Figure 6.6).

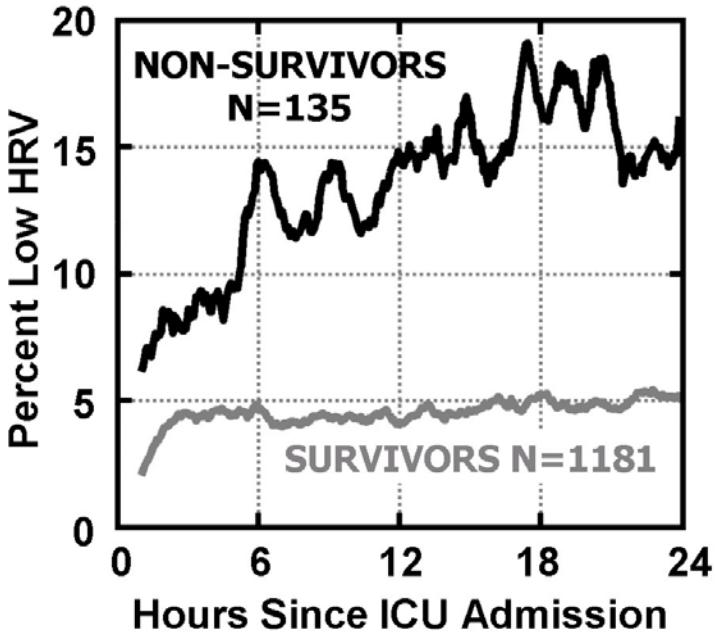

Figure 6.5: Rolling Heart Rate Variability Percentage Over First 24 Hours. Points on the curves represent the average percent of time within the previous hour that integer HRV was between 0.3 and 0.6 bpm, over all patients in the respective outcome group.

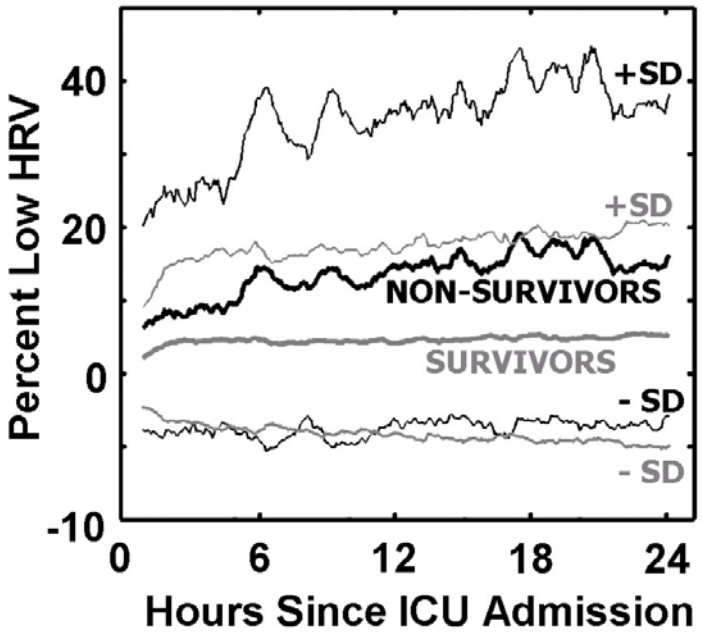

Figure 6.6: Rolling Heart Rate Variability Percentage with Standard Deviation. Bold lines show same data as Figure 6.5, thin lines show ± standard deviation.

Discussion

From a pool of over 8,500 trauma admissions, 1,316 patients were studied to refine the "new vital sign" integer heart rate variability (HRV). We have previously shown that reduced integer HRV correlates with morbidity and mortality in a trauma population[3,4]. Others have traditionally measured HRV via spectral analysis of the EKG waveform[6], and noted similar correlations[7,8]. Additionally, integer HRV and spectral HRV appear to be similar measures of failure of the autonomic nervous system[5,9].

This is important for two reasons. First, spectral HRV has been demonstrated in the laboratory setting to be associated with multiple physiologic derangements including: sepsis or systemic inflammatory response syndrome in adults[10-13], children[14], and neonates[15-17]; multiple organ failure[18-20]; insulin resistance[21-24]; and central nervous system injury in adults[7,25-28] and children[29].

Second, integer HRV is far easier to incorporate into the ICU workflow than spectral analysis. Integer heart rate is less expensive to collect and store because it requires orders of magnitude (10^{-2}) less disk space than high-fidelity EKG waveform data[7]. Most importantly, integer HRV can be displayed in real time at the bedside because it can be acquired and calculated automatically without the manual filtering and manipulation demanded by spectral HRV.

In this manuscript we have proposed a conceptual framework for displaying integer HRV data for both individual patients and populations of patients: the rolling % HRV. We postulate that rolling % HRV is a tool which will allow us to monitor patient's progress or deterioration in real time at the bedside. Trends in integer HRV over time should be as predictive of impending sepsis and other milestones as spectral HRV.

Additionally, in this manuscript we refine the definition of integer HRV and suggest its significance in predicting outcome is bimodal. While our work to date has focused on poor outcomes (morbidity and mortality) in patients experiencing reduced HRV, there appears to be a group in which high frequency HRV (1.8 to 2.6 bpm) is also associated with outcome. We hypothesize that, just as patients with reduced HRV have relatively poor outcomes, patients with increased HRV have improved outcomes. Future characterization of this group should provide insight into this potential "protective effect" of increased HRV.

Finally, we have defined the predictive ability of integer HRV over the initial 24 hours of ICU stay. While predictive power appears to increase over time, the bimodal significance and the critical predictive ranges are discriminators early in the patient's hospital course. In fact, looking at figure 6.5, the survivors and non-survivors appear to be two discrete groups at one hour and continue to diverge over the following 24 hours.

It appears to be the high degree of variation that prevents discrimination early in the ICU course. This is to be expected given the high intensity of the early hours of resuscitation. If the sources of this extraneous variability can be determined and filtered, it is possible that integer HRV can become a powerful triage tool. Potentially, integer HRV and other new vital signs may provide a battlefield commander a simple discriminator between the ubiquitous tachycardia of combat and the unique aberrations in variability associated with traumatic injury. These new vital signs could then be used to triage patients, prioritize helicopter evacuations, and define the moribund.

Strengths and Limitations

The strengths of this work include the large prospective data set collected automatically in a working ICU. Bedside physicians and nurses were blinded to the HRV data to preclude study bias. The data was collected and stored in real time without manual manipulation.

We are, however, limited by the nascent nature of this work. Integer HRV has not been studied as extensively as spectral HRV and the association with autonomic dysfunction is still embryonic. We have additional work to do to clarify the effect of host factors (age, gender, and ethnicity), injury patterns, and physiologic reserve, on integer HRV and outcome.

Our future work will focus on characterizing the sources of variability in our data and developing automatic filters and algorithms to "purify" the data. Our goal is to transform raw data into information, and information into decision support tools. These tools must be available and displayed in real time and incorporated into critical care workflow. Finally, these tools must assist in stratifying patients by: therapy, resource utilization, and the probability of survival.

Conclusions

Integer HRV:

1) Independently predicts death as early as 12 hours.

2) Can be displayed using a moving window.

3) Has a bimodal pattern of significance for predicting death.

4) Has implications for military and civilian triage.

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CHAPTER VII

CONCLUSION

Summary of Chapters

This work represents early steps towards identifying and validating new vital signs in critical care. Chapter 1 outlines the significance and specific aims of this work, and provides a brief overview of other efforts in ICU decision support based on dense physiologic data, discovering new measurements providing better assessment of patient status, and defining underlying physiologic regulatory mechanisms.

Chapter 2 describes the SIMON architecture and implementation for capturing and providing decision support based on dense physiologic data. SIMON has been proven portable by implementing it at another major university medical center.

Chapter 3 illustrates how SIMON can be used to provide real-time decision support in the form of alphanumeric pager alerts based on changes in patient physiology, and how feedback from those alerts can inform decision-support strategies and modify work process for members of the critical care team.

Chapter 4 details integer heart rate statistics over ICU stay in 923 patients, and describes correlations between various statistics and mortality and morbidity. Measurements of heart rate variability over ICU stay correlated with death and increased ventilator days. Measures of central tendency were not associated with mortality or morbidity.

Chapter 5 describes a measurement of short-term heart rate variability in integer heart rate data, and shows how this measurement predicts outcome. In 1316 patients, heart rate variability measured within the first 24 hours, and in conjunction with covariates, predicts hospital death occurring a mean of 7 days after admission.

Chapter 6 discusses how the measurement of heart rate variability can be refined, shows the predictive value of the refined measurement within the first 12 hours of ICU stay, and describes a technique of displaying reduced HRV continuously in real-time.

Future Directions

This work describes a general tool and prototype new vital sign based on a single physiologic parameter (heart rate), studied in a single environment (trauma ICU), for a single application (predicting death). As of February, 2005, SIMON contained 13 other physiologic parameters from more than 3200 patients. One extension of this work is to study heart rate and these other parameters, alone or in concert, by testing various algorithms aimed at improving the timeliness and accuracy of prediction.

Also exciting is the potential to use new vital signs in a variety of other clinical and basic science research applications. Clinically, stratifying populations by outcome is a first step toward detecting and predicting adverse events (i.e. sepsis, organ failure, hemorrhage) in individual patients. Such predictions will identify opportunities for early therapeutic intervention in some patients, and futility of therapy in other patients.

Opportunities for clinical and basic science collaborations to emerge from this work are abundant. Physiologic patterns in response to injury provide a rich definition of the human phenotype. Emerging techniques for correlating genetic factors across large

numbers of variables, in large datasets, can link physiologic response to the genome. Such correlations, over time, should reveal the genetic basis of physiologic regulation, and inform design of clinical genetic assays for identifying populations of at-risk patients.

Finally, the trauma ICU of an academic medical center represents only one of many possible venues for introducing new vital signs. Outside the ICU, the concept of patient trajectory becomes paramount. How do we identify, early in the health care process, clinical deterioration in the one patient out of hundreds or thousands? New vital signs could give advance warning of deterioration, automatically notify appropriate responders, and potentially even initiate the first line of therapy.

Prior to reaching a medical facility, new vital signs might be measured at the scene or during transport to inform triage decisions. In disaster or battlefield scenarios where casualties potentially overwhelm medical resources, triage decisions informed by better information will stratify patients, optimize deployment of resources, identify futility and potentially reduce mortality.

CHAPTER VIII

PROTECTION OF RESEARCH SUBJECTS AND SOCIETAL IMPLICATIONS

Protection of Research Subjects

These studies utilize physiologic data from trauma ICU patients, collected in the course of routine medical care ("on the shelf" data). An individual subject's participation was determined solely by their presence in an operational SIMON bed, and by the suitability of physiologic signals available for analysis. Study populations reflect the age, gender, and ethnic distribution of the general trauma ICU population. No medical interventions, or other changes to routine care processes, were implemented as part of any study. All data were de-identified (all 18 HIPPA identifiers removed) prior to analysis and publication. The Vanderbilt University Institutional Review Board reviewed and granted exemption for all studies.

Societal Implications

New measurements of human physiology, and the tools to monitor and deliver these measurements to clinicians, will improve quality and efficiency of medical care. Even modest improvements result in significant savings in costs and lives, if they can be replicated across health care systems. This work describes tools, methods, and a prototype new vital sign suggesting that dense physiologic data capture and analysis will lead to such improvements, and eventually change the delivery of medical care.

Risk and cost inevitably accompany significant change, especially change associated with health care delivery. Realizing the potential of new vital signs will require far more than tools and studies showing efficacy, even if the tools are inexpensive and the efficacy doubtless. Organizations and individuals will need to make initial investments of time and money to bring new vital signs to the bedside, and to manage risks associated with change. Industry will need to build and market the tools, care providers will need to be educated to properly interpret new measurements, and clinical workflows will dramatically change as a result of new, higher quality information about patient status. In the long term, success depends not only on the validity and feasibility of the concept, but also on individuals' and society's ability to manage the costs and risks associated with change.

APPENDIX

A. Dissertation Manuscript Publication

Chapters three through six have been published in peer-reviewed journals or conference proceedings:

Chapter 3: Norris PR, Dawant BM. Closing the loop in ICU decision support: physiologic event detection, alerts, and documentation. *Proc AMIA Symp 2001*:498-502, 2001.

Chapter 4: Grogan EL, Norris PR, Speroff T, Ozdas A, France DJ, Harris PA, Jenkins JM, Stiles R, Dittus RS, Morris JA Jr. Volatility: A new vital sign identified using a novel bedside monitoring strategy. *J Trauma* 58(1):7-12, 2005.

Chapter 5: Grogan EL, Morris JA Jr, Norris PR, France DJ, Ozdas A, Stiles RA, Harris PA, Dawant BM, Speroff T. Reduced heart rate volatility: an early predictor of death in trauma patients. *Ann Surg* 240(3):547-54, 2004.

Chapter 6: Norris PR, Morris JA Jr, Ozdas A, Grogan EL, Williams AE. Heart rate variability predicts trauma patient outcome as early as 12 h: implications for military and civilian triage. *J Surg Res* 129(1):122-8, 2005.

B. Other Published Manuscripts

The following related manuscripts, not included herein, were authored or co-authored by the student during the dissertation period:

1. Dawant BM, Norris PR. Knowledge-based systems for intelligent patient monitoring and management in critical care environments. In: Bronzino JD, editor, The Biomedical Engineering Handbook:2746-2756. CRC press, 1999.

2. Morris JA Jr, Norris PR. Role of reduced heart rate volatility in predicting death in trauma patients. *Adv Surg* 39:77-96, 2005.

3. Norris PR, Dawant BM, Geissbuhler A. Web-based data integration and annotation in the intensive care unit. *Proc AMIA Symp 1997*:794-8, 1997.

4. Norris PR, Ozdas A, Cao H, Williams AE, Harrell FE Jr., Jenkins JM, Morris JA Jr. Cardiac Uncoupling and Heart Rate Variability Stratify ICU Patients by Mortality: A Study of 2088 Trauma Patients. To appear: *Ann Surg*, 2006.

5. Morris JA Jr., Norris PR, Ozdas A, Waitman LR, Harrell FE Jr., Williams AE, Cao H, Jenkins JM. Reduced Heart Rate Variability: An Indicator of Cardiac Uncoupling and Diminished Physiologic Reserve in 1425 Trauma Patients. To appear: *J Trauma*, 2006.

C. Contribution of the Student to the Dissertation

Overall Contributions

The student's work to build technical infrastructure, secure funding, and analyze data was essential to the completion of each manuscript and the continuing success of the project as a whole.

Technical Infrastructure: The student designed, implemented, and maintained the current version of SIMON, a dense physiologic data capture and management system, during the course of the dissertation work. While implementation details differ, SIMON's current version builds on a number of valuable concepts and experiences of prior implementations[1-3]. SIMON was used to collect all data and generate all alerts referenced in this manuscript. The student designed and implemented low-level physiologic data collection components of the system with the assistance of Dr. Dawant and two other graduate students on the project, Eric J. Manders and Karlkim Suwanmongkol. The student exclusively designed and implemented all database components, the current event detector (based on past work by Suwanmongkol[4]), and a number of other components to generate alerts and reports, interface with external systems, and perform automated system management and troubleshooting. The student maintained the system from initial deployment on two trauma ICU beds, through several expansion efforts to include all 14 Trauma ICU beds. Trauma staff assisted with cable manufacture and connections to mobile bedside devices, and with implementing reliable patient identification mechanisms.

Funding: During the dissertation period the student applied for and received funding to support the work. During the early phases of the dissertation period, funding was provided by a National Library of Medicine Individual Training Grant (LM00053-01A1). The student wrote and submitted this application under the direction of Drs. Benoit Dawant and Randolph Miller, prior to beginning work described in this manuscript. The student exclusively wrote and submitted a dissertation enhancement award to the Vanderbilt University Graduate School, which funded SIMON expansion to two additional beds. The student assisted in obtaining funds from a major pharmaceutical manufacturer to expand SIMON to 6 additional beds.

Analysis: In addition to work described below ("Specific Contributions to Each Chapter"), the student performed a number of preliminary analyses aimed at assessing data validity and discovering new, clinically relevant, measurements of patient physiology. The most notable of these resulted in the observation that heart rate variability, measured by the standard deviation of integer heart rate data over 5 minute epochs, was associated with patient outcome. This observation formed the basis for Chapters 4, 5, and 6.

Collaboration: The student initiated or played a critical role in establishing and maintaining professional relationships essential to this effort. The student worked with: 1) Clinical, technical, and administrative hospital staff to ensure SIMON's reliable, consistent operation; 2) Physicians, medical informaticians, and health services researchers at VUMC to design and undertake various analyses; and 3) Physicians and technical staff at Wake Forest University to implement SIMON on four of their trauma ICU beds.

Specific Contributions to Each Chapter

Chapter 1: The Introduction was written entirely by the student.

Chapter 2: This manuscript was written entirely by the student. The student prepared all data and performed the analyses described.

Chapter 3: This manuscript was written entirely by the student. The student designed the study, prepared all data, and performed the analyses described.

Chapter 4: This manuscript was written by several authors, including the student. The student prepared all data, designed the majority of the study, and verified all analyses.

Chapter 5: This manuscript was written by several authors, including the student. The student prepared all data, assisted in study design, and verified all analyses. Final results came largely from the student's revised analyses.

Chapter 6: This manuscript was written by the student and the second author (Morris). The student designed the study, prepared all data, and performed all analyses.

Chapter 7: The Conclusion was written entirely by the student.

D. Appendix References

1. Dawant BM, Manders EJ, Lindstrom DP. Adaptive signal analysis and interpretation for real-time intelligent patient monitoring. *Methods Inf Med* 33(1):60-63, 1994.

2. Manders EJ, Dawant DM. Data acquisition for an intelligent bedside monitoring system. *Proceedings of the 18th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*:957-958, 1996.

3. Manders EJ, Dawant BM. Design of a dynamically reconfigurable critical care monitor. *Proceedings of the 19th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*:1032-1035, 1997.

4. Suwanmongkol K. SIMON: A distributed real-time system for critical care patient monitoring. Masters Thesis in Electrical and Computer Engineering, Vanderbilt University, 2001.