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**TITLE:** Improving Diagnosis of Sepsis After Burn Injury Using a Portable Sepsis Alert System

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**RECIPIENT:** The University of Texas Medical Branch at Galveston

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<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> <b>Background:</b> Sepsis is the leading cause of death after significant burn injury. Severely burned patients (TBSA >20%) have sepsis rates < 40%. Early initiation of antibiotics within 1 hour of recognition of sepsis is the only factor associated with better survival. Diagnosis of sepsis after burn injury is not amenable to standard sepsis criteria. To address this problem, the American Burn Association developed specific criteria to prompt sepsis workup. Despite these guidelines, these findings can be subtle leading to delays in recognition of sepsis. <b>Hypothesis:</b> Best practice guidelines using 'new vital signs' of heart rate variability, regional tissue oxygenation, and noninvasive cardiac output can diagnose burn sepsis earlier, reducing morbidity and mortality. <b>Rationale:</b> Heart Rate Variability (HRV), regional Tissue Oxygenation, and non-invasive Cardiac Output (CO), have shown promise in detecting sepsis in other patient populations. These modalities have not been evaluated for sepsis detection after burn injury. <b>Specific Aims/Study Design:</b> 1. Prospectively collect traditional and 'new vital signs' and compare the diagnostic accuracy, time to diagnosis, and prediction of outcome. 2. Develop a best practice guideline for the early diagnosis and treatment of sepsis in the burn patient, integrating current and new vital signs, and incorporating these into a bedside decision-support tool. 3. Design and conduct a prospective, multicenter, randomized study to test the efficacy of the newly developed bedside tool in detecting sepsis. <b>Relevance:</b> The use of 'new vital signs' will provide an improved assessment of burn sepsis, enabling earlier detection of sepsis. The results of the study may change the standard of burn care if it is found that 'new non-invasive vital signs' can detect sepsis earlier, leading to earlier initiation of antibiotics and improved morbidity and mortality.					
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## 1. INTRODUCTION:

Despite multiple advances in critical care and resuscitation, sepsis is the leading cause of death in patients who sustain a significant burn injury. Our over-arching hypothesis is that best practice guideline using ‘new vital signs’ of heart rate variability, regional tissue oxygenation, and noninvasive cardiac output can be used to diagnose sepsis earlier, reducing morbidity and mortality after burn injury.

## 2. KEYWORDS:

Burn injury, sepsis, mortality, heart rate variability, regional tissue oxygenation, noninvasive cardiac output

## 3. ACCOMPLISHMENTS:

### What were the major goals and objectives of the project?

Task 1. Test the efficacy of “new noninvasive vital signs” of HRV, regional tissue oxygenation, and noninvasive cardiac output in detecting sepsis after burn injury. Proposed Timeline: Months 0-18. Patients to be enrolled: 18. Completion date: Month 48.

Task 2. Identify and use best conventional and “new” vital signs for early detection of burn sepsis to create a best practice guideline for identification of burn sepsis. Proposed Timeline: Months 6-40. Adjusted completion date: Month 72.

Task 3. Create decision support tool using best practice guidelines. Proposed Timeline: Months 12-48. Adjusted completion date: ongoing.

### What was accomplished under these goals?

Task 1. Test the efficacy of “new noninvasive vital signs” of HRV, regional tissue oxygenation, and noninvasive cardiac output in detecting sepsis after burn injury.

During the past year, we have worked to resubmit IRB paperwork and obtain approval in accordance with external review of our institution’s burn studies. We have obtained IRB approval and are able to analyze the data collected. No new patients have been enrolled on this study in the prior reporting year (see table below taken from prior report).

	Screened	Eligible for Study	Enrolled in Study
# of Patients (total)	112	38	18 (2 enrolled at Shrine and will be removed bringing total to 16)
# of Patients (reporting period)	0	0	0

Task 2. Identify and use best conventional and “new” vital signs for early detection of burn sepsis to create a best practice guideline for identification of burn sepsis.

Results of analysis to date are included in appendix at end of document. Progress has been made and will continue

Task 3. Create decision support tool using best practice guidelines.

Progress ongoing in this task.

**What opportunities for training and professional development has the project provided?**

Nothing to Report.

**How were the results disseminated to communities of interest?**

Nothing to Report.

**What do you plan to do during the next reporting period to accomplish the goals?**

n/a

**4. IMPACT:**

**What was the impact on the development of the principal discipline(s) of the project?**

The multiple nonlinear parameters could quantify and verify the relative importance of nonlinear, chaotic, and stochastic dynamics in HRV. FD could be the first clinic grid graph tool to outline the overall or examine the microscope of the HRV in a series of exponent scales. For verifying FD, the most approximate parameter is the ApEn of which the fast ApEn could quickly calibrate the variability with time-axis or became faster in processing the ultra-short-term data (10-seconds). CD and its similar graph method – RQA, are a pair of tools to explore HRV on condition of embedding dimension  $m=2$  and the fixed ED threshold. Recurrence rate (Rr) of RQA is the graph of one state of CD. CD and RQA(Rr) could verify each other. Because HRV is need to be measured at different observation windows and plot against the size of the observation window on a log–log scale for exploring time-series self-similarity. DF is useful to determine the statistical self-affinity. Although HE is less sensitive than DF, it could verify DF box plot too. If need more complex analysis, such as the spectrum of exponent or velocity of phase variability, LL is a reasonable tool. Especially, LL could cut off signal by a wide range of periods or a short window in several milliseconds to find the HRV trend. With optimization of threshold value ( $r$ ) of Euclidean distance (ED), embedding dimension ( $m$ ), time-delay parameter ( $\tau$ ), and spectrum range of signal (Hz), time-series reconstitution space could further improve HRV nonlinear analysis of Burn Sepsis.

**What was the impact on other disciplines?**

Nothing to report.

**What was the impact on technology transfer?**

Nothing to report.

**What was the impact on society beyond science and technology?**

Nothing to report.

**5. CHANGES/PROBLEMS:**

**Changes in approach and reasons for change**

Approach was same as reported in prior quarterly reports.

**Actual or anticipated problems or delays and actions or plans to resolve them**

Data analysis will continue on this project beyond the term of this grant with attempt to publish a paper in peer-reviewed literature.

**Changes that had a significant impact on expenditures**

No recent changes that have had significant impact on expenditures.

**Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

**Significant changes in use or care of human subjects**

No significant changes in reporting period.

**Significant changes in use or care of vertebrate animals.**

Not applicable.

**Significant changes in use of biohazards and/or select agents**

Not applicable.

**6. PRODUCTS:**

**• Publications, conference papers, and presentations**

**Journal publications.**

Nothing to report.
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**Books or other non-periodical, one-time publications.**

Nothing to report.

**Other publications, conference papers, and presentations.**

Nothing to report

- **Website(s) or other Internet site(s)**

Nothing to report.

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

Nothing to report.

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

### What individuals have worked on the project?

Name: Ravi Radhakrishnan  
Project Role: PI  
Researcher Identifier (e.g. ORCID ID):  
Nearest person month worked: 2  
Contribution to Project: Dr. Radhakrishnan has been working on data analysis and IRB resubmission.

Name: Min Zhu  
Project Role: Postdoctoral Fellow  
Researcher Identifier (e.g. ORCID ID):  
Nearest person month worked: 12  
Contribution to Project: Dr. Zhu was working with our collected data with Dr. Radhakrishnan to refine decision support algorithm development as well as data analysis.

Name: Claire Cummins  
Project Role: Research Associate/Fellow  
Researcher Identifier (e.g. ORCID ID):  
Nearest person month worked: 8  
Contribution to Project: Dr. Cummins has worked on IRB resubmission and approval as well as data analysis

Name: Jian-Jun Wen  
Project Role: Research Associate  
Researcher Identifier (e.g. ORCID ID):  
Nearest person month worked: 10  
Contribution to Project: Dr. Wen was brought into the lab on 11/2017 to assist with patient enrollment and data collection and was working with Dr. Zhu on these tasks prior to the administrative hold being placed..

### Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

### What other organizations were involved as partners?

Nothing to report.

## 8. SPECIAL REPORTING REQUIREMENTS

### COLLABORATIVE AWARDS:

### QUAD CHARTS:

Attachment 2: Quad Chart

## 9. APPENDICES:

Appendix 1 – Results of analysis to date.

Table 1 The demographic and physical vital sign record in ICU

Pt	Race	Age (y)	Gen 1/0	TBSA %	TBSA %3rd	Ad2Bur (hrs)	Pulse	Resp	Temp	T2Bur (day)	Infec 1/0	Sepsis 1/0	Inf2Bur (day)
P01	1	34	1	90	85	3.0	115	15	37.3	4	1	1	1.3
P02	2	18	1	35	23	0.9	136	25	37.8	1.5	0	0	
P03	2	52	1	38	15	1.5	96	16	37.4	4	1	0	13.0
P04	2	31	1	45	35	0.8	125	18	35.4	23	1	1	7.4
P05	2	26	1	60	25	1.5	127	23	36	0.5	1	0	35.0
P06	1	19	0	75	75	2.0	122	13	38	5	1	1	16.4
P07	2	44	0	45	0	0.5	83	17	37	0.5	0	0	
P08	2	28	1	81	66	3.3	140	12	37.8	5.5	1	1	0.5
P09	3	24	1	40	8	0.9	117	32	37.4	2	0	0	
P10	1	43	1	25	15	7.1	102	18	37.5	3	0	0	
P11	3	18	1	72	72	1.5	121	25	37.7	2	0	0	

Ad2Bur: the hours from admission to burn time;

Gen: gender, 1-male, 0-female;

Infec: infectious, 1-yes, 0-no;

Inf2Bur: the days from Infectious report to burn time;

Pt: patient with ECG or heart rate record, signed IRB, age>=18;

Race: 1-black,2-hispanic,3-white ;

Resp: respiratory;

Sepsis: 1-yes; 0-no;

T2Bur: the days from Pulse/Resp/Temp to burn time;

Temp: temperature;

Table 2 the statistic comparison between non-sepsis and sepsis patients

	(NS) mean	(NS) std	(S) mean	(S) std	p-value
TBSA%	35.5	14.2	75.0	21.0	0.019
3rd %	16.8	13.7	64.0	20.2	0.019
Age	34.5	13.6	28.8	6.3	0.762

NS: non-sepsis patient; S: sepsis patient; std: standard deviation;

Table 3 The Frequency/Time to Nonlinear Domain values of NS and S patients

no.	T(1)	NS		S		T(2)		NS		S		T(3)		NS		S	
		mean	std	mean	std	mean	std	mean	std	mean	std	mean	std	mean	std	mean	std
1	R	116.9	27.9	134.7	11.2	111.7	23.0	136.6	12.6	112.6	25.1	128.2	19.6				
2	stR	18.8	24.4	24.3	34.4	20.2	34.6	26.8	29.9	19.0	24.5	28.9	43.2				
3	RR	536.4	112.1	448.2	39.6	556.5	110.7	442.8	47.0	556.3	124.0	478.8	86.2				
4	SDRR	64.8	67.0	117.5	175.2	57.1	62.2	114.5	155.7	67.4	77.3	107.4	173.1				
5	SDSD	78.7	98.7	154.0	233.2	69.7	81.4	157.3	217.3	76.8	95.2	155.2	251.7				
6	RMSSD	78.1	98.8	154.0	233.2	67.6	82.2	157.0	217.2	76.8	95.2	155.0	251.8				
7	pNN10	0.3	0.3	0.3	0.4	0.2	0.3	0.2	0.3	0.3	0.3	0.2	0.4				
8	pNN30	0.1	0.2	0.2	0.4	0.1	0.2	0.2	0.3	0.1	0.2	0.2	0.4				
9	pNN50	0.1	0.2	0.2	0.4	0.1	0.2	0.2	0.3	0.1	0.2	0.2	0.3				
10	SD1	55.7	69.8	108.9	164.9	49.3	57.5	111.2	153.7	54.3	67.3	109.7	178.0				
11	SD2	70.8	66.6	125.5	185.0	63.3	67.4	117.5	157.8	77.4	87.1	104.7	168.3				
12	SD1/SD2	0.7	0.34	0.7	0.20	0.7	0.3	1.0	0.3	0.6	0.3	1.1	0.5				
13	VLF	1175	1586	3616	5566	1078	2517	3485	5307	2447	5780	3896	7237				
14	LF	5914	7781	44810	81541	3594	7046	19152	22159	36100	89663	23493	33755				
15	HF	10877	16738	302893	705805	6948	12655	44198	52640	51489	113884	53732	73595				
16	LF/HF	0.7	0.3	0.8	0.7	0.7	0.4	0.6	0.3	0.9	0.6	0.5	0.3				
17	FD	1.3	0.0	1.3	0.1	1.3	0.0	1.3	0.1	1.3	0.0	1.3	0.1				
18	ApEn	0.931	0.011	0.960	0.024	0.923	0.019	0.959	0.025	0.933	0.011	0.964	0.025				
19	CD	1.2	0.3	1.5	0.4	1.2	0.3	1.5	0.5	1.2	0.4	1.5	0.5				
20	DF	0.7	0.3	1.0	0.6	0.7	0.2	1.0	0.5	0.7	0.3	1.0	0.7				
21	HE	0.8	0.1	0.8	0.2	0.8	0.1	0.9	0.1	0.8	0.1	0.8	0.2				
22	LL	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.1				
23	Rd	99.8	0.3	99.8	0.1	99.8	0.3	99.7	0.2	99.8	0.2	99.8	0.2				
24	Re	7.3	0.8	6.6	0.4	7.4	0.9	6.6	0.5	7.4	0.5	6.7	0.4				
25	Rl	99.8	0.2	99.8	0.1	99.9	0.2	99.8	0.2	99.9	0.1	99.9	0.1				
26	Rm	7001	4140	4877	4030	7048	4065	4337	4492	8638	2974	4884	4086				
27	Rr	90.4	40.2	41.4	27.8	102.2	39.4	40.1	22.9	92.5	34.4	45.5	33.9				
28	Rt	124.7	79.7	60.9	24.1	129.5	67.5	63.1	15.0	125.9	75.9	70.8	22.8				

T(1), T(2) and T(3) are three times of ECG collection in three-first days after patient admission.

Table 4 The statistic comparison between NS and S patients.

PV01	NS vs S	T(1)	T(2)	T(3)	p-value	T(1)	T(2)	T(3)
1	R	0	0	0		0.142	0.054	0.345
2	stR	0	0	0		0.662	0.491	0.950
3	RR	0	0	0		0.142	0.054	0.345
4	SDRR	0	0	0		0.573	0.573	0.755
5	SDSD	0	0	0		0.755	0.414	0.950
6	RMSSD	0	0	0		0.755	0.414	0.950
7	pNN10	0	0	0		0.573	0.950	0.282
8	pNN30	0	0	0		0.659	0.783	0.837
9	pNN50	0	0	0		0.850	0.596	1.000
10	SD1	0	0	0		0.755	0.414	0.950
11	SD2	0	0	0		0.414	0.491	0.573
12	SD1/SD2	0	0	1		0.662	0.181	0.029
13	VLF	0	0	0		0.573	0.142	0.573
14	LF	0	0	0		0.573	0.142	1.000
15	HF	0	0	0		0.491	0.181	1.000
16	LF/HF	0	0	0		0.662	0.491	0.345
17	FD	0	0	0		0.755	0.573	0.662
18	ApEn	1	1	1		0.001	0.008	0.013
19	CD	0	0	0		0.282	0.282	0.345
20	DF	0	0	0		0.414	0.282	0.852
21	HE	0	0	0		0.755	0.228	0.852
22	LL	0	0	0		0.228	0.662	0.228
23	Rd	0	0	0		0.755	0.108	0.228
24	Re	0	0	1		0.142	0.059	0.020
25	Rl	0	0	0		0.662	0.142	0.491
26	Rm	0	0	0		0.382	0.196	0.107
27	Rr	1	1	1		0.029	0.008	0.043
28	Rt	0	0	1		0.059	0.081	0.013

PV01: 1 is p-value $\leq$ 0.05; 0 is p-value $>$ 0.05;