Correlation of Admission Troponin Levels with Cardiac Markers in Burn Patients

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Abstract

Background: Patients who experience severe burn injury undergo systemic changes with specific regards to the cardiovascular system ultimately resulting in systemic hypermetabolism, increased cardiac stress and dysfunction. Troponin I has been used as a biomarker for ischemic disease and cardiac dysfunction for years. The current relationship between TnI levels and clinical cardiac markers such as HR and BP have not been well studied in burn patients.

Objective: To assess if admission troponin levels correlate with BP and HR findings in patients with burn injury.

Methods: A prospective observational trial of 40 burn patients with burn injury (TBSA 10% or greater) admitted to the burn unit at Valleywise Health Medical Center in Phoenix. Criteria for elevated TnI levels were based upon reference ranges provided by the hospital lab, where TnI levels less than 0.034ng/mL were considered normal, and levels >0.034ng/mL were considered elevated. Initial TnI levels, BP, HR, TBSA were collected alongside demographic information. The groups were analyzed using Wilcoxon Rank Sum for the primary continuous parameters.

Result: No significant difference in Age, Gender, Ethnicity, initial SBP, DBP, MAP, HR, and total # deceased between the group of burn patients with significantly elevated TnI versus the group of burn patients with normal TnI. There was a statistically significant difference in the TBSA burned with the significantly elevated TnI having significantly more surface area burned compared to the normal TnI group, where p=0.0264.

Conclusion: The level of TnI increase in burn injury does not appear to correlate with clinical markers of cardiac function such as HR and BP. Additionally, TBSA appears to be positively correlated with the level of TnI rise.

Keywords: Burn, Troponin-I, Cardiac Dysfunction, Shock

Abbreviations
TBSA – total body surface area; SBP – Systolic blood pressure; DBP – Diastolic Blood Pressure; MAP- mean arterial pressure; HR – heart rate; TnI – troponin I; TnT – troponin T; Kg- kilogram; M – meters; mmHg – millimeters of mercury; bpm- beats per minute

1. Introduction

Patients with major burn injury often have systemic physiologic changes as a direct result of the trauma. These changes occur in various organ systems, but the cardiovascular system is one that is greatly affected. Burn injury often leads to abnormal cardiac function which manifest in the immediate setting as reduced HR, blood pressure, cardiac contractility, and cardiac output. One of the major drivers of these changes [1–4]. It appears that the major driving force behind these cardiac changes following burn injury is a loss of blood volume secondary to loss of plasma, which can occur in the magnitude of 4mL of plasma lost per Kg bodyweight per hour with TBSA ≥ 30% resulting additionally in acutely decreased cardiac output [1]. It appears that after the immediate burn period, the physiology of the cardiovascular system begins to shift as the burn injuries result in increased concentrations of plasma catecholamines which lead to systemic hypermetabolism which clinically manifest as elevated HR and cardiac output which could sometimes be seen years post burn injury [2,3]. Essentially, the immediate post burn setting is characterized by depressed cardiac function, which evolves into increased cardiac output and cardiac stress as the injury progresses.

Cardiac function can be monitored in a variety of ways, such as vital sign monitoring, EKG monitoring, and the use of cardiac biomarkers. The latter of which can additionally be used to diagnostically evaluate a patient in situations of heart failure, myocardial ischemia, and other severe cardiovascular diseases and often serves as a predictive factor in certain clinical scenarios [5–7]. There are numerous biomarkers used in the clinical setting. Troponin, creatine kinase, and lactate dehydrogenase have all been used as biomarkers in the workup and diagnosis of acute coronary syndrome and other cardiac disorders, but it is typically accepted that troponins remain the gold standard as highly specific cardiac biomarkers for ischemia [6]. Troponin is a regulatory protein complex made up of three subunits (T, I, C) that interact with actin and myosin and is involved in calcium regulation, with TnI and TnT most often being used as biomarkers [5–7]. The BiomarCaRE study displayed that elevated TnI has been associated with increased cardiovascular related mortality, indicating that it is may not just a marker of ischemia but general cardiac dysfunction as well [8].

Connecting the above two points with regards to burn injury causing significant cardiac dysfunction and TnI being used as a biomarker for cardiac dysfunction, it is not unreasonable to assume that troponins may play a role in monitoring burn injury. Mice studies have shown that when subjected to significant burns of 25% their total body surface area (TBSA), mice have significantly elevated TnI levels hours after injury [9]. Other studies have also shown similar findings in human burn patients with significantly elevated TnI levels with a TBSA as low as 15% [10–12]. However even through it is likely that troponins increase with burn injury, currently the relationship between troponin rise in burn injury and correlation with clinical signs of cardiac function such as heart rate and blood pressure have not been well studied. For this reason, the purpose of our study was to explore the relationship between the elevation of TnI in burn injury and the acute cardiac changes that occur in heart rate and blood pressure and determine its efficacy as a potential marker or predictor of severity of cardiac dysfunction in burn patients.

2. Materials and Methods

2.1 Patients

A registry of patients admitted with burn injuries to the Arizona Burn Center at Valleywise Health Medical Center meeting inclusion criteria starting April 2018 was created.

The registry was synthesized via prospective chart review. Inclusion criteria were as follows: (1) male or female, (2) any age, (3) admitted for burn injury of ≥ 10% TBSA, (4) received troponin levels drawn as part of their routine hospital care. Exclusion criteria is any admissions to the burn center for non-burn related injuries.

2.2 Methods

As part of the prospective chart review multiple pieces of information was collected. Demographic information collected included age, ethnicity, gender, height, and weight. Pertinent past medical history included any potential conditions that may confound results (i.e., existing cardiac dysfunction or disease). Information related to the burn history that was collected included the date of injury, mechanism of injury, burn location, burn depth, and TBSA. General hospital data that was included is length of stay, disposition, objective data such as SBP, DBP, MAP, HR, TnI. All data was stored on a Valleywise Health Medical Center drive. Only investigators and study personnel had access to this file and no identifiers were recorded into the study database. This study is a prospective, observational trial, and does not pose physical risk to subjects and has been approved by an institutional review board (IRB).

2.3 Statistical Analysis

There are 40 patients currently enrolled in this this study. The primary outcome for this power and sample size calculation will be the mean difference in blood pressure between low and high troponin levels (< 0.034 vs >0.034 ng/ml). If the mean difference in blood pressure is equal to its standard deviation, 40 patients will achieve a statistical power of 89%. If the standard deviation increases to twice that of the mean difference, the statistical power will decrease to 35%. Conversely, if the standard deviation is half of the mean difference, the statistical power will approach 100%.

Outcome measures in this study included admission TnI levels and markers of cardiac function which were specifically initial BP and HR. Patient demographic and clinical characteristics between low and high troponin levels (< 0.034 vs >0.034 ng/ml respectively) will be assessed using means, standard deviations for continuous variables and frequencies, proportions for categorical variables. The Non-Parametric Wilcoxon Rank sum will be used to compare the continuous variables while the Fisher's Exact test will be used to compare the categorical variables due to the expectation that the data will not approximate a normal distribution.

3. Results

From the period between April 2018 through December 2020, a total of 40 patients were admitted to the Arizona Burn Center that fit our inclusion criteria. Those 40 patients were divided and analyzed based upon their initial troponin I values, and placed into either the normal or elevated group, with there being a statistically significant difference between the two of them where $p<0.0001$. Continuous variables such as blood pressure, heart rate, height, weight, and age were analyzed using the Non-Parametric Wilcoxon Rank sum test and non-continuous categories such as gender and ethnicity were analyzed using the Fisher's Exact test. A summary of demographic information and those analyses can be seen in Table 1. Of the 40 patients, 25 of them had normal initial TnI levels and 15 had elevated levels over 0.034ng/mL. There was no significant difference in gender or ethnicity between the two groups. There was also no

significant difference between the ages of the patients in either group. Other characteristic data such as height and weight also showed no significant findings. With regards to clinical cardiac markers, there was no statistical difference between initial systolic blood pressure, diastolic blood pressure, mean arterial pressure, or heart rate between either of the two groups. There was however a statistical difference in the total body surface area that was burned with the elevated TnI group having a statistically significantly more % of body area injured via burns. Within the elevated TnI group 7 out of 15 patients have since died and 4 out of 25 of the normal TnI group have died, this is statistically non-significant with a p value of 0.0654. A detailed array of all data regarding patients enrolled in the study can be seen in table 2.

Table 1: Demographics, TnI levels, Cardiac Markers (HR, BP), Burn information

		High Troponin I (>0.034 ng/mL)	**Normal Troponin I (<0.034 ng/mL)**	**Wilcoxon Rank sum (P-Value)**	**Fisher's Exact test (P-Value)**
N		15 (37.5%)	25 (62.5%)	**-**	**-**
Sex	Males (%)	12 (80%)	21 (84%)	-	1
Ethnicity	Hispanic (%)	1 (6.67%)	3 (12%)	-	1
Age	Years	50±22	53±17	0.549	-
Height	meters	1.74±0.1	1.76±0.1	0.327	-
Weight	kilograms	79.2±16.6	87.76±16.0	0.137	-
TBSA	%	42.4±29.4	24.66±17.2	**0.0264**	**-**
Initial TnI	ng/mL	0.405±0.59	0.0186±0.01	**<0.0001**	**-**
Initial Systolic BP	mmHg	128±27	130±30	0.857	-
Initial Diastolic BP	mmHg	76±21	75±17	0.968	-
Initial MAP	mmHg	93±21	94±20	0.889	-
Initial Heart Rate	bpm	108±28	100±21	0.529	-
Deceased	# (%)	7 (46.67%)	4 (16%)	-	0.0654

Values above are represented as n (%) or as mean ± SD. P values are shown with boldface indicating statistically significant values of $p<0.05$. Groups were compared using either Wilcoxon rank sum or Fisher's Exact test depending on if the variable was continuous or non-continuous.

Table 2: Detailed Array of All Study Participants

Subject ID	Age (years)	Gender	Ethnicity	Height (m)	Weight (kg)	Initial TnI (mmHg)	Initial SBP (mmHg)	Initial DBP (mmHg)	Initial MAP (mmHg)	Initial HR (bpm)	TBSA (%)	Status
1	61	Male	Not Hispanic	1.73	100.0	<0.012	147	98	114	126	52	Alive
2	24	Male	Not Hispanic	1.91	86.0	<0.012	154	84	107	123	30	Alive
3	58	Male	Not Hispanic	1.70	90.3	0.248	85	50	62	74	30	Deceased
4	59	Male	Hispanic	1.78	80.0	<0.012	84	57	66	94	12	Alive
5	73	Female	Not Hispanic	1.68	68.0	<0.012	169	71	104	111	13	Alive
6	61	Female	Not Hispanic	1.65	60.0	0.061	153	88	110	160	82	Deceased
7	19	Male	Not Hispanic	1.83	90.7	0.065	131	109	116	122	95	Deceased
8	59	Female	Not Hispanic	1.68	130.0	<0.012	135	81	99	95	20	Alive
9	82	Male	Not Hispanic	1.63	81.6	0.63	134	75	95	67	20	Deceased
10	65	Male	Not Hispanic	1.52	76.2	0.013	133	67	89	84	26	Deceased
11	57	Male	Not Hispanic	1.88	86.2	<0.012	117	65	82	112	23	Alive
12	63	Male	Not Hispanic	1.73	100.0	<0.012	147	98	114	126	52	Alive
13	48	Male	Hispanic	1.70	86.2	<0.012	123	82	96	97	11.5	Alive
14	23	Male	Not Hispanic	1.75	70.0	1.184	173	96	122	144	75	Alive
15	21	Female	Not Hispanic	1.60	70.0	0.029	151	75	100	89	60	Alive
16	24	Male	Not Hispanic	1.75	67.0	0.054	158	116	130	117	41	Alive
17	56	Male	Not Hispanic	1.85	109.7	<0.012	143	82	102	87	10	Alive
18	60	Male	Not Hispanic	1.83	85.0	0.051	89	63	72	97	84	Deceased
19	72	Male	Hispanic	1.73	77.1	<0.012	99	55	70	86	20	Alive
20	30	Male	Not Hispanic	1.78	99.8	<0.012	170	96	121	99	19	Alive
21	89	Female	Not Hispanic	1.60	47.6	0.171	136	70	92	143	15	Alive
22	52	Male	Not Hispanic	1.73	80.7	<0.012	114	72	86	90	17	Alive
23	60	Male	Not Hispanic	1.88	107.7	<0.012	771	46	288	97	55	Alive
24	71	Male	Not Hispanic	1.78	70.3	<0.012	133	80	98	91	12	Alive
25	49	Male	Not Hispanic	1.83	107.5	0.4477	103	58	73	88	18	Alive
26	51	Female	Not Hispanic	1.63	90.7	<0.012	107	56	73	68	10	Alive
27	76	Male	Not Hispanic	1.75	99.8	0.236	140	90	107	86	41	Deceased
28	65	Male	Not Hispanic	1.82	64.0	<0.012	163	105	124	94	13	Alive
29	41	Male	Not Hispanic	1.85	63.5	2.221	94	44	61	130	15	Alive
30	53	Male	Not Hispanic	1.82	76.8	0.089	107	69	82	81	64	Deceased
31	40	Male	Not Hispanic	1.80	101.1	<0.012	190	99	129	78	18	Alive
32	30	Male	Not Hispanic	1.72	78.0	0.175	117	67	84	91	20	Alive
33	27	Male	Not Hispanic	1.93	87.4	0.017	146	95	112	153	10	Alive
34	70	Male	Not Hispanic	1.80	106.0	<0.012	140	82	101	111	29	Deceased
35	50	Male	Not Hispanic	1.70	75.0	0.021	101	63	76	130	62	Deceased
36	21	Male	Not Hispanic	1.83	68.0	<0.012	128	66	87	96	20	Alive
Table 2 Continued												
Subject ID	**Age (years)**	**Gender**	**Ethnicity**	**Height (m)**	**Weight (kg)**	**Initial TnI**	**Initial SBP**	**Initial DBP**	**Initial MAP**	**Initial HR**	**TBSA (%)**	**Status**

						(mmHg)	(mmHg)	(mmHg)	(mmHg)	(bpm)		
37	60	Male	Not Hispanic	1.85	83.2	0.013	115	56	76	118	10	Alive
38	34	Male	Not Hispanic	1.67	70.8	0.128	140	79	99	103	17.5	Alive
39	73	Male	Not Hispanic	1.80	90.7	<0.012	73	52	59	57	12	Alive
40	53	Female	Hispanic	1.65	99.8	0.31	154	66	95	121	18	Deceased

Boxes shaded green indicate participants who have an elevated troponin level (>0.034ng/mL). Initial values were measured by chart review to determine date of admission to the burn unit, and first recorded data points were captured. TBSA % were gathered from chart review of physician notes when the patient was initially evaluated, all burn physicians at Valleywise Health use a standardized method to estimate TBSA. Age listed is current age the patient would be at the time of the writing of this manuscript. Ethnicity was gathered from demographic intake information in the chart.

Discussion and Conclusions

Our study focused on the relationship between burn injury and cardiac function with specific relation to whether TnI levels correlated with clinical markers of cardiac function such as heart rate and blood pressure. What we learned what that in our trial of 40 patients, there was no significant difference in any of those markers between burn patients with normal serum TnI and burn patients with significantly elevated TnI. What was significant in our study was that burns with higher TBSA percentages are significantly correlated with elevated TnI. This is a phenomenon that has been mentioned a few years ago by Alexander et al. where they showed in a retrospective analysis of over 1600 patients that burns with a TBSA of 15% or greater were associated with elevated troponin levels, and those patients with elevated troponin levels had increased cardiac complications [10]. In a case study of a 49 year old man who had burns of 50% TBSA presented with significant cardiac abnormality and ultimately had a myocardial infarction that required stenting which was likely a result of inflammatory mediators released during burn injury [13]. There are other studies that have linked the use of TnI to cardiac damage in burn patients, for example a study by Zeng et al. that describes patients with suspected cardiac damage in the absence of acute MI, either secondary to acute heart failure or post burn injury. In the post burn injury group, plasma TnI was elevated in 90% of burn patients and was significantly higher in patients with a TBSA over 30% which potentially indicates that TnI is a useful marker in non-ischemic myocyte damage [14]. When taken in conjunction with our findings, it can hypothesized that be clinical vital signs are not the most effective determinant of cardiac function.

We saw no significant changes in blood pressure and heart rate depending on troponin elevation in burn injury. However, with multiple studies displaying that TnI is a sensitive biomarker for myocyte damage making clinical decisions based solely upon clinical markers of cardiac function can easily lead one astray. With burn injury being associated with systemic inflammatory response [15] and increased catecholamine release [2], it can be difficult to determine which patients are suffering from true myocardial tissue damage. While vital signs and clinical judgement should always be the first tools in one's arsenal, the use of TnI as a biomarker is an important factor to consider in the treatment of burn injury as studies have shown that a positive troponin test is strongly correlated with increased risk of cardiac death [10]. In our data we saw that a larger percentage of the elevated troponin group died over the course of data collection

versus the normal troponin group, while this had a p=0.0654, it still matches the trend seen in numerous other studies.

Drawing of TnI labs in burn patients should be considered more heavily based upon the data in this study. One should additionally consider more widespread use in patients with a higher TBSA% as we saw that the TBSA burned was significantly correlated to TnI levels in a positive manner. Major conclusions that can be drawn are that clinical markers and vital signs are not correlated to TnI levels. Since TnI levels are used as a gold standard biomarker to assess myocyte damage and have a direct correlation with cardiac death in burn patients, it can be said heart rate and blood pressure measurements are not necessarily as useful as biomarkers in the evaluation of true cardiac health in the setting of burn injury.

There were numerous limitations to this study. Due to the limitations of an observational study, we could not control for many of the parameters such as time of TnI draw. Serum biomarkers are not elevated in a consistent fashion overtime and there was potentially a large variation in the time between burn injury and troponin draw in our patient population. This is a limitation that is very difficult to overcome as patients are admitted to the hospital at varying times following their burn injuries and as a result one patient may have had their serum TnI checked hours after the injury while another patient may have had it checked over a day later. Additionally, we did not have exclusion criteria for patients who had pre-existing cardiac conditions which could have confounded the results. Finally, the study is under-powered. The primary outcome measure for the power analysis is the mean difference in BP between low and high troponin groups. Since the mean difference is very small in comparison to the standard deviation, the statistical power suffers considerably, and the study would benefit from increased participants.

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Conflicts of Interest

None

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References

1. Abu-Sittah, G. S., Sarhane, K. A., Dibo, S. A., & Ibrahim, A. (2012). Cardiovascular dysfunction in burns: Review of the literature. In *Annals of Burns and Fire Disasters*.
2. Williams, F. N., Herndon, D. N., Suman, O. E., Lee, J. O., Norbury, W. B., Branski, L. K., Mlcak, R. P., & Jeschke, M. G. (2011). Changes in cardiac physiology after severe burn injury. *Journal of Burn Care and Research*. https://doi.org/10.1097/BCR.0b013e31820aafcf
3. Guillory, A. N., Clayton, R. P., Herndon, D. N., & Finnerty, C. C. (2016). Cardiovascular dysfunction following burn injury: What we have learned from rat and mouse models. In *International Journal of Molecular Sciences*. https://doi.org/10.3390/ijms17010053
4. Cox, C. S., Traber, D. L., Zwischenberger, J. B., & Herndon, D. N. (1993). Cardiovascular Function in Acute Burns. In *Pathophysiology of Shock, Sepsis, and Organ Failure*. https://doi.org/10.1007/978-3-642-76736-4_18
5. Antman, E. M., Tanasijevic, M. J., Thompson, B., Schactman, M., McCabe, C. H., Cannon, C. P., Fischer, G. A., Fung, A. Y., Thompson, C., Wybenga, D., & Braunwald, E. (1996). Cardiac-Specific Troponin I Levels to Predict the Risk of Mortality in Patients with Acute Coronary Syndromes. *New England Journal of Medicine*. https://doi.org/10.1056/nejm199610313351802
6. Chacko, S., Haseeb, S., Glover, B. M., Wallbridge, D., & Harper, A. (2018). The role of biomarkers in the diagnosis and risk stratification of acute coronary syndrome. In *Future Science OA*. https://doi.org/10.4155/fsoa-2017-0036
7. Twerenbold, R., Boeddinghaus, J., Nestelberger, T., Wildi, K., Rubini Gimenez, M., Badertscher, P., & Mueller, C. (2017). Clinical Use of High-Sensitivity Cardiac Troponin in Patients With Suspected Myocardial Infarction. In *Journal of the American College of Cardiology*. https://doi.org/10.1016/j.jacc.2017.07.718
8. Blankenberg, S., Salomaa, V., Makarova, N., Ojeda, F., Wild, P., Lackner, K. J., Jørgensen, T., Thorand, B., Peters, A., Nauck, M., Petersmann, A., Vartiainen, E., Veronesi, G., Brambilla, P., Costanzo, S., Iacoviello, L., Linden, G., Yarnell, J., Patterson, C. C., … Kuulasmaa, K. (2016). Troponin i and cardiovascular risk prediction in the general population: The BiomarCaRE consortium. *European Heart Journal*. https://doi.org/10.1093/eurheartj/ehw172
9. Oppeltz, R. F., Zhang, Q., Rani, M., Sasaki, J. R., & Schwacha, M. G. (2010). Increased expression of cardiac IL-17 after burn. *Journal of Inflammation*. https://doi.org/10.1186/1476-9255-7-38
10. Alexander, W., Schneider, H. G., Smith, C., & Cleland, H. (2018). The incidence and significance of raised troponin levels in acute burns. *Journal of Burn Care and Research*. https://doi.org/10.1093/jbcr/irx020
11. Murphy, J. T., Horton, J. W., Purdue, G. F., & Hunt, J. L. (1998). Evaluation of troponin-I as an indicator of cardiac dysfunction after thermal injury. *Journal of Trauma - Injury, Infection and Critical Care*. https://doi.org/10.1097/00005373-199810000-00012
12. Bose, A., Chhabra, C. B., Chamania, S., Hemvani, N., & Chitnis, D. S. (2016). Cardiac troponin I: A potent biomarker for myocardial damage assessment following high voltage electric burn. *Indian Journal of Plastic Surgery*. https://doi.org/10.4103/0970-0358.197225
13. Gregg, S. C., Fidler, P. E., & Atweh, N. A. (2006). Coronary stenting during burn shock: Diagnostic and treatment considerations. *Journal of Burn Care and Research*. https://doi.org/10.1097/01.BCR.0000246050.67205.EB

14. Zeng, L., Chen, Y., & Wu, M. (2001). Cardiac troponin I: a marker for detecting non-ischemic cardiac injury. *Zhonghua Yi Xue Za Zhi*.
15. Barber, R. C., Maass, D. L., White, D. J., & Horton, J. W. (2008). Increasing percent burn is correlated with increasing inflammation in an adult rodent model. *Shock*. https://doi.org/10.1097/SHK.0b013e318164f1cd