Modeling Acute Compartment Syndrome

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Contents

Abstract

English

Acute compartment syndrome occurs when elevated pressure compromises blood supply to an area of the body and is treated by surgical release of the pressure. It continues to be a condition associated with morbid outcomes that is difficult to diagnose and study. New sensor technology affords the opportunity to advance our understanding and management. This work utilized a continuous pressure sensor to model compartment syndrome in three models, human cadaver leg, live rat abdominal, and human cadaver foot. Each model was utilized to study an element of compartment syndrome including relationship between compartments, sensor location, and pressure release. This thesis describes successfully modeling compartment syndrome level pressures and reports on the relevant findings for each model.

French

Le syndrome du compartiment aigu se produit lorsque la pression élevée compromet l'apport sanguin à une zone du corps et est traitée par une libération chirurgicale de la pression. Elle continue d'être une condition associée à des issues morbides qui est difficile à diagnostiquer et à étudier. La nouvelle technologie des capteurs offre la possibilité de faire progresser notre compréhension et notre gestion. Ce travail a utilisé un capteur de pression continu pour modéliser le syndrome du compartiment dans trois modèles, jambe de cadavre humain, ventre de rat vivant et pied de cadavre humain. Chaque modèle a été utilisé pour étudier un élément du syndrome des loges, y compris la relation entre les compartiments, l'emplacement du capteur et la libération de pression. Cette thèse décrit avec succès la modélisation des pressions au niveau du syndrome des loges et rend compte des résultats pertinents pour chaque modèle.

Acknowledgements

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Contribution of Authors

1. Drew Schupbach, MD – Primary author of thesis. Intricately involved with project design, planning, execution, data analysis, and literature review.
2. Yazan Honjol, MD – Co-researcher. Assisted with project planning, execution, and literature review.
3. Geraldine Merle – Co-Primary Investigator. Provided resources and guidance throughout project planning, data analysis, and thesis revision.
4. Edward Harvey – Co-Primary Investigator. Provided resources and clinical expertise during project design, execution, and thesis revision.

Introduction

Acute Compartment Syndrome (ACS) is a condition where elevated pressures within a fascial compartment in the body compromise its blood supply leading to death of the tissues within. While a simple concept from a physics standpoint, its clinical presentation, diagnosis, and treatment present a more complex picture. This also makes study difficult, but still is a crucial initiative to advance diagnosis and treatment. New technological advances in pressure sensors have provided us with the opportunity to better study and manage this condition. The objective of this work was to use a novel but validated pressure sensor (MY01) to create models of compartment syndrome for the foot, abdomen, and lower leg to better understand the condition and how to manage it.

Acute compartment syndrome most commonly occurs in the extremities as a result of trauma and swelling, but can also occur in the abdominal cavity due to abdominal hypertension.[1, 2] The incidence of extremity ACS is estimated at 3.1 per 100,000 people/yr with a strong male predominance (1-9% of lower extremity fracture reported).[3] Currently the diagnosis of compartment syndrome is primarily through clinical symptoms of ischemia with pressure measurement used as an adjunct. Treatment of ACS involves emergent release of the pressure through fasciotomy.[4] If not released within a few hours, it can progress to tissue death resulting in paralysis, loss of limb, or even death.[5] Early research suggested that a compartment was at risk with an absolute pressure as low as 30 mmHg.[6-8] More recent studies have shown that the continuous monitoring of the difference in diastolic pressure and compartment pressure may be more sensitive with sensitivities reported as high as 94%, compared to reported sensitivity of clinical symptoms of 13-19%.[9, 10] The clinical heterogenicity of ACS and the lack of reliable clinical pressure sensors have prevented a true gold standard pressure diagnosis. The ongoing need for more reliable diagnosis is highlighted in the prevalence of malpractice lawsuits involving missed diagnoses.[11]

Modeling compartment syndrome has been challenging due to its heterogenous presentation and complex physiology. In vivo human models are limited to reversible induction via tourniquet due to obvious ethical restrictions.[3] True compartment syndrome models

therefore are studied using animal and cadaver studies. Cadaver models are limited to infusion of saline or colloid to increase intercompartmental pressure due to the absence of physiology. Animal models most commonly utilize ischemia-reperfusion through tourniquet/direct pressure, or infusion of saline to induce pressure.[3, 12] Both methods have shown success in recreating compartment syndrome level pressures. Models of both extremity and abdominal compartment syndrome are reported in animals. Many different species have been utilized including canine[8], porcine[13], rodent[14], rabbit[15], and turkey[16]. One of the main problems both clinically and subsequently in research is the lack of availability and variability in pressure measuring techniques. Clinically, arterial pressure lines and the Stryker pressure needle are commonly used in extremities.[3] Neither has shown reliability in ACS monitoring and the Stryker needle was recently removed from the market.[17] A recent review of pressure measuring in compartment syndrome studies showed 38 different non-invasive modalities and 35 invasive modalities.[3] Near infrared spectroscopy was the most common non-invasive, but correlation with pressure is variable between patients and can be difficult to standardize.[18, 19]

Recent advances in microfabrication have produced miniaturized sensors that are revolutionizing many different fields, including medicine. A novel continuous pressure sensor (MY01) utilizing micro-electro-mechanical-system (MEMS) technology has been recently developed and already approved for clinical use. This technology has been validated in an in vivo compartment syndrome model and shown to have 670% superior precision in comparison to Synthes and Stryker pressure sensors.[20] The primary investigators of this project represent an academic-corporate relationship with interests in the corporate entity in the form of ownership and future possible stock holdings. Based on the continued evidence that continuous pressure monitoring has a role in diagnosing compartment syndrome[9, 21, 22], this device has the potential to provide reliable, much needed clinical information. It is currently the only device to offer continuous pressure readouts.

For this project, the pressure sensor was used to study three different ACS models. A lower leg compartment syndrome model was studied using human cadavers, an abdominal compartment syndrome model using live rats, and a foot compartment syndrome model using human

cadavers. These models were chosen based on their thorough descriptions in the literature and are also among the most common locations for compartment syndrome.[22, 23] Each model was utilized to investigate a different aspect of compartment syndrome. In the lower leg model, the functional relationships of the four anatomical compartments was explored through alternating pressurization sequences. In the abdominal model, the accuracy of retroperitoneal monitoring compared to intraperitoneal monitoring was investigated. For the foot model, the presence of discrete compartments and the ability to decompress the forefoot through percutaneous incisions was studied. A saline infusion pump was utilized for all three models based its reported success in achieving ACS level pressure and to have uniformity between models.[3] This thesis describes successful modeling of compartment syndrome in three scenarios, the results of each scenario, and the clinical and academic implications.

Methods

Infusion Pump and Pressure Sensor Methods

All three models utilized the same pressure-controlled infusion pump (**Figure 1**) and pressure monitoring setup. A PHD ULTRA™, Syringe Pump Series (Harvard Apparatus) was utilized with an inline Hugo-Sachs Elecktronik, APT300, pressure sensor (Harvard Apparatus). The pump was loaded with four 60 mL syringes filled with normal saline (0.9% NaCl) and programmed to adjust an infusion rate to maintain a set pressure as measured by the inline sensor. Syringes were connected with IV tubing that merged into one line at the inline pressure sensor before splitting into 4 individual infusion lines with stopcocks and terminating as 14G catheters as depicted in **Figure 2**. Pressure sensor was zeroed according to device instructions before each infusion. Continuous pressure monitoring of the compartments was done using the MEMS pressure sensor (MY01). Placement of both infusion catheters and sensor tips was confirmed using an ultrasound device (Philips Lumify L12-4 Transducer). The infusion pump and pressure sensor were set to record pressure and volume once per second. Data was recorded continuously by the sensor and continuously during infusion by the pump.

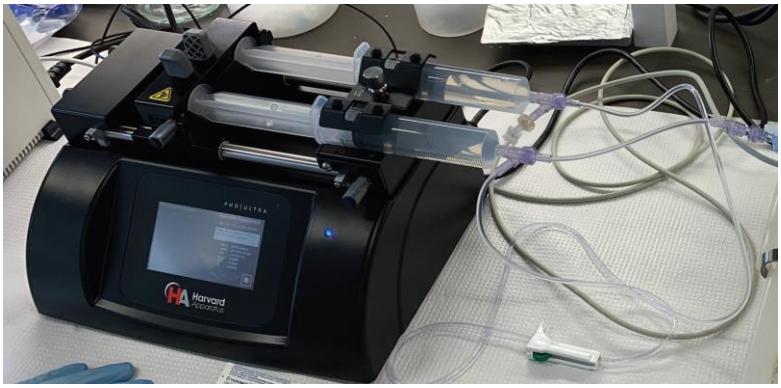

Figure 1. Infusion pump with syringes.

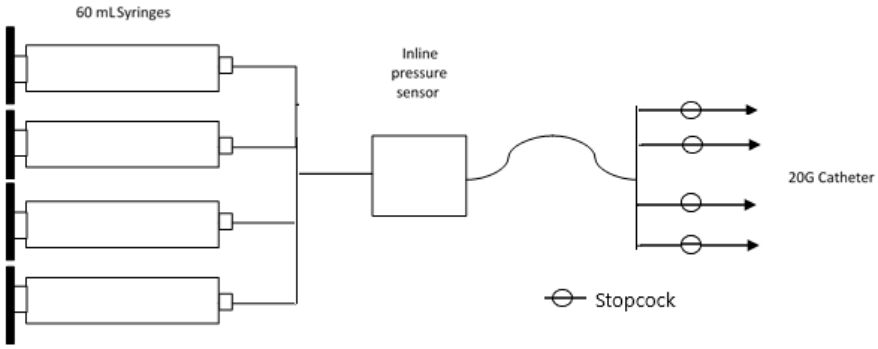

Figure 2. Diagram of inline pressure sensor and infusion catheters.

Lower Leg Model Methods

Fresh frozen human cadaver legs (n=8) amputated above the knee were allowed to equilibrate at room temperature. The legs were examined to exclude any signs of systemic disease or surgical scars that could suggest compromised anatomy. Bolsters were placed under the knee and ankle to minimized disturbance of the compartments and maintain consistent elevation in each compartment. One infusion line catheter was placed in a proximal-to-distal fashion in each of the four lower leg compartments (anterior, lateral, posterior, deep posterior). One MY01 device was inserted per device protocol into each compartment centrally in the distal ½ of the compartment. After ultrasound confirmation of placement, baseline pressures were noted.

Infusion was performed one compartment at a time. The pump pressure setpoint was set between 25-30 mmHg. For each sample, the compartments were infused sequentially. Each compartment was infused aiming for a stable pressure >30 mmHg for at least 5 min before proceeding to the next compartment making note of the stable pressure for each compartment. Once all compartments were pressurized, a standard lateral incision using the fibular head as reference was performed and each compartment was released sequentially noting the pressures after each release.[24, 25] The sequence of infusion and fasciotomy (**Table 1**) was alternated between samples in order to investigate the effect of sequence on individual compartment pressures.

Table 1: Infusion and fasciotomy sequence of lower leg model

Leg #	**Infusion Sequence**				**Fasciotomy Sequence**			
	A = Anterior L = Lateral P = Posterior D = Deep							
	1st	2nd	3rd	4th	1st	2nd	3rd	4th
Leg 1	A	L	P	D	A	L	P	D
Leg 2	L	A	P	D	L	A	P	D
Leg 3	P	D	A	L	P	D	A	L
Leg 4	D	P	A	L	P	D	L	A
Leg 5	D	A	L	P	P	A	L	D
Leg 6	A	D	P	L	A	P	L	D
Leg 7	D	P	L	A	A	L	P	D
Leg 8	D	L	P	A	L	P	A	D
Leg 9	D	L	A	P	L	A	P	D
Leg 10	D	P	A	L	P	L	A	D

Abdominal Model Methods

Adult male Sprague-Dawley rats (n=8) acquired from the retired breeders maintained at the Charles River facility rats were prepared for surgery as per institutional procedures (SOP 531.01, SOP 201.02). The animals were anesthetized by breathing isoflurane in an induction box and mask. Anesthesia was maintained with isoflurane throughout the entire experiment and euthanasia. The animals were placed on a heating plate and the abdomen and back were shaved and sterilized with surgical scrub chlorhexidine. Retroperitoneal placement of the MY01 sensors was accomplished by inserting per device protocol from the posterior aspect of the rat into the anterior paraspinal muscles (**Figure 3**). Placement was alternated from right to left paraspinal muscles between rats. A second pressure device was placed intra peritoneally via an anterior abdominal approach. A single pump catheter was inserted into the abdomen via on anterior and the other three infusion lines closed. The position of the rat during infusion was alternated from supine to prone between rats. The baseline pressure prior to beginning infusion is monitored for 5 minutes. In order to minimize the volume required for induction of ACS level pressure, we utilized a simple external support of the abdominal wall. A split soft cast (**Figure 4**) was loosely modeled around the abdomen of an anesthetized animal as described by Meier et al.[26] After baseline pressure were noted, infusion was performed until stable pressures >30 mmHg were achieved for at least 5 min. The pump was set to 20 mmHg. After monitoring was completed, the position of the sensors was again confirmed via ultrasound to ensure no significant motion during the infusion. Once completed the animals were anesthetized according to institutional procedures.

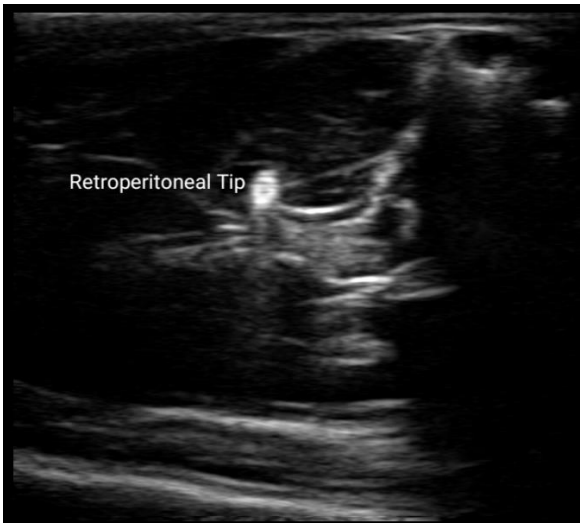

Figure 3. Ultrasound view of sensor tip located in anterior paraspinal muscle.

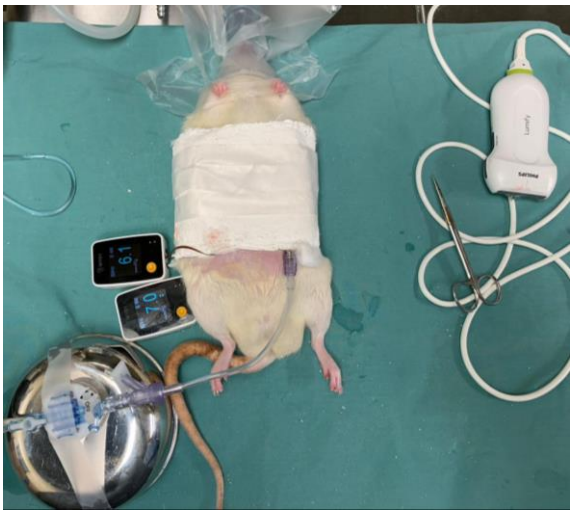

Figure 4. Anesthetized rat in split Plaster cast with inserted sensors and catheters

Foot Model Methods

Fresh frozen human cadaver legs (n=8) amputated above the knee were allowed to equilibrate at room temperature. The legs were examined to exclude any signs of systemic disease or surgical scars that could suggest compromised anatomy. Bolsters were placed under the knee and ankle to minimized disturbance of the compartments and maintain consistent elevation in each compartment. For this model, the major compartments of the forefoot were utilized excluding the interossei compartments. There is not a clear consensus on the number of compartments in the forefoot, but it is generally accepted that there is a lateral compartment, a central compartment (superficial), a medial compartment, and an adductor compartment. [27-29] One infusion line catheter was placed in a proximal-to-distal fashion in each of the four forefoot compartments being studied (medial, adductor, central, lateral). One MY01 device was inserted per device protocol into each compartment centrally in the distal ½ of the compartment. After ultrasound confirmation of placement, baseline pressures were noted, and all compartments were simultaneously infused until stable pressure >30 mmHg was achieved for a minimum of 5 minutes in all compartments. The pump setpoint was set to 25 mmHg. Once

pressurized, infusion was stopped, and a dorsal decompression was performed through two 1 cm incisions located just medial to the midpoint (4 cm from webspace) of the 2nd metatarsal and just lateral to the midpoint (4 cm from webspace) of the 4th metatarsal. Using blunt dissection with Metzenbaum scissors, release of forefoot compartments (medial, lateral, superficial, and adductor) was performed as seen diagrammed in **Figure 5**. This technique was determined based on described fasciotomy techniques [28, 29], and by clinical experience of the primary investigator. Once pressures had stabilized post release, a surgical dissection (**Figure 6**) was performed to evaluate for any soft tissue damage and proximity to incisions. Structures that were identified and examined include cutaneous nerve branches, extensor tendons, and dorsalis pedis artery. Any identifiable injuries and proximity to vital structures were noted.

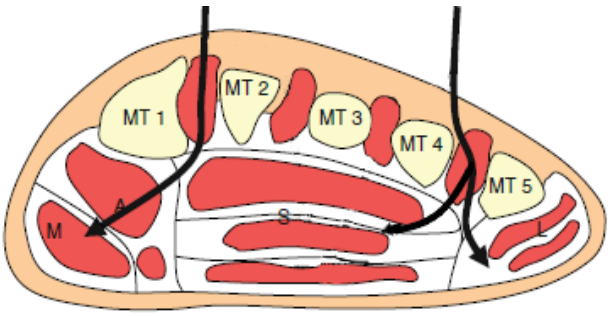

Figure 5. Diagram of forefoot release (M: Medial, A: Adductor, S: Superficial/Central, L: Lateral).

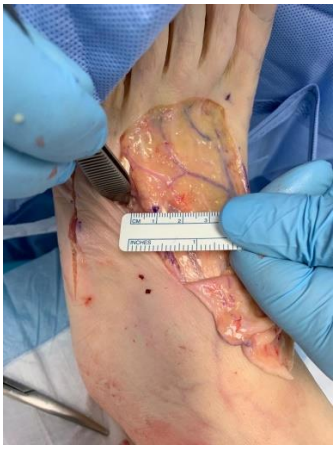

Figure 6. Post fasiotomy dissection.

Statistics

Statistical analysis of baseline, infusion, and post fasciotomy pressures was reported as mean and standard deviation. Statistical difference was determined using students T-test, α=0.05. Pearson correlation coefficient was used to determine relationships between pump setpoint and compartment pressures and relationship of intraperitoneal to extraperitoneal pressure readings. Confidence intervals reported using 95% confidence intervals. All statistical analysis done using Microsoft Excel.

Results

All Models

For all three models, continuous pressure monitoring was accomplished using a novel continuous pressure sensor, MY01 (NXTSens Inc., Montreal, Canada). The compartment pressures at baseline, during infusion, and after release corresponded to target values and the averages are shown in **Tables 3-5**. Pressures rises to >30 mmHg were accomplished in all compartments in all models with return to near baseline after release in the foot and lower leg models (Avg 9.5, SD 2.5). The inline arterial sensor pressure was found to not accurately represent compartment pressure when compared to the intra-compartmental MY01 device. The infusion pump was able to adjust the infusion rate based on the inline arterial sensor pressure reading and perfectly maintain the setpoint pressure during the duration of all infusions. The Pearson correlation coefficient between the setpoint pressure and all pressure measurements across infusion was 0. The differences between stable infusion pressure and pump setpoint are shown in **Table 2**.

Table 2. Difference between pump setpoint pressure and stable infusion compartment pressure.

Model	Setpoint (mmHg)	Avg (Infusion P – Setpoint P) (mmHg)	SD (mmHg)
Foot	25	19.1	7.7
Abdomen	20	22.8	5.9
Lower Leg	25-30	14.8	10.9

Table 3. Baseline pressure averages for all models.

Model	Avg(mmHg)	SD(mmHg)	Max(mmHg)	Min(mmHg)
Foot	4.5	2.9	11	1
Abdomen	6.4	3.2	12	3
Lower Leg	2.5	2.1	9	1

Table 4. Stable Infusion pressures for all models.

Model	Avg(mmHg)	SD(mmHg)	Max(mmHg)	Min(mmHg)
Foot	43.8	7.7	60	31
Abdomen	43	7.4	56	31
Lower Leg	42.3	11.2	62	20

Table 5. Average post fasciotomy pressures for all models.

Model	Avg (mmHg)	SD (mmHg)	Max (mmHg)	Min (mmHg)
Foot	9.5	3.6	16	0
Abdomen	x	x	x	x
Lower Leg	3.8	2.4	9	1

Lower Leg Results

The average volume infused per leg was 540 mL with a SD of 183.5 mL. The average volume per compartment is detailed in **Table 6**. The average pressures across all compartments was listed prior in **Tables 3-5**. The average pressures for each individual compartment are shown below in **Table 7**. The infusion pressures reported are the pressures in that compartment at the time it was individually infused. The infusion pressures for the anterior, lateral, and posterior compartments were all >30 mmHg regardless of infusion sequence. For the posterior compartment, a pressure >30 was not able to be achieved in 3/10 samples at the time of individual infusion. All three instances occurred when the deep posterior compartment was the first compartment infused. At the time of fasciotomy, the pressure in all compartments was >30 mmHg for all samples.

Table 6. Average volume infused in each compartment.

Compartment	Average Volume (mL)	Average % of total	% SD
Anterior	77.9	14%	11%
Lateral	47.0	8%	4%
Posterior	218.1	38%	22%
Deep Posterior	187.1	38%	26%

Table 7. Average pressures for each compartment in the lower leg model at baseline, stable infusion pressure, and after release.

Compartment	Baseline (mmHg)	Max/Min (mmHg)	Infusion (mmHg)	Max/Min (mmHg)	Released (mmHg)	Max/Min (mmHg)
Anterior	2.6	9/1	47.4	60/33	4.9	9/1
Lateral	1.5	5/1	47.6	55/32	2.4	5/1
Posterior	3.8	9/1	39.8	60/32	4.8	9/1
Deep Posterior	2	5/1	34.6	50/20	3.2	7/1

The variation in pressure relative to infusion sequence for the deep posterior compartment was further examined by looking at the samples where the deep posterior compartment was infused first (n=6). The three times a pressure >30 mmHg was achieved, two of the three were accompanied by a rise in pressure >30 mmHg in an adjacent compartment (anterior or posterior). The was also a significant difference between the percent volume infused into the deep posterior when infused first vs. last: 54±14% vs. 5±1% (p value: 0.009). The deep posterior compartment was also found to be decompressed by release of the other three compartments. When the deep posterior compartment was the last compartment released (n=8) the average pressure just prior to release was 8±1 mmHg as seen in **Table 8**.

Table 8. The Deep Posterior Compartment (DP) In Isolation

Sample Number	Highest Infusion pressure (When DP Infused First)	Pressure prior to release (When DP Released Last)
Leg 1	x	9 mmHg
Leg 2	x	11 mmHg
Leg 3	x	x
Leg 4	20 mmHg	x
Leg 5	21 mmHg	6 mmHg
Leg 6	x	4 mmHg
Leg 7	41 mmHg	8 mmHg
Leg 8	40 mmHg	9 mmHg
Leg 9	27 mmHg	10 mmHg
Leg 10	50 mmHg	8 mmHg

Abdominal Results

For the rat intraperitoneal model, seven of eight rats were used in statistical analysis due to one of the rats having a retroperitoneal sensor that dislodged during the infusion. The average volume infused was 191. 5 mL with a SD of 30.2 mL.

The retroperitoneal sensor readings closely mirrored the readings of the intraperitoneal sensor as is demonstrated in the example graph of the two pressures over the infusion period in **Figure 7**. When the paired readings across all samples were compared, the Pearson Correlation Coefficient was 0.99. While there was a statistically significant ($p>0.05$) difference between the retroperitoneal measurements and intraperitoneal, the average absolute difference was only 2.2 mmHg with an SD of 1.4 mmHg. The retroperitoneal sensor true average was -0.9 ± 0.06 mmHg less than the intraperitoneal sensor.

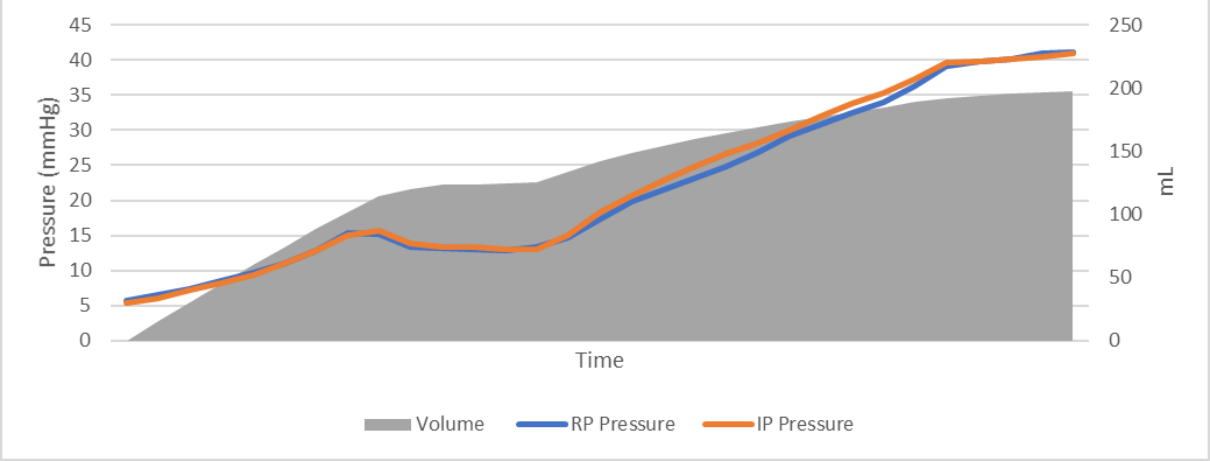

Figure 7. Example of continuous pressure readings from retroperitoneal (RP) and intraperitoneal (IP) sensors compared to volume infused.

Foot Model Results

The average volume infused into each foot (n=8) was 178 mL with a SD of 35.7 mL. Percutaneous decompression produced a statistically significant (p value <0.05) decrease in pressure of all four compartment to well below compartment syndrome levels in all samples. The average pressure decrease was statistically significant at 34.6 mmL with a SD of 7.7 mmHg and a p-value of zero. The average post fasciotomy pressure was 9.5 mmHg with a SD of 3.6 mmHg. Post fasciotomy dissection did not reveal any injuries to soft tissue structures. Proximity measurements revealed that all extensor tendons and arteries were >1cm from the incisions. On three samples a cutaneous nerve branch was identified <1cm from the incision.

Discussion

The ease and reliability demonstrated in the three compartment syndrome models are promising for future studies seeking to investigate ACS using continuous pressure monitoring. Since live human models will always be impossible, the necessity of good modeling techniques will remain paramount. These results are consistent with reported extremity infusion models of achieving compartment pressures of 25-60 mmHg[30-33]. The abdominal model pressures match those seen in colloid infusion rat models (20 mmHg)[26], as well as porcine CO_2 inflation

models (30 mmHg)[34]. The successful continuous monitoring demonstrated in these models has already spurred research using this device into clinical trials in the lower leg, which the results of will be greatly anticipated. Furthermore, the significant discrepancy between inline pressure measurements and compartment pressure measurements provides insight into modeling compartment syndrome. Some studies utilize an inline pressure sensor as representative of compartment pressure.[26, 35] The results of this work suggests that pressure readings measured inline to the infusion may not always be representative of the compartment pressure. The discrepancies noted could be reflective of the varying resistance encountered between the inline sensor and the compartment sensor (IV tubing, muscle tissue). Since the inline pressure was not used in the statistical analysis of the individual models, this discrepancy did affect our results. The inline sensor was still utilized throughout the experiment as its feedback enabled a steady pump infusion.

The results of the lower leg model suggest that the deep posterior compartment may not function as a discrete compartment. This is most apparent when looking at the pressure of the DP compartment when the other three compartments had been released (max 12 mmHg). These findings suggest that the deep posterior compartment may not be able to sustain ACS level pressures without adjacent compartment pressurization. This is further supported by the discrepancy in infusion volumes of the DP compartment suggesting fluid leakage out of the compartment. Additionally, the inability of the DP compartment to sustain a pressure >30 when infused first also brings into question its relevance in compartment syndrome. Currently, it is widely accepted that there are four individual compartments and that fasciotomy should ideally release all four individually.[1, 24, 36] Since the clinical population of ACS is young trauma patients, there is certainly reasonably concern that cadaveric specimens may not accurately represent the anatomy of the clinical population. With this in mind, these results certainly do not disprove the functional existence of the DP compartment, but question it enough to make studying it in a clinical population worthwhile.

The abdominal compartment model demonstrated that retroperitoneal pressure monitoring for intra-abdominal compartment syndrome may be a reliable method. While standard diagnosis typically involves intra-vesicular pressure measurements with physical exam being unreliable,

debate still exists about the most effective method. [2, 37-40] Since there exists obvious anatomical spatial differences between a rat and human, an attempt should be made to reproduce these promising results in a larger mammal before progressing to clinical trials.

The successful percutaneous decompression of the forefoot in a cadaver model is promising for the development of less invasive treatments for compartment syndrome. In a standard dorsal approach, the infection rate has been shown to be as high as 20% with an average of three additional procedures to close the wound.[41] Successful percutaneous releases have been described previously in chronic compartment syndrome and for single compartment release.[35, 42] With minimally invasive techniques already starting to be employed in the treatment of compartment syndrome, it is only logical to continue to investigate its utility in new locations in an attempt to improve patient outcomes.

While the experiments described were designed to be as robust as possible, several limitations do exist. The lack of physiologic response in cadaveric models does impose some limitation on clinical translatability. Additionally, the sample sizes were adequate for demonstration of modeling and concepts, but larger sample sizes would strengthen the clinical applicability of the results. Finally, the academic-corporate relationship between the primary investigators and MY01 could introduce a source of bias.

Conclusions

The main objective of this project to create three models of compartment syndrome using a novel continuous pressure sensor was successful as demonstrated by the average baseline (4.5 mmHg), pressurized (43 mmHg), and post release (6.1 mmHg) pressures. The functional relationship of lower leg compartments was able to be studied by alternating study sequences and revealed the deep posterior compartment might not be a separate compartment. The rat abdominal model demonstrated the utility of retroperitoneal pressure monitoring by showing a strong correlation (0.99) with intrabdominal pressure and little variation (2.2 ± 1.4). The success of percutaneous release in the foot model bolsters the push towards more minimally invasive

treatments of ACS. These results have strong implications for the future of modeling compartment syndrome as well as guiding clinical studies in the constant pursuit to improve the management of acute compartment syndrome.

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