Acute Compartment Syndrome:
In Vivo Models Using a Novel Continuous Pressure Sensor

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ABSTRACT

Acute compartment syndrome (ACS) is a devastating condition associated with lasting consequences or even death if not treated adequately or in time. It is a surgical emergency whereby the pressure within a closed osteofascial compartment increases to a point where tissue perfusion is compromised. As a result, ischemia, necrosis, and neuromuscular dysfunction develop. It is commonly seen after high-energy trauma to the lower leg however may occur in other anatomical compartments including the abdomen. The incidence and prevalence of ACS varies amongst populations, such as that between civilian and military, yet the importance remains the same. With no gold standard or defined decision algorithm, the diagnosis of compartment syndrome remains challenging and is based predominantly on findings from clinical exam. Currently, the only successful treatment of ACS is by means of fasciotomy – a procedure also associated with significant risks of its own and a decreased quality of life lasting years after injury. Furthermore, the medico-legal implications associated with ACS can be dire, with higher-than-average indemnity payment. Given the vast burden of disease and absence of a clear algorithm for treatment, there is a definite need for an objective gold standard of diagnosis. The use of serial or continuous intracompartmental pressure (ICP) monitoring using a differential pressure <30mmHg as a threshold for fasciotomy has shown significant sensitivity and specificity. Differential pressure is defined as the diastolic blood pressure minus intracompartmental pressure (DBP-ICP). However, the differential pressure cannot be taken as a stand-alone value and is only used to assist clinical findings. Invasive and non-invasive techniques to monitor ICP have been developed, yet there remain high levels of variability between measurements as well as lack of clinical validation. A recently developed continuous pressure sensor (MY01) based on novel Micro-Electro-Mechanical-System (MEMS) technology has been tested and validated showing superior precision

as compared to alternative devices. Additionally, it provides excellent sensitivity to fluctuations in pressure with minimum variability between readings.

RÉSUMÉ

Le syndrome des loges aigu (SLA) est une condition dévastatrice associée à des conséquences chroniques voire fatales sans traitement adéquat effectué à temps. Il s'agit d'une urgence chirurgicale lors de laquelle la pression dans un compartiment aponévrotique augmente au point de compromettre la perfusion tissulaire, menant au développement d'ischémie, nécrose et dysfunction neuromusculaire. Habituellement observé suite à des traumatismes sévères de la jambe inférieure, ce syndrome peut également survenir dans d'autres compartiments anatomiques incluant l'abdomen. L'incidence et la prévalence du SLA varient parmi les populations, notamment entre les civils et les militaires, mais son importance demeure nonnégligeable. Sans méthode de réference ou d'algorithme décisionnel établis, le diagnostic du SLA demeure difficile, car il se base principalement sur des données de l'examen clinique. Présentement, le seul traitement efficace du SLA demeure la fasciotomie – une procedure associée à des risques inhérents significatifs et une qualité de vie diminuée perdurant des années suite à la blessure initiale. De plus, les implications medico-légales associées au SLA peuvent être complexes, requérant des compensations d'indemnité au-dessus de la moyenne. Compte tenu du fardeau considérable de la maladie et de l'absence d'un algorithme de traitement clair, le besoin explicite d'une méthode diagnostique de réference persiste. La surveillance de pression inta-compartemintale (PIC) en série ou en continu utilisant un seuil de pression différentielle pour la fasciotomie de <30mmHg a démontré une spécificité et une sensibilité significatives. La pression différentielle se définit comme la tension artérielle diastolique moins la pression intracompartimentale (TAD-PIC).

Cependant, la pression différentielle ne peut pas servir de valeur unique et doit seulement être utilisée afin de completer les données cliniques. Des techniques invasives et non-invasives de surveillance de la PIC ont été développées, mais une grande variabilité demeure parmi les mesures, ainsi qu'un manque de validation clinique. Un capteur de pression en continu (MY01) récemment développé se base sur la nouvelle technologie de Micro-Electro-Mechanical-Systems (MEMS) et a été testé et validé, démontrant une precision supérieure lorsque comparé aux dispositifs alternatifs. De plus, MY01 procure une excellente sensibilité aux fluctuations de pression, avec une variabilité minimale entre les mesures.

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CONTRIBUTION TO ORIGINAL KNOWLEDGE

To our knowledge, the work presented in this thesis is original and has not been investigated or published before. Techniques aimed at artificially inducing ACS in porcine and rodent models (i.e. infusion techniques and tourniquet-induced injury) have been previously investigated. However, this thesis also describes a modified technique of tourniquet-induced injury not previously studied.

CONTRIBUTION OF AUTHORS

This thesis consists of three separate experiments in preparation for publication.

Yazan Honjol (primary author): planned and performed the experiments as well as data collection and analysis. Completed the literature review and write-up of this manuscript with critical review by co-authors.

Edward Harvey (primary supervisor): involved with experimental plan and implementation. Dr. Harvey provided valuable surgical and scientific guidance, laboratory space, access to the animal facility, generous donation of MY01 sensors, and supervision throughout manuscript preparation. Dr. Harvey was also involved with critical review of thesis.

Geraldine Merle (co-supervisor): provided valuable scientific knowledge and input throughout the study and manuscript preparation. Dr. Merle was also involved with critical review of thesis.

Drew Schupbach: assisted with experiment planning, implementation, and data analysis.

Rachel Monk: assisted with experiment planning, implementation, and data analysis.

CHAPTER 1

INTRODUCTION & REVIEW OF LITERATURE

CHAPTER 1: INTRODUCTION & REVIEW OF LITERATURE

1.1 COMPARTMENT SYNDROME

Acute compartment syndrome (ACS) is defined as an increase in pressure within a closed osteofascial compartment that compromises blood flow and tissue perfusion, ultimately leading to tissue ischemia and necrosis [1-5]. If urgent fasciotomy is not performed, the damages to neuromuscular function are irreversible and can result in chronic pain, contractures, rhabdomyolysis, renal failure, infection, limb amputation, or even death [1, 6-8]. Although most commonly seen in high-energy trauma to the lower leg [1, 4, 9], various other locations where skeletal muscle is enclosed by fascia can also exhibit ACS. Such include, but are not limited to, the gluteal, thigh, foot, forearm, hand, and abdominal compartment. Although ACS most commonly develops from high-energy trauma, it can also result from low-energy trauma such as burns, crush, vascular or ischemia/reperfusion injures [1]. It is also noteworthy to mention that iatrogenic causes such as tibial nailing, tourniquet use, mispositioning of the patient, or even tight casts or stockings could have the potential to produce a compartment syndrome [10]. Missed diagnosis of ACS or incorrect/incomplete compartment release is an increased source of litigation [11], with an average indemnity payment of $426,000 over nine settled cases [12]. Therefore, it is extremely important to properly investigate and understand this complex and deadly syndrome in order to diagnose and treat in the most appropriate manner.

1.1.1 Pathophysiology

The pathophysiology of compartment syndrome has yet to be fully elucidated and remains an important topic of discussion and research. Richard von Volkmann first described deformity of

the hand and wrist after application of splints or bandages for distal humeral fractures [13]. In 1881, Volkmann went on to describe that such deformities occur because of deprivation of blood supply to the muscular tissue due to venous congestion coupled with arterial insufficiency. This ultimately led to ischemia and contractures – as well as coining of the term Volkmann's contracture. Since then, a number of theories have been aimed at clarifying the complex mechanisms behind ACS. The basic understanding is that normal functional tissue requires patent vessels for perfusion and delivery of essential nutrients. The intravascular pressure of capillaries can be anywhere between 20 – 33 mmHg [2], with interstitial fluid pressures averaging approximately 10 mmHg [5]. The microvascular occlusion theory is based on these average values. A compartment syndrome is likely to ensue when absolute compartment pressure is close to or higher than the internal pressure of the vasculature running within it, consequently clamping down and occluding the vessels [2]. However, a study conducted by Vollmar and colleagues seemed to disprove this theory [14]. Using a skinfold model in hamsters, no signs of spasm or collapse of the various vessels were found in response to graded external pressures. Alternatively, the critical closing pressure theory is based on transmural pressure – the difference between intravascular pressure and pressure exerted on the outside of the vessel wall. Significant reduction of the transmural pressure or a significant elevation of tissue pressure surrounding the vasculature may shut off flow to tissues leading to ischemia [15, 16]. However, this theory does not explain the development of ACS in borderline cases [5] and does not take into account the autoregulatory mechanisms in peripheral tissue, which work to inhibit vascular tone in response to decreased pressure [17]. Matsen provided a reasonable explanation to the development of ACS using the arteriovenous (AV) gradient theory (the difference between local arterial and venous pressures) [1]. This theory states that an increase in tissue pressure consequently increases venous pressure.

As a result of increased venous pressure, the AV gradient is lowered leading to a decrease in local perfusion. In this case, ACS develops when the metabolic demands of tissue are greater than the amount of perfusion available to the tissue. Despite the different theories put forward, the majority of research supports the underlying theme of increased compartment pressure as being a key factor driving the syndrome.

1.1.2 Incidence and Prevalence

The incidence of ACS varies depending on the population studied. In the general civilian population, ACS is predominantly seen in young males aged 35 years and under, with an average annual incidence of 7.3 per 100,000 for men and 0.7 per 100,000 for women [9]. The majority of cases occur as a result of high-energy trauma to the lower limb, specifically after fractures of the tibia [9, 18-20]. The incidence and prevalence of ACS drastically increases amongst the military population due to the severe nature of battlefield trauma, which includes explosions and blast injuries in sometimes remote and austere environments [8]. The significantly decreased blood pressure typically seen in polytrauma patients also lessens the threshold for injury as compared to patients with an otherwise normal blood pressure. Furthermore, complications associated with fasciotomy are increased with an incidence of 87% in battlefield trauma and 77% in civilian trauma [20]. A study looking at 10-year outcomes of extremity fasciotomies during Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) found that out of 25,731 casualties, 17,166 sustained at least one limb injury, of which 19% (3,313) had a fasciotomy performed [7]. It is difficult to determine the exact number of true positive diagnoses resulting in fasciotomy, especially when the consequences of a missed diagnosis far outweigh the consequences associated with an unnecessary fasciotomy.

1.1.3 Diagnosis

With the constant risk of a missed diagnosis, performing a fasciotomy has been considered synonymous with the diagnosis of ACS. Relying primarily on serial physical exam, the sensitivity of clinical findings has been brought into question [9, 21]. The symptoms may vary and are based on assessment of the "6 P's": pain, pallor, pulselessness, paresis, paresthesia, and pressure. Pain out of proportion to the injury is typically the first sign of an impending compartment syndrome. In fact, it has been found that pain with passive stretch is the most sensitive finding prior to onset of muscle ischemia [21], however findings associated with pain would be non-existent in the case of nerve damage. Furthermore, it is almost impossible to assess pain in a polytrauma, sedated, or obtunded patient unable to verbalize. In this case, a more objective form of examination is needed to assist in correct diagnosis. According to the most recent AAOS guideline, serial or continuous compartment pressure monitoring is recommended as opposed to singular measurement. However, it is also recommended that pressure measurements be used only as a supplement to the physical exam and not as a sole indicator of ACS. McQueen and colleagues illustrated the rationale of continuous monitoring while using differential pressure as a threshold to diagnose ACS and perform fasciotomy [9]. Differential pressure is calculated as diastolic blood pressure (DBP) minus intracompartmental pressure (ICP) and has shown notable sensitivity and specificity when values are <30mmHg [9, 21]. Unfortunately, there is still lack of evidence indicating a specific cut-off measurement for fasciotomy.

1.2 MONITORING COMPARTMENT SYNDROME

With pressure being the key driver of ACS, many techniques looking at monitoring compartment pressure have been studied and developed in hopes of better understanding its complex course and finding a standardized threshold for fasciotomy.

1.2.1 Invasive pressure monitoring

A number of invasive techniques exist to monitor ICP and aid in diagnosis of ACS. Whitesides and colleagues developed one of the first methods of measuring ICP by insertion of a needle into the compartment, which is then connected to a mercury manometer for reading [22]. Further modification of this technique has given rise to the wick catheter [21], which includes fibrils extending from the end of the catheter and into the compartment thus increasing surface area for measurement. The slit catheter is similar to the wick catheter in terms of principle and methodology; however, the end of the slit catheter is cut axially in order to further increase surface area. Both the wick and slit catheter techniques use a fluid column attached to a transducer to provide pressure measurements. Matsen described an infusion technique whereby a syringe pump infuses sterile saline at a rate of 0.7 cc/day and can provide continuous measurement for up to three days [1]. Measurements are made through a pressure transducer connected by tubing to a needle or catheter inserted into the affected compartment. Another technique that has garnered attention is the solid-state transducer intracompartment (S.T.I.C.) catheter. This has been studied and compared to the previously described methods, showing it to be functionally superior and easier to use [9].

1.2.2 Non-invasive monitoring

Non-invasive methods to diagnose ACS have also been studied [20], however the clinical relevance of such technologies have yet to be validated. Muhlbacher et al. found changes of the tibia-fascia angle (TFA) using ultrasound to be beneficial in estimating compartment pressure [23]. Ultrasound measurements of fascial displacement as a way to identify elevated ICP has also been investigated [24, 25]. Herring and colleagues took a step further by adding a pressure sensor on the ultrasound probe in order to calculate compartment fascia flattening pressure (CFFP) [26]. Radiographic indicators of ACS have also been analyzed, showing that tibial plateau fractures are in fact more likely to result in a compartment syndrome [18, 27]. Near-infrared spectroscopy (NIRS) has shown promise as a form of non-invasive measure by correlating decreased tissue oxygen saturation with elevated ICP, however a threshold has yet to be established [3, 28-30]. Correlations between serum biomarkers and ACS have also been studied, albeit in a retrospective population [31]. Myoglobin and creatine kinase (CK) have shown significant elevation in diagnosed ACS cases; however, they lack specificity and cannot quantify the extent of muscle damage [28, 32, 33].

1.3 TREATMENT OF COMPARTMENT SYNDROME

The only known treatment for ACS remains invasive fasciotomy, performed to relieve pressure within a compartment. Therefore, in order to achieve best results and decrease morbidity, it is extremely important to be familiar with the proper anatomy and mark superficial landmarks as well as incision lines prior to operating.

1.3.1 Anatomy of the leg

The leg is comprised of 12 muscles that are grouped within 4 discrete compartments – anterior, lateral, superficial posterior, and deep posterior. Each of the compartments are surrounded by a thick inelastic fascia. The anterior compartment holds the tibialis anterior, extensor hallucis longus, extensor digitorum longus, and peroneus tertius muscles, which work to dorsiflex the foot and ankle. This compartment includes the deep peroneal nerve and anterior tibial vessels. The lateral compartment consists of the peroneus longus and peroneus brevis muscles which both plantarflex and evert the foot. The superficial peroneal nerve also arises in this compartment. The superficial posterior compartment has the gastrocnemius, soleus, and plantaris muscles that mainly plantarflex the foot and ankle and contains the sural nerve. The deep posterior compartment includes the tibialis posterior, flexor digitorum longus, and flexor hallucis longus, which plantarflex and invert the foot. In this compartment, the tibial nerve is found along with posterior tibial vessels.

1.3.2 Fasciotomy

There exist two established methods amongst surgeons: the two incision four compartment fasciotomy as well as the single incision parafibular approach. Given the technical difficulty of the single incision approach and potential for an incompletely released compartment, the two-incision approach has been preferred by surgeons. Fasciotomy of the anterior compartment is most commonly performed followed by the deep posterior compartment [6]. Marking incision lines and appropriate landmarks decreases potential for a missed compartment.

1.3.2.1 Two incision approach

With the patient lying in the supine position, on the lateral side of the leg the fibula is located by using the lateral malleolus along with the fibular head as landmarks. Once located, it is important to mark the appropriate landmarks and incision line. The incision should be made approximately one fingerbreadth or two centimeters above the fibula [6, 34]. The distance of the incision from the fibula should be maintained to avoid injury of the superficial peroneal nerve. Length of the incision should be approximately 15 centimeters in total [34], or approximately three fingerbreadths below the fibular head to three fingerbreadths above the lateral malleolus [6]. The location of the incision should be directly above the anterior intermuscular septum, which separates the anterior and lateral compartments. Once identified, fasciotomy should be performed one centimetre above and one centimeter below the septum in order to release both the anterior and lateral compartments respectively [6, 34]. The incision distance from the septum should be maintained in order to avoid injury to the deep peroneal nerve, which perforates the septum in the distal one third of the lower leg. On the opposite side of the affected leg, the appropriate landmarks and incision line should also be marked accordingly – approximately one fingerbreadth or two centimetres below the edge of the tibia [6, 34]. After incision, it is important to identify both the deep and the superficial posterior compartments and incise the fascia longitudinally along the posterior border of the tibia, from the tibial tuberosity to the medial malleolus. In order to enter and release the deep posterior compartment, the soleus muscle fibers attached to the underside of the tibia must be dissected [6, 34]. Release of the deep posterior compartment may be missed or incomplete if the incision line is not made correctly or anatomical knowledge is weak. Caution must be taken not to mistake the plane between the gastrocnemius and soleus muscle for the deep compartment.

1.3.2.2 Single incision approach

The single incision approach is more technically challenging and may increase the risk of missing or incompletely releasing a compartment. After making the appropriate markings on the lateral aspect of the leg, a longitudinal skin incision is made one centimeter anterior to and in parallel with the fibula. The incision should start approximately four to seven centimeters from the fibular head to approximately five centimeters from the lateral malleolus [34]. Once the skin flaps are retracted, longitudinal fascial incisions are performed in the superficial posterior, lateral, and anterior compartment respectively [34]. The deep posterior compartment can be accessed through the plane between the lateral and superficial posterior compartment. When the posterior aspect of the fibula is located, the attached muscle fibers can be dissected with care taken not to injure the peroneal vessels. The deep posterior compartment can also be accessed and released via the anterior compartment by retracting the tibialis anterior muscle laterally and locating the interosseus membrane [35]. An incision is made in the interosseus membrane from the proximal third of the leg and advanced distally.

1.3.2.3 Complications

Complications after fasciotomy can be severe and, in the most severe cases, have even led to death. Given the extremely invasive nature of the procedure, the wound is at increased risk of infection. An incomplete or delayed fasciotomy may cause long-term disability to the patient such as permanent nerve damage or painful contractures. Furthermore, myoglobin can be released as a result of reperfusion after fasciotomy, causing rhabdomyolysis and multi-system organ failure [6].

1.4 MODELS OF COMPARTMENT SYNDROME

Modelling compartment syndrome in healthy human volunteers has been difficult for obvious ethical reasons. As an alternative, the use of cadavers and live animal models have certainly helped advance our understanding of this complicated disease. Various models and techniques have been established to investigate ACS in hopes of finding the best diagnostic methods and therapies. It is always important to choose the right model while also making sure it translates to man.

1.4.1 Cadaver model

Human cadaver models have been used extensively because of their anatomical relevance. Such models provide valuable insight into the dynamic nature of ACS and the relationship between affected and non-affected compartments. However, the only way to study ACS in cadavers is through infusion techniques which may be cumbersome and subject to variability amongst researchers. Furthermore, a major pitfall of cadaver models is that they do not portray the pathophysiology behind a true ACS.

1.4.2 Porcine model

Porcine models are preferred because of their physiological and anatomical relevance when studying ACS. The anterior compartment of the porcine hindlimb is similar to that seen in humans and has been used to investigate a number of various techniques including but not limited to near-infrared spectroscopy, direct pressure monitoring, as well as serum biomarkers [24, 28, 29, 32]. Xanthos et al. studied baseline hemodynamics such as blood pressure in Landrace swine (similar to the swine used in the current experiments) and found relatively similar values to those of humans, which is important when assessing Delta P and compartment pressures for fasciotomy. The most popular methods of artificially inducing ACS in these models are through infusion

techniques and tourniquet-induced reperfusion injury. However, the translatability of results should always be carefully assessed prior to making any significant conclusions.

1.4.3 Rat model

The rat model is also a preferred model given the availability and low cost of maintenance. They have been pivotal in furthering our understanding of the pathophysiology driving ACS [36]. The same popular techniques used to artificially induce ACS in porcine models are also used in rat models. Both infusion and tourniquet-induced injury techniques have been widely used however the anatomy of this animal differs significantly from humans, especially when studying pressure associations. The extremely thin and highly elastic fascia of the rat hindlimb may not be fully relatable to the thick and rather inelastic fascia found in humans.

1.5 NOVEL PRESSURE SENSOR

Innovative applications of novel and existing sensors in healthcare have allowed practitioners to harness their skills with the aid of data driven technologies [37]. Decision making under certain circumstances can be extremely difficult and time sensitive. Measuring compartment pressures has long been used as an aid for decision making in suspected ACS cases yet still depends on repeated needle stick and can only monitor one compartment at a time. On the other hand, the recently developed and validated MY01™ pressure sensor (NXTSens Inc., Quebec, Canada) is able to continuously track and monitor compartment pressures through one-time injection of an indwelling sensor [38]. Furthermore, the sensor was found to be 670% more precise than alternative devices [39]. Without the need for repeated needle sticks, this new sensor accurately and continuously monitors fluctuations of compartment pressures in real-time. It also displays

pressures on a readout screen while transferring data wirelessly to a connected device via Bluetooth.

1.6 OBJECTIVES

The heterogeneous clinical course of ACS has made it difficult to investigate, with many limitations; research into the best methods of diagnosis and treatment are of utmost importance. Various cadaveric and animal models have been explored and developed to help us understand the complex and debilitating nature of this condition. The objective of this thesis is to investigate, establish, and validate a relevant clinical model of ACS in both small and large animals. We also aim to evaluate the performance of novel MEMS pressure sensing technology in vivo.

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CHAPTER 2

PRE-CLINICAL ACUTE COMPARTMENT SYNDROME WITH A PORCINE CONTINUOUS MEASUREMENT MODEL

CHAPTER 2: PRE-CLINICAL ACUTE COMPARTMENT SYNDROME WITH A PORCINE CONTINUOUS MEASUREMENT MODEL

2.1 INTRODUCTION

Acute Compartment Syndrome (ACS) is a surgical emergency most commonly occurring in the extremities as a result of trauma and swelling within a closed osteofascial compartment. It is seen to ultimately be the result of increasing pressure leading to circulatory compromise, tissue ischemia, necrosis, and neuromuscular dysfunction (1-5). It can lead to devastating and lasting consequences if not treated adequately or in time (6-8). Although compartment syndrome may occur in a variety of locations where skeletal muscle is surrounded by fascia, it is most commonly seen in high-energy trauma to the lower leg and is accompanied with fracture in 69% of cases, usually involving the tibial diaphysis (9). However, it can also be seen in low-energy trauma such as burns, bleeding disorders, vascular injury, injection injury, or even tight cast application. While the precise mechanisms driving this condition are yet to be fully elucidated, it is commonly understood that abnormally elevated pressure within a compartment is an early and important marker of ACS (10). The AAOS has released guidelines for diagnosis and treatment of ACS based on evidence-based evaluation of the literature (11). Continuous pressure monitoring of the affected compartment is a keystone part of the guidelines. However, it is also recommended that pressure measurements be used only as a supplement to the physical exam.

The heterogeneous clinical course of ACS has made it difficult to investigate. Various cadaveric and animal models have been developed to help understand the complex and debilitating nature of this condition (12-26). The most popular methods used by these papers for induction of a compartment syndrome include the use of tourniquets or infusion techniques directly into the

compartment. Human cadaveric models are anatomically most relevant yet are restricted to infusion methods and do not take into account the pathophysiological events that make up a true compartment syndrome. Live animal models have proven useful in the investigation of pressure sensing techniques as well as histological analysis of muscle damage after injury (22, 27-29), however care needs to be taken when analyzing results as certain anatomical and physiological differences between models exist. Fortunately, modelling ACS using a porcine hind limb has proven especially useful given their similar anatomy, size better suited for human instrumentation, and blood pressure: a physiological parameter vital in compartment syndrome (26, 30).

In the current study, a previously established balloon catheter technique (25) is used alongside a newly described technique involving an ischemia-reperfusion injury with superimposed direct crush of the anterior compartment using two custom-made tourniquet cuffs. The new concept of continuous pressure measurement is implemented with solid state MEMS pressure monitors (31, 32). We aimed to investigate, establish, and validate a live porcine ACS model while evaluating the performance of a continuous pressure measurement device. We postulated that the new model ideally should result in an elevated pressure seen within a short period after direct trauma, with sustained or increasing pressure until released by fasciotomy at which time the pressure should return to physiological levels.

2.2 METHODS

2.2.1 Anesthesia and Surgical Preparation

All experimental methods and practices were approved and in accordance with the institutional Facility Animal Care Committee (FACC). Six female Landrace Hybrid swine each weighing 40kg were ordered (Elevages du Haut-St-Laurent Inc (Quebec, Canada)). Anesthesia

protocol was performed. Standard Operating Procedure 203 for general surgery of large animal species was followed. Hemodynamic parameters were monitored to assure adequate gas exchange with administration of IV fluids to maintain adequate hydration and blood pressure. Core temperature was maintained at 37°C and continuously monitored rectally throughout the experiment. The anterior compartment of the lower hindlimb was palpated and the boundaries marked with a surgical marking pen. The animal was placed in the dorsal recumbent position within a custom-made frame to allow for proper exposure of the hind limbs (Figure 1).

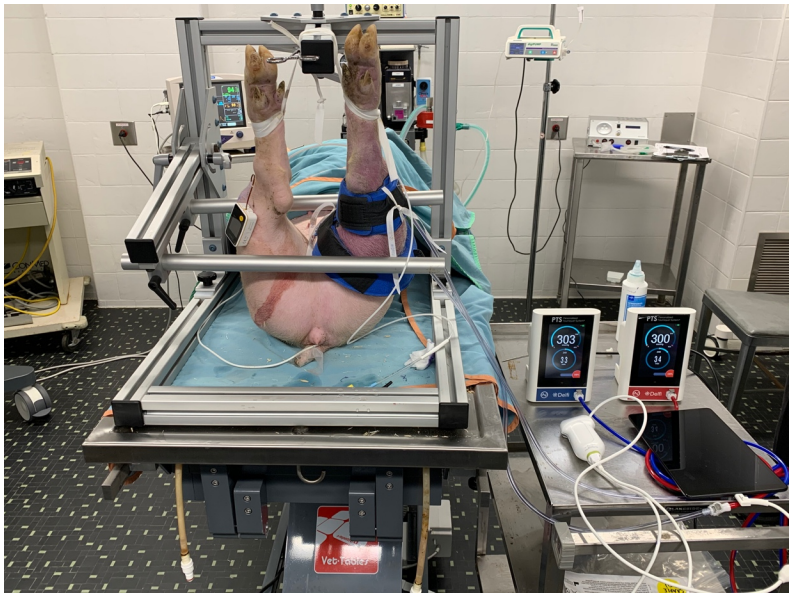

Figure 1: Set-up of the porcine model within a custom-made frame. Inflation of two custom-made conical tourniquets to 300 mmHg around the left proximal thigh and left anterior compartment. Balloon catheter inserted under the right anterior compartment musculature with MY01 pressure sensor inserted into the anterior compartment.

2.2.2 Acute Compartment Syndrome Models & Experimental Protocol

Injury was caused to the anterior compartment of both hind limbs using two different methods bilaterally- one to each side. In one limb, an established model as described by Kalns et al. was performed using a balloon catheter (25). In the alternate limb, two separate tourniquets were used. The initial tourniquet was higher on the leg to stop blood flow to the limb. This is similar to techniques described in smaller animals (29). The second was applied directly over the anterior compartment of the leg to cause a direct crush of the anterior compartment.

Tourniquet induced ischemia-reperfusion plus direct crush technique: A Delfi Personalized Tourniquet System (PTSii Inc, Vancouver, British Columbia) along with a custom-made Delfi Contour Tourniquet Cuffs were used to induce compartment syndrome in the hind limb. With the hind limb elevated and tied to the frame (Figure 1), blood flow was confirmed using doppler ultrasonography (Philips Lumify L12-4 Transducer) of the popliteal artery. The first tourniquet cuff was placed as proximal as possible on the thigh and inflated to 300mmHg. Decreased blood flow was confirmed using ultrasound of the popliteal artery. The second tourniquet cuff was placed directly over the anterior compartment and also inflated to 300mmHg. Both tourniquets were inflated for a period of five hours. After deflation and removal of the distal tourniquet, a MY01 pressure sensor (MY01 Inc, Montreal QC) sensor was placed into the anterior compartment in a distal to proximal fashion as per manufacturers specifications. The proximal tourniquet was then deflated and removed, after which an observation period of two hours ensued.

Balloon catheter technique: A 1cm skin incision was made at the medial distal end of the tibia whereby a size 16Fr ARGYLE™ Trocar Catheter was inserted and carefully pushed rostrally to

atraumatically make space for the balloon. Care was taken to slide the trocar between the anterior surface of the tibia and anterior compartment while following the path of least resistance. Another 1cm skin incision was made over the proximal end of the anterior compartment, lateral to the stifle to allow easy exit of the trocar. Once in place, the thoracic trocar was removed with the catheter left in place. A balloon catheter (#PDZ339, Numed Inc., Hopkintin, NY) was inserted into the funnel end of the thoracic catheter and drawn into position directly underneath the anterior compartment musculature. Following placement of the balloon, the thoracic catheter was removed and a MY01 (MY01 Inc, Montreal QC) sensor was placed into the anterior compartment in a distal to proximal fashion. After allowing baseline measures to stabilize for 10 minutes, the balloon was inflated with saline to pressure >30mmHg above mean arterial pressure (MAP) for a period of five hours. A two-hour observation period also followed after deflation and removal of the balloon. The MY01 sensor was kept in place for the duration of this method.

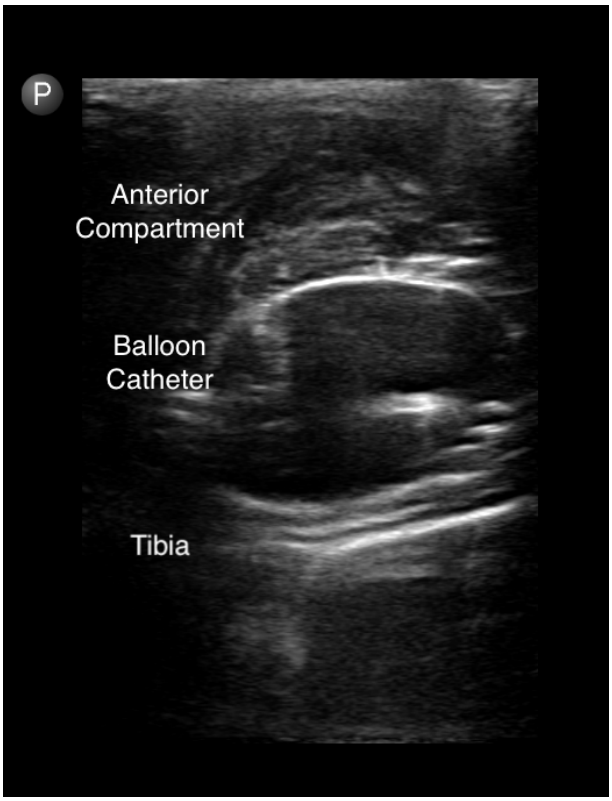

Figure 2: Ultrasound showing the inflated balloon catheter between the anterior compartment musculature and face of the tibia.

2.2.3 Statistical Analysis

Results are presented as means ± SD unless otherwise mentioned. Student's paired t-test was used to compare baseline (control) averages, balloon catheter technique averages and ischemia-reperfusion + direct crush averages. Differences were considered significant at $p < 0.05$.

2.3 RESULTS

Continuous monitoring in vivo was successful in all hindlimbs studied (n=12) using MY01 pressure sensing devices. No morbidity was associated with sensor injection into the anterior compartment during the injury period as well as observation period. A custom-built frame was useful for proper positioning of the animal in the supine position while keeping the hindlimbs exposed for both techniques studied. The use of a 16Fr thoracic trocar was found to be optimal for insertion and positioning of a balloon catheter underneath the anterior compartment musculature without compromising compartment integrity. An anterior compartment pressure of 30 mmHg above MAP was achieved with infusion of 12 – 15 mL of normal saline into the balloon and confirmed in the correct location using ultrasound (Figure 2). Similar to a previously established threshold model [25], inflation of the balloon for a period of five hours was found to produce spontaneous rise in anterior ICP during the two-hour observation period. In the alternate limb, placement of two custom tourniquets around the proximal thigh and directly over the anterior compartment was effective at creating a double insult of ischemia-reperfusion with direct crush. This newly described technique was also found to be successful at creating a spontaneous rise in anterior ICP after the five-hour injury period in six of six hindlimbs studied. Average baseline pressure of the porcine hind limb was found to be 12.9 ± 5.0 mmHg with a maximum of 19.3 mmHg and minimum of 6.5 mmHg. No significant differences were found when comparing

baseline pressures between the pigs studied. Average pressure of the anterior compartment while the balloon catheter was in place and inflated was 145.9 ± 28.4 mmHg while the pressure of the inflated tourniquets remained constant at 300 mmHg. During the two-hour observation period, the balloon catheter technique achieved an average pressure of 25.1 ± 8.8 mmHg with a maximum reading of 38.2 mmHg and minimum reading of 14.1 mmHg. During this same period, the ischemia-reperfusion + direct crush technique achieved an average pressure of 33.7 ± 7.3 mmHg, with a maximum reading of 43.5 mmHg and minimum reading of 23.5 mmHg. Percutaneous approach to fasciotomy was attempted in all hind limbs studied (n=12). The use of a fasciotome to release the anterior compartment showed positive results in eight out of 12 hind limbs. Furthermore, three attempts were undertaken in two of the hind limbs studied prior to achieving full release. Average pressure post-fasciotomy for the balloon catheter technique was -0.6 ± 4.8 mmHg with a max of 6.9 mmHg and minimum of -5.8 mmHg. For the I/R + crush technique, average value post-fasciotomy was 2.0 ± 5.7 mmHg with a max of 9.7 mmHg and minimum of -3.5 mmHg. After open fasciotomy of the unreleased hind limbs, it was realized upon gross examination that porcine fascia is relatively thicker than human fascia and may be multilayered (Figure 3).

Table 1. Average pressures (mmHg) of hind limbs during baseline (control) and observation period. Successful attempts at percutaneous fasciotomy are also presented under the respective limbs.

	Baseline	Injury Period		Observation Period		Post-fasciotomy	
		Balloon Catheter	I/R + Crush	Balloon Catheter	I/R + Crush	Balloon Catheter	I/R + Crush
Average (mmHg)	12.9	145.9	-	25.1	33.7	-0.6	2.0
SD (mmHg)	5.0	28.4	-	8.8	7.3	4.8	5.7
Maximum (mmHg)	19.3	194.1	-	38.2	43.5	6.9	9.7
Minimum (mmHg)	6.5	115.3	-	14.1	23.5	-5.8	-3.5

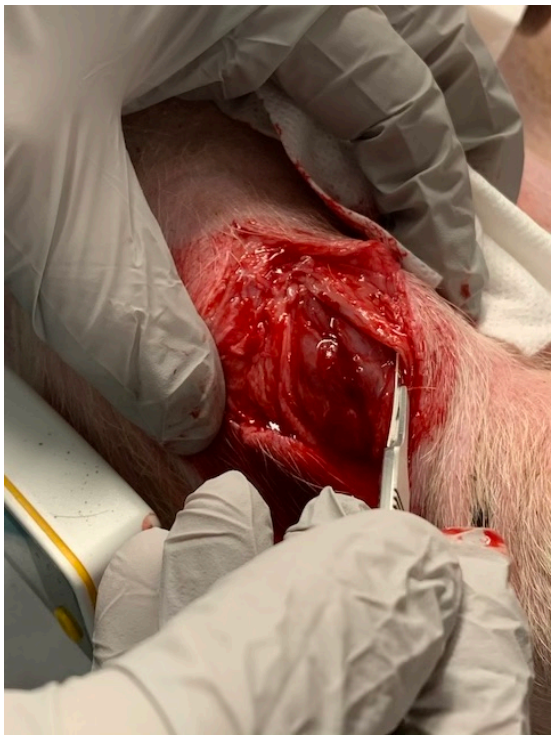

Figure 3. Open anterior compartment fasciotomy showing the relatively thick nature of porcine fascia.

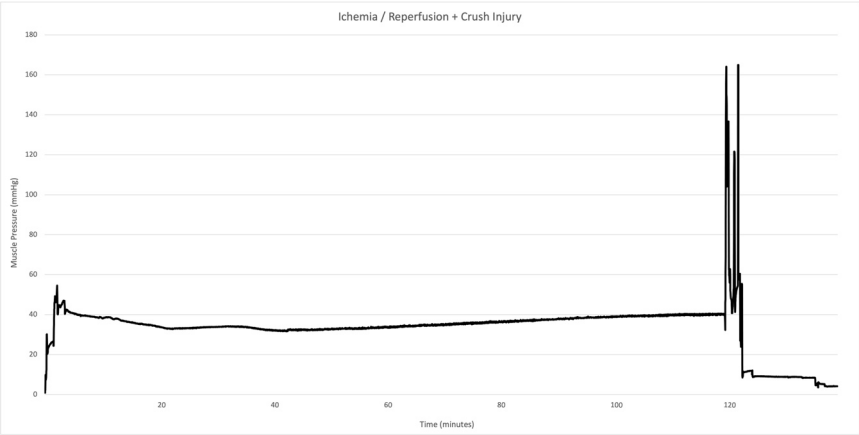

Figure 4. Continuous pressure measurement of the anterior compartment during the two-hour observation period using the double tourniquet technique (I/R + direct crush injury).

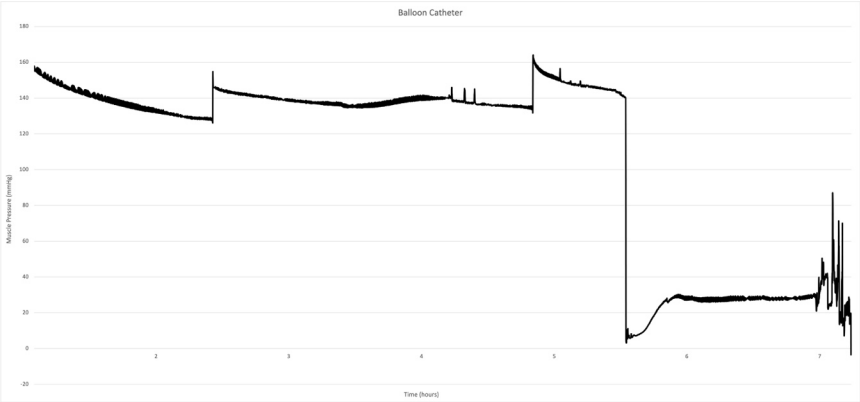

Figure 5. Continuous pressure measurement of the anterior compartment during the five-hour injury period followed by two-hour observation period using the balloon catheter technique.

2.4 DISCUSSION

The development of an acute compartment syndrome (ACS) is driven by a complex physiological process that is yet to be fully understood. It occurs when elevation of pressure within a compartment is significant enough to cut off its blood supply, leading to potentially catastrophic consequences (1-7, 33). Various mechanisms of injury can lead to ACS; however, it is well understood that high-energy trauma to the lower limb is most common (9). The only successful treatment is fasciotomy - a procedure that may carry significant morbidity and long-term complications (3). Diagnosis of ACS relies predominantly on clinical exam findings, with intracompartmental pressure (ICP) monitoring used only as an aid. However, in polytrauma, sedated, or obtunded patients that cannot verbalize, a more objective form of examination is needed. Although ICP cannot be used as a standalone value for diagnosis of ACS, a differential threshold pressure (calculated as the diastolic pressure minus compartment pressure) of <30mmHg has been shown to have high sensitivity and specificity (10). Unfortunately, there still remains no evidence of a specific or absolute cut-off value for fasciotomy. With no defined decision algorithms or gold standard for diagnosis, there is an urgent need for the development of an objective form of assessment to help predict and treat this debilitating condition.

In the current study, monitoring compartment pressure in vivo was successfully performed using a previously validated MY01 device (32, 34). No significant injury or complications were seen upon insertion of the sensors into the compartment thus indicating its safe use in vivo. Similar to previous studies (22, 25, 35), inflation of an angioplasty balloon catheter placed between the anterior compartment musculature and anterior face of the tibia for a period of five hours was found to induce spontaneous rises in ICP. This increase in ICP was seen in four of the hind limbs studied (n=6). Tourniquets have also been used to induce a compartment syndrome by way of

ischemia-reperfusion (17, 19, 21, 29, 36, 37). In the first pig studied, only one tourniquet cuff was used for the tourniquet technique and inflated around the proximal thigh. Although an initial increase in anterior ICP was seen, the pressure gradually declined to baseline levels in the second hour of the observation period. Therefore, a new technique using two custom-made contoured cuffs was established. With one cuff inflated around the proximal thigh and another cuff inflated directly over the anterior compartment, a double insult of ischemia-reperfusion with superimposed direct crush injury was achieved. This new technique was found to significantly increase ICP in all hind limbs studied (n=5). In light of these results, the newly described double insult technique is able to easily, efficiently and consistently induce a spontaneous rise in ICP significantly higher than that of the balloon catheter technique, thereby validating this novel porcine continuous measurement model. After the two-hour observation period, a percutaneous approach to fasciotomy was performed using a fasciotome in all hindlimbs studied for both techniques (n=12). Complete release of the compartment was shown by a return of ICP equal to or below physiological baseline levels, which was seen in eight hind limbs indicating a success rate of 67%.

The findings in this study suggest that both the balloon catheter and double tourniquet techniques are effective at inducing a spontaneous rise in ICP consistent with ACS danger levels. This was confirmed by using MY01 pressure sensors, which are built on a micro electromechanical systems (MEMS) framework allowing for extremely reliable and accurate pressure measurements. The balloon catheter technique is fairly replicable and provides the advantage of inducing injury localized to the anterior compartment. However, this technique requires surgical manipulation of the hind limb with tunneling of a thoracic trocar underneath the anterior compartment musculature. Furthermore, initial incorrect placement of the balloon catheter requires re-insertion of the thoracic trocar. As a consequence, this could compromise compartment integrity potentially leading to

unusual results. On the other hand, the tourniquet technique is extremely simple to set up without any prior expertise and able to produce damage without entering the muscle compartment. As opposed to the focal muscle damage seen with the balloon catheter technique, the use of tourniquets placed around the proximal thigh and directly over the anterior compartment causes injury to the whole limb possibly explaining the higher ICP readings during the observation period. In the first pig, a single tourniquet was placed around the proximal thigh to induce an ischemia-reperfusion injury as previously described in the literature (17, 19, 21, 29, 36, 37). However, this technique showed pressure levels to decrease significantly towards baseline during the observation period [Figure 3]. This could be attributed to the five-hour injury period that was used instead of a greater time period of injury. It could also be due to collateral or residual micro-circulation feeding into the anterior compartment. Although uncertain results may occur under six hours of ischemia (25, 38), the use of two tourniquets to create a double insult achieved significant rises in ICP 100% of the time during the five-hour period. This increases efficiency and cost-effectiveness of the model while also decreasing the burden of injury on the animal. The double tourniquet may also act to impede any remaining microvascular supply to the limb.

Alternative techniques used to induce ACS have been previously described in the literature. The infusion technique is a popular method that has been used considerably and in various animal models (21, 23, 24, 26, 27, 39, 40). Despite its popularity the technique has noteworthy limitations. It requires insertion of an infusion catheter into the appropriate location within the compartment, which may pose a challenge in regard to replicability. Also, the infusion of fluid into the compartment may not represent the heterogeneity of a true compartment syndrome as related to traumatic injury of the leg. Although fluid infusion is used to replicate the effusive nature of ACS, one study showed that pressures could not be held at a specific level in the compartment without

being infused with more fluid (40). A reason for such a finding could be explained by the type of fluid used, thus allowing for potential systemic absorption. Another popular method described in the literature is the use of single tourniquets placed around the thigh to produce an ischemia-reperfusion injury in the lower limb (17, 19, 21, 36, 37). This technique is easy to reproduce and requires minimal manipulation of the animal, with no prior experience. Furthermore, it provides valuable information on the complex pathophysiology and management of ischemia-reperfusion syndrome of the lower limb – a direct cause of ACS. However, this technique is also not without disadvantages. One study using murine and porcine models has shown residual blood flow to the limb after inflation of a thigh tourniquet (41), and others have stated the presence of collateral circulation upon ischemia (21, 42). Nonetheless, the residual blood flow may not be enough to sustain the increased demands of aerobic metabolism. Given the conical nature of animal limbs, standard rectangular tourniquets do not fit naturally well. In fact, a review looking at tourniquet-induced injury found that type and shape of tourniquet could be a factor in the pathophysiology of inducing such an injury (17). For this reason, the current study used conical tourniquets custom made to specifically fit porcine hind limbs. Surgical devascularization – another technique noteworthy of mention albeit unfrequently used for the study of ACS provides the advantage of studying muscle injury localized to the anterior compartment (16, 43). Furthermore, it guarantees no residual blood flow to the area studied. Although effective, this invasive method involves significant manipulation of the limb and may not be the most efficient or replicable way of inducing ACS. Fasciotomy techniques have also been investigated with studies describing the importance of releasing at least 90% of the fascia (27). In the current study, a fasciotome using the percutaneous approach was able to fully release the anterior compartment with a success rate of

only 67%. However, the thick nature of porcine fascia and skin may be the main cause associated with the observed result.

To our knowledge, this is the first study using two custom made tourniquets to create an ischemia-reperfusion with superimposed direct crush injury in a porcine hind limb model. However there exists several limitations that must be mentioned. There is the obvious limitation that ACS is a clinical diagnosis based on subjective and objective findings on physical examination, which is impossible to obtain in an animal model. Although this model is clinically relevant in terms of an ischemia-reperfusion with soft tissue injury, it still does not complete the picture seen with additional bone injury. The porcine model is an excellent surgical model and has shown anatomical and physiological similarities to humans, yet it is still uncertain whether it can be fully translated without looking at various alternative aspects such as immunological status. Furthermore, the thickness of the porcine skin and fascia need to be taken into account when analyzing compartment pressures during injury and release. In this study, only one time point was used given that only acute changes in pressure were required. A longer observation period would have been constructive to see whether pressures return to baseline and when, if they do. Given this study only measured pressure changes, no histological samples, serum biomarkers, or tissue oxygenation readings were taken for further analysis. Future studies correlating these with the use of accurate and validated pressure sensing technology would be extremely valuable in hopes of determining a threshold for surgical intervention.

2.5 CONCLUSION

This study has shown that the use of a newly described technique is efficient, effective, and easier to reproduce as compared to alternative ACS inductions techniques. The in vivo use of a novel

MY01 pressure sensor was also found to give accurate and reliable pressure readings in real-time. The application in human studies would be invaluable for future research with the addition of physical examination to help guide appropriate decision making.

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CHAPTER 3

TOURNIQUET-INDUCED INJURY IN A RAT HINDLIMB ACUTE COMPARTMENT SYNDROME MODEL

CHAPTER 3: TOURNIQUET-INDUCED INJURY IN A RAT HINDLIMB ACUTE COMPARTMENT SYNDROME MODEL

3.1 INTRODUCTION

The diagnosis and management of acute compartment syndrome (ACS) has remained a major challenge for clinicians. It is characterized by an increase in pressure within a muscular compartment, significant enough to cut-off its blood supply ultimately leading to ischemia [1]. With a wide etiology, it can occur as a result of high- or low-energy trauma including blast, crush, burn, vascular or ischemic injuries. Even though ischemic episodes may be reversible up to a certain point, an additional secondary insult may ensue with reperfusion of the muscle – an occurrence dubbed as ischemia/reperfusion (I/R) injury [2]. Currently, there is no clear threshold or gold standard for diagnosis of ACS with treatment still limited to morbidly invasive fasciotomies aimed at relieving pressure.

Animal models have been instrumental in our understanding of human disease as well as the testing the potential of novel therapies and methods of management. Unfortunately, the diverse clinical progression and lack of fully translatable models has made ACS difficult to investigate. Various techniques of artificially inducing ACS have been developed and established in human cadavers and live animal models [3], yet still possess significant limitations that necessitate caution when translating findings to humans. Inducing ACS in healthy human volunteers would be optimal however, obvious ethical restrictions hold back such practice. Although human cadaver models have proven beneficial given their anatomical relevance, they do not take into account the underlying complex pathophysiological processes driving ACS. Modelling compartment syndrome in various live animals has been key in advancing our understanding through

investigation of pressure sensing techniques [4-7] and histological analysis of muscle damage after injury [2, 5, 7-11]. Porcine models closely resemble human anatomy and physiology [12] however remain costly and often require the help of veterinary technicians. Rodent models such as the rat model are extremely cost-effective, relatively low to maintain, and phylogenetically inferior making them a favourable option amongst many researchers. However, as with all animal models, various limitations exist that warrant careful consideration and interpretation.

This manuscript focuses on a rat ischemia-reperfusion model of ACS via tourniquet placement around the proximal hindlimb, as previously described in the literature [2, 11]. Continuous pressure measurement of the hindlimb was accomplished using a previously validated MEMS pressure sensing device [4, 13]. Our aim is to explore and validate the induction of ACS in a rat hindlimb tourniquet model while assessing in vivo use of novel pressure sensing technology.

3.2 METHODS

3.2.1 Anesthesia and Experimental Protocol

Two adult male Sprague-Dawley rats from the retired breeders maintained at the Charles River facility were received and allowed to acclimatize for a minimum of 72 hours as per SOP 531.01. Animals were prepared for surgery as per SOP 201.02.

The animals were anesthetized by breathing isoflurane in an induction box and mask. Anesthesia was maintained with isoflurane throughout the experiment and euthanasia. The animals were placed in supine position on a heating plate and provided with periodic subcutaneous saline infusion (0.2 – 0.5 mL/10 grams) to maintain adequate hydration. Both hind limbs were shaved

with wide margins around the experimental site and sterilized using 2% chlorhexidine solution. One MY01 pressure device was deployed into the tibialis anterior muscle of each hindlimb, with one of the hindlimbs serving as a control. The experimental and control conditions were alternated between the legs studied (Table 1). A pneumatic digit tourniquet (DC1.6, Hokanson, WA) attached to a tourniquet regulation system was placed as proximal as possible around the upper hindlimb (Figure 1). Baseline compartment pressures were measured for five minutes prior to inflation of the tourniquet. Inflation to a pressure of 300 mmHg for a period of three hours was completed followed by an observation period of three hours with continuous pressure measurement throughout. Compartment pressure was observed after fasciotomy and exploration of the fascia and compartment was performed.

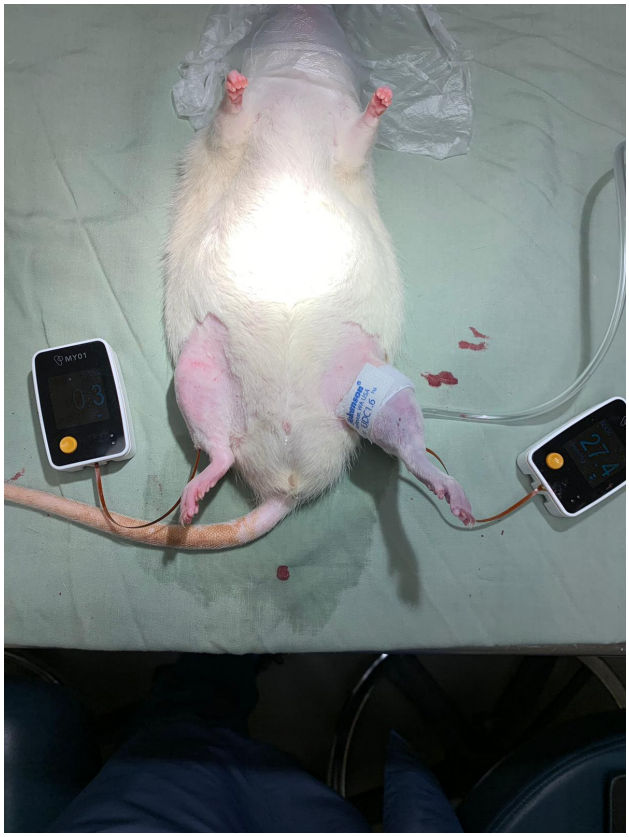

Figure 1. Pneumatic digit tourniquet wrapped proximally around the left hindlimb with MY01 sensors placed into each anterior compartment. The right hindlimb served as control.

3.2.2 Statistical Analysis

Results are presented as means □ SD unless stated otherwise. Student's paired t-test was used to compare baseline pressure values prior to tourniquet inflation, during the injury period, as well as during the observation period. Differences were considered significant at $p < 0.05$.

3.3 RESULTS

Continuous monitoring was successfully achieved using MY01 devices placed into the anterior compartment of a rat hindlimb. No significant injury was noticed with injection of the devices. Although a standard cylindrical pneumatic tourniquet was able to wrap around the proximal thigh of a rat, it was consistently displaced to mid-thigh upon inflation. Nonetheless, the tourniquet was deemed successful at causing stasis of blood flow as seen by the colour changes distally and a cool temperature upon palpation of the limb as compared to the control. Prior to inflation of the tourniquet in the first animal, baseline pressure in the control limb averaged 5.0 □ 0.3 mmHg. During the three-hour observation period, average pressure of the control limb increased to 6.0 □ 0.4 mmHg. During the injury period in the experimental limb, inflation of the tourniquet to 300 mmHg yielded an average anterior compartment pressure of 68.8 □ 12.8 mmHg while reaching a maximum of 76.5 mmHg. After deflation of the tourniquet, pressure of the experimental hindlimb immediately declined to approximately control levels of 6.8 □ 0.1 mmHg and failed to rise further. In the second animal, a baseline pressure average of 4.2 □ 0.9 mmHg was established in the control limb, increasing to an average of 8.1 □ 1.0 mmHg during the observation period. During inflation of the tourniquet, the experimental limb saw an increase in pressure to an average of 70.7 □ 12.6 mmHg and reaching a maximum of 76.1 mmHg. Similar to the first animal, deflation of the tourniquet saw an immediate decrease in compartment pressure

of the experimental limb to an average of 8.9 □ 1.0 mmHg. Dissection and exploration of the hindlimb showed a small anterior compartment surrounded by a particularly thin and elastic fascia (Figure 2).

Table 1. Anterior compartment pressures of both control and experimental hindlimbs during baseline, injury, and observation period in each of the rats studied.

	Hindlimb	Baseline (mmHg)	SD (mmHg)	Injury Period (mmHg)			Observation Period (mmHg)		
				Average	SD	Maximum	Average	SD	Maximum
Rat 1	Control (Right)	5.0	0.3	6.1	0.4	6.3	6.0	0.4	6.1
	Experimental (Left)	5.7	0.4	68.8	12.8	76.5	6.8	0.1	7.0
Rat 2	Control (Left)	4.2	0.9	7.8	1.2	8.4	8.1	1.0	8.2
	Experimental (Right)	4.4	1.0	70.7	12.6	76.1	8.9	1.0	8.9

Figure 2. Extremely think nature of rat hindlimb fascia observed during surgical dissection and exploration.

3.5 DISCUSSION

Various techniques aimed at artificially inducing ACS have been developed and widely explored. Infusion techniques are one of the preferred methods of modelling ACS but possess the limitation of the fluid infused being absorbed back into the circulatory system [3]. Ischemia-reperfusion through tourniquet use [5, 14] as well as surgical devascularization [15, 16] have also been shown to induce significant muscle injury resulting in spontaneous increase of ICP. However, surgical manipulation of the animal prior to experimentation may be complicated and dependent on experience. Tourniquet use, although simple and effective, has been argued to create a global ischemic injury of the limb instead of a focal injury as most commonly seen in the anterior compartment [17]. Despite the different techniques that have been developed, trauma to the limb is not uniform and may manifest in multiple ways. Therefore, it is important to investigate and develop the most appropriate and relevant model for studying a true compartment syndrome. The current study uses previously validated MY01 devices to confirm the presence of increased compartment pressure – a key component in guidelines released by the AAOS for the diagnosis and treatment of ACS [Schmidt 2018].

The results in this study show that continuous pressure monitoring in vivo was achieved using a MY01 sensor inserted into the anterior compartment of a rat hindlimb. The lack of morbidity upon sensor insertion indicates that it is safe to use without causing any unnecessary injury. Baseline pressures of the rat hindlimb served as a control and were found to average at 5 mmHg prior to injury. No significant difference was found between baseline control pressures prior to or after the injury period (Table 1). Although initially placed as proximal as possible, continuous displacement of the tourniquet to approximately mid-thigh was seen upon inflation, most likely attributed to the conical nature of the rat hindlimb. Despite this, the use of a pneumatic

tourniquet was able to cause stasis of blood as seen by a colour change distally. Furthermore, palpation of both hindlimbs revealed the injured limb to be significantly colder than the control limb. Immediately after deflation of the tourniquet, temperature as well as colour of the hindlimb normalized. However, hindlimb pressure in the injured limb also declined to baseline levels (Table 1) without a subsequent rise to ACS danger levels during the three-hour observation period. Dissection and exploration of the hindlimb after the observation period revealed an extremely thin and compliant fascia.

These outcomes may be attributed to a number of reasons specific to the model used. The conical nature of the rat hindlimb may require a custom-made tourniquet that takes into account anatomical shape and size. In fact, research has shown that type of tourniquet used may indeed be a factor in pressure distribution and vascular occlusion [18]. Although stasis of blood flow was confirmed through palpation and observation of colour changes, this remains a relatively subjective method. The amount of residual microcirculation distal to the inflated tourniquet can be confirmed through more objective means such as intravital videomicroscopy (IVVM) and ethidium bromide (EB)-labelled nuclei. In a saline-infusion model, Lawendy and colleagues [9] have demonstrated the functional and inflammatory response to a compartment syndrome using such techniques and also witnessed both intermittent and non-perfused capillaries in an injured limb. The rat tourniquet model, while effective for studying histological and functional damage to tissue [2, 5, 8, 10, 11], may not be as effective for studying pressure increase due to the particularly thin and elastic nature of the fascia. Kim et al. [2] described an excellent analogy whereby a tourniquet placed around the rat hindlimb is similar to squeezing one end of a balloon, making the alternate end expand. This compensatory mechanism seems counterintuitive for the study of

compartment syndrome, which is defined by an increase in pressure within a compartment enveloped by a thick inelastic fascia.

The current study raises important questions about the nature of the tourniquet model however, certain limitations need to be considered. Although only one time-point was used, the main objective was to continuously track pressure changes directly after inducing an ACS. In light of the similar findings between the rats studied, only two were used. Although a larger sample size would be beneficial to ensure consistency of results, slight modification to the methodology would be constructive prior to further experimentation. A circular tourniquet may necessitate a higher pressure to effectively stop blood flow [18]. Previous literature has shown that pressures between 220 - 300 mmHg are able to cease microvascular flow to the limb [2, 5, 8, 10, 11]. Based on such findings, inflation to a pressure of 300 mmHg was used in this study. Using a custom-made tourniquet would provide for a more controlled model looking at I/R or possibly even crush injury. Furthermore, measuring the extent of residual perfusion with IVVM and fluorescent dye would clarify and strengthen the findings seen using the tourniquet model. Histological analysis of muscle injury as it correlates to the pressure values measured would also provide valuable insight into the pathophysiology of ACS.

3.6 CONCLUSION

An ischemia-reperfusion model of ACS was investigated via tourniquet placement around the proximal hindlimb of a rat. Although an increase in hindlimb pressure was observed throughout the three-hour injury period, immediate return to baseline levels after deflation imply that the model was unsuccessful at inducing an appreciable compartment syndrome from an I/R injury. Furthermore, the anatomy of the rat may not be ideal for measurements of pressure increase

associated with compartment syndrome. The location of the leg relative to the pelvis, use of a circular tourniquet, and expandable fascia in the limb all contribute to the lack of success in this model.

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CHAPTER 4

ABDOMINAL COMPARTMENT SYNDROME: EXPLORATION OF CONTINUOUS MONITORING IN A RAT MODEL

CHAPTER 4: ABDOMINAL COMPARTMENT SYNDROME: EXPLORATION OF CONTINUOUS MONITORING IN A RAT MODEL

4.1 INTRODUCTION

Abdominal compartment syndrome (ACS) occurs with several common illnesses [1-4]. Sustained increase in abdominal pressure results in a cascade of abdominal and systemic sequelae [3-5]. Reported incidences of 30-50% are seen in critically ill patients [6]. The outcome is often fatal if missed or untreated [1, 3, 5]. The need for timely diagnosis and management is paramount. Surgery in these patients is also complicated by difficulty in primary abdominal wall closure [7, 8]. Assorted late abdominal closure techniques have been necessary with high hospital costs from prolonged ICU stays and repeated surgeries.

ACS can be primary – caused by direct abdominopelvic injury or disease – or secondary – caused by injury or disease outside the abdominopelvic region [9, 10]. The World Society of the Abdominal Compartment Syndrome (WSACS) has guidelines looking to standardize diagnostic and treatment protocols involving intraabdominal hypertension (IAH) and ACS [9]. Although frequently seen together, it is important to distinguish IAH and ACS as two separate clinical entities. A sustained or repeated intraabdominal pressure (IAP) > 12 mmHg is suggestive of IAH, whereas ACS refers to sustained IAP > 20 mmHg that is associated with organ damage [9, 10]. While one causes the other, the onset of pressure changes is hard to clinically determine giving rise to the importance of continuous or serial IAP monitoring. Although current guidelines recommend routine IAP measurements [9], there has yet to be consensus on what is the most effective method [11, 12]. The physical exam of a patient with elevated IAP has proven to be an unreliable predictor of ACS [2, 10, 13, 14], with more than 50% of providers failing to correctly

identify its presence [15]. Given that most ACS cases are seen in the critically ill, obtunded, or comatose patients unable to verbalize, there is a need for a more objective form of examination. Intravesicular pressure (IVP) monitoring was seen as the standard with a rationale of cost effectiveness and use of commonly available supplies [9]. First introduced by Kron and colleagues, this indirect method involves infusion of sterile saline (50 – 100 cc) through a foley catheter into an emptied bladder into a supine patient. A pressure transducer is used that is manually zeroed at the level of the symphysis pubis [16]. Various other techniques for monitoring IAP have been proposed and investigated such as, but not limited to the use of a Foleymanometer™, intragastric catheter with air pouch system, inferior vena cava pressure monitoring, and rectal and uterine pressure monitoring. However, many of these techniques are procedure and care intensive with many hours of nursing care in order to perform adequately. Some of the issues of technique or device design are due to lack of an accepted pre-clinical model. While studies have simulated IAH/ACS in canine [17] or porcine models [18-22], Meier et al. developed and validated a new, effective, and easy to reproduce model in rodents by infusing warmed gelatin succinate directly into the peritoneal cavity [23]. A simple rat model may be the most effective – cost and resource wise- to model ACS.

New devices have been developed with reproducibility and the size needed to allow easy monitoring. Among them, piezoresistive pressure sensors have shown excellent sensitivity to fluctuations in pressure [19]. Unfortunately, such devices may be too costly for centers to readily use and have been observed to display sensor drift (loss of accuracy) potentially decreasing the precision of measurements over time [12, 19]. Capacitive pressure sensors built on a micro electromechanical systems (MEMS) framework provide excellent sensitivity to fluctuations in

pressure while maintaining accuracy of pressure readings over time [24, 25]. These sensors are composed of inert biocompatible silicon and have almost no drift at body temperature.

The objective of this work is to further establish and validate a rodent intra-abdominal infusion model by monitoring with both commercially available sensor packages and the novel MEMS pressure sensing technology. Additionally, the accuracy of retroperitoneal (RP) monitoring with intraperitoneal monitoring (IP) in an abdominal compartment syndrome model was compared to determine if a less invasive direct monitoring is possible.

4.2 METHODS

Saline infusion pump setup consisted of an automatic infusion pump (PHD ULTRA™, Syringe Pump Series, Harvard Apparatus) (Figure 1) and inline pressure sensor (Hugo-Sachs Elecktronik, APT300, Harvard Apparatus). The pump was loaded with two 60 mL syringes filled with normal saline (0.9% NaCl). Syringes were connected with IV tubing that merged into one line at the inline pressure sensor, terminating into a 20G catheter. Inline pressure sensor was zeroed according to device instructions. Pump was set for constant pressure infusion with maximum infusion rate of 20 mL/min.

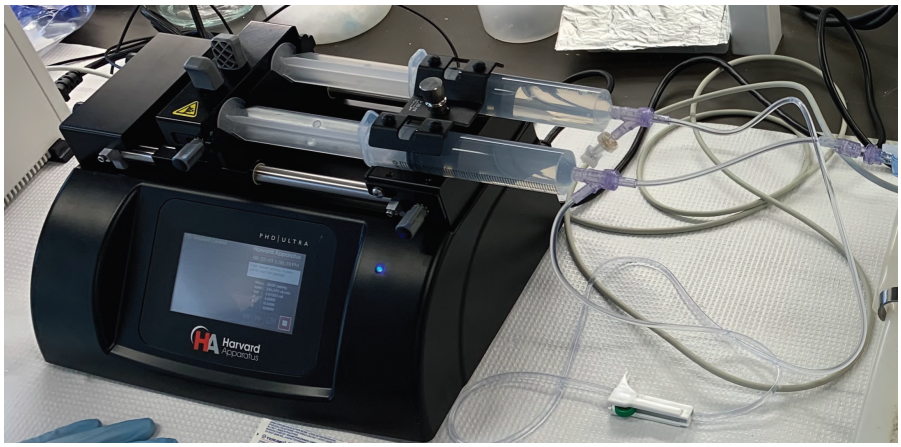

Figure 1. Infusion pump setup with saline-filled syringes

4.2.1 Experimental Protocol and Device Insertion

Eight retired breeders Sprague-Dawley rats from Charles River facility were anesthetized with isoflurane throughout the surgery. The animals were placed on a heating plate during infusion and position was alternated from supine to prone between rats. Device insertion was also alternated between right and left paraspinal muscles. After shaving and sterilization, retroperitoneal placement of a MEMS sensor (MY01 Inc, Montreal Canada) was accomplished by inserting the device from the posterior aspect of the rat into the anterior paraspinal muscles just outside the peritoneal cavity. Placement alternated from right to left paraspinal muscles between rats. Correct placement was confirmed via ultrasound (Philips Lumify L12-4 Transducer) (Figure 2). A second commercial pressure device serving as a control, was placed intraperitoneally via an anterior abdominal approach and confirmed with ultrasound. Purse string suture technique was used to seal the cavity from leakage. Likewise, the pump catheter for fluid instillation was inserted into the abdomen via an anterior approach and confirmed with ultrasound. Baseline pressures were monitored for 10 minutes before infusion.

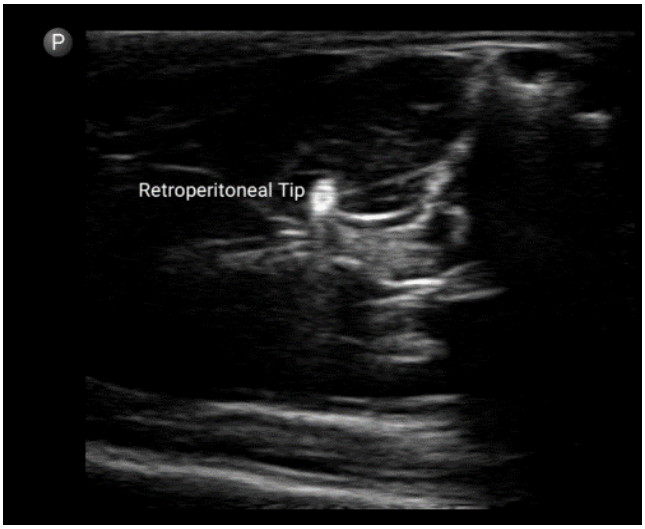

Figure 2. Sensor tip shown in anterior paraspinal muscle using ultrasound

4.2.2 Abdominal Compartment Syndrome Model

In order to minimize and keep consistent the volume required for induction of ACS, a simple external support of the abdominal wall was used as described by Meier et al [28]. Briefly, a Plaster of Paris cast was activated with water and loosely modeled around the abdomen of an anesthetized animal prior to infusion (Figure 3). Care was taken to mold the hard cast below the rib cage to allow for non-restricted breathing. Once settled, the cast was longitudinally split on opposite sides and loosely taped into place for each animal prior to infusion. The pump pressure was initially set to 20 mmHg and adjusted as necessary to maintain an intrabdominal pressure of > 30 mmHg. Continuous monitoring of pressure was performed until 10 minutes of stable pressures above ACS threshold. After completion of monitoring, the position of the sensors was again confirmed via ultrasound to ensure no significant motion had occurred during infusion.

Figure 3. Abdominal Plaster of Paris cast with infusion catheter and MY01 sensors inserted.

4.2.3 Statistical Analysis

Results are given as means ± SD unless mentioned otherwise. Student's paired t-test was used to compare weight between control and post-infusion of saline, as well as pressure prior to infusion (control) and pressure after 10 minutes of saline infusion. Differences were considered significant at $p < 0.05$.

4.3 RESULTS

Continuous pressure measurements using novel MEMS technology were successfully obtained in a rat saline infusion model (Figure 4). Continuous infusion of saline into the intraperitoneal cavity using the continuous infusion pump was also successful. The use of a loosely modeled split soft cast was found effective at mimicking decreased wall compliance as well as keeping infusion volumes relatively consistent between animals. No morbidity related to sensor insertion was observed in any of the eight animals. No leakage of saline was seen from either insertion points of the sensors or insertion point of the saline infusion catheter. No significant differences were found between baseline pressures when animals were positioned either supine or prone (Table 1). Furthermore, no significant pressure difference was appreciated between sensor placement in the left or right paraspinal muscles (Table 1). Prior to saline infusion, mean body weight of the animals was 493 ± 16 g. At the end of infusion, body weight of the animals was 685 ± 45 g with an average of 192 ± 30 mL infused into each peritoneal cavity. Although baseline IP pressures (6.8 ± 3.7 mmHg) were found to be higher than baseline RP pressures (6.1 ± 2.9 mmHg) this difference was clinically insignificant. During infusion of one animal the RP sensor was accidently dislodged from the paraspinal muscle, as confirmed by ultrasound. Therefore, statistical analysis was performed on seven of eight rats. 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. The infusion pump was able to adjust the infusion rate based on the inline arterial sensor pressure reading and maintain the setpoint pressure during the duration of all infusions. However, the inline arterial sensor pressure was found to not accurately represent compartment pressure when compared to the intra-compartmental MY01 device. Differences between stable infusion pressure and pump setpoint are shown in Table 2.

Table 1. Baseline pressure values of rat position and sensor placement.

Position / Sensor Placement	Baseline Pressures (mmHg)	
	Average	SD
Supine	6.9	3.2
Prone	6.0	3.3
Left paraspinal	7.1	3.7
Right paraspinal	5.1	1.7
Intraperitoneal	6.8	3.7
Retroperitoneal	6.1	2.9

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

Rat & Sensor Position	Infusion - Setpoint Pressure (mmHg)	
	Average	SD
Supine	20.6	7.4
Prone	25.8	6.9
Left paraspinal	28.5	6.9
Right paraspinal	18.6	4.6
Intraperitoneal	22.1	7.3
Retroperitoneal	23.6	8.0

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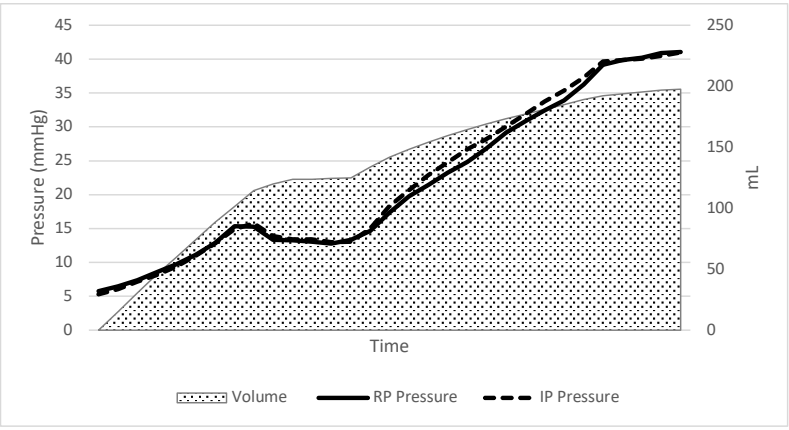

Figure 4. Continuous IP monitoring vs. continuous RP monitoring vs. volume of saline infused in rat #3.

4.4 DISCUSSION

The rat saline infusion model has been shown to be a reliable, cheap, and easily reproducible model to study the effects of IAH/ACS [28], with further validation in this study. Using this model, continuous intra-abdominal pressures were successfully measured by placing pressure sensors both intraperitoneally and retroperitoneally via ultrasound guidance. The pressures measured retroperitoneally mirrored those measured intraperitoneally providing promising evidence that a less invasive, less nursing intensive, yet equally accurate method of IAP monitoring can be performed. As illustrated by the results, we were successful in proving the accuracy of continuous RP pressure monitoring vs. IP pressure monitoring with no significant differences seen between the two. Furthermore, placement of the animals in either the supine or prone position had no significant effects on pressure readings. These findings open up new avenues for studying and monitoring abdominal compartment syndrome.

The importance of measuring IAP to diagnose and manage IAH/ACS has been well documented in the literature [1-3, 6, 9, 10, 12-16, 31, 32]. Although patients may present with pain and abdominal distention [1], clinical examination of the suspected ACS patient has proven to be unreliable with more than half of providers failing to correctly identify its presence [2, 3, 13, 15]. Despite there being no concrete evidence showing the optimal frequency of measurement, it is currently recommended to continuously or intermittently monitor IAP at least every 4 hours in critically ill patients [3, 6, 9]. Routine measurements of IAP have been shown to predict ACS within 6 hours of hospital admission, and a decrease in mortality seen when ACS was managed with decompression within 24 hours as opposed to 48 hours [33]. However, it was also reported that no difference in patient mortality was seen when the abdomen was decompresses within 12 hours of patient admission [33]. Although intermittently measuring pressures has proven to be

valuable- if not costly in procedure time and care- it still does not provide a complete picture of the dynamic process of ACS. Continuous real-time monitoring can provide further insight into the pathophysiology of ACS while also monitoring patient's response to treatment after injury [14].

To date, the most accurate and sensitive manner of measuring IAH/ACS is through direct methods, which include intraperitoneal monitoring using a peritoneal dialysis catheter or laparoscopic Veress needle [1-3]. Unfortunately, these techniques are limited largely due to their level of practicality and invasiveness, with the potential of striking major vascular structures or even puncturing intra-abdominal organs [3, 34]. Despite such complications, these methods are used only when necessary, typically in the most acute or critical cases [9]. The use of a Foley catheter measurement variant is more commonly used. This method has been modified [18] and developed since its first inception by Kron and can now be used to measure IAP continuously [35, 36]. The classic bladder technique has limitations and potential contraindications. In critically ill patients, head elevation is important to help prevent complications such as aspiration, ventilator associated pneumonia (VAP), and pressure ulcers [37, 38]. Studies have shown that IAP readings may vary almost 10 mmHg higher with position changes as simple as elevation of the patient's head [38]. Given these potentially management-changing elevations in pressure, a more accurate and sensitive technique would allow better understanding of the dynamics of body or sensor positioning on IAP. Formation of air bubbles within the fluid-based system may give rise to erroneous measurements if a flush test is not performed properly [12]. An absolute contraindication to using this technique is any major trauma where there is kidney, bladder or urethral damage, in which most cases a Foley catheter cannot be inserted [1, 2, 12, 14, 19, 20] or hematuria would affect the results. The classic Harrahill technique [39] is performed by injecting 100 mL saline into an empty bladder with the patient supine and then holding the urinary tubing

at a 90-degree angle, approximately 30-40 cm above the symphysis pubis. The height of the urine is measured from the pubis to the meniscus, which reflects the bladder pressure (thus IAP) in centimeters. A chart can be used to convert readings from centimeters to millimeters of mercury [39]. This method is effective as a quick screening tool given there is minimal manipulation, can be repeated as many times as needed, and provides no risk of injury or infection to the patient. However, it remains a fluid-filled system prone to errors in measurement and can only be performed when there is enough urine in the bag. Otherwise 50 – 100 mL of saline can be injected into the bladder through the urinary catheter [12, 39] to increase the urine volume. This brings into question the methodical consistency between different health providers or health centers using the technique [12]. The Foleymanometer, another technique similar to Harrahill's, has a 50 mL container with a bio-filter built into the catheter system allowing a standardization of the amount of urine infused back into the bladder. Unfortunately, this has similar disadvantages to the previously described method. Furthermore, the bio-filter may experience blockage which could also lead to incorrect measurements of IAP [12].

When there exist contraindications to inserting a Foley catheter, gastric pressure measurements have been used to track IAP. Similar to the Foley catheter, nasogastric (NG) tubes are almost necessary for all critically ill patients and can provide a comparable way to estimate IAP [21, 25, 40]. Although there is no risk of infection and no interference with urine output, it may interfere with NG feeds or stomach function [12, 35, 41]. Furthermore, intraluminal contents may affect readings [35]. Air within the stomach must be removed prior to measurement, which can be challenging to verify [12]. It is also a fluid-filled system and therefore the same disadvantages apply. Gastric tonometry, a method of assessing hypoperfusion by measuring intra-luminal CO2 levels, has also been used to estimate IAP [12, 40, 41]. The balloon at the tip of the

gastric tonometer can be filled with air, thereby avoiding disadvantages of a fluid-filled system. There is also no need for alterations in patient positioning and no issues with zero-referencing [12]. With the ability to measure both IAP and CO2 levels, this method may provide benefit during laparoscopic procedures as studied by Sugrue and colleagues [41] however, not all studies have been promising [42]. Unfortunately, tonometry is a costlier option as compared to the classic NG or intravesicular method [41] and is still in experimental stages with no evidence of improved outcomes [12]. It also cannot be left in the same place for a long duration. Further development of this technique has seen fully automated devices with an inflatable air-pouch at the tip. The Spiegelberg balloon-tipped catheter (Spiegelberg, Hamburg, Germany) as well as the CiMON balloon-tipped catheter (Pulsion Medical Systems, Munich, Germany) are two methods that provide continuous IAP monitoring. Both methods have been validated to provide measurements significantly similar to direct intra-peritoneal IAP measurements as well as IVP monitoring [12, 25, 42]. The systems are connected to an external device and are fully automated with no need for calibration or further manipulation. It is less time-consuming and requires less effort than previously described procedures. Although this technique provides promising evidence, it lacks multicentric validation and is used mostly for research purposes [12]. Chopra and colleagues [43] also studied IAP using the CiMON gastric pressure system in comparison to the IVP method and direct intraperitoneal measurement (using piezoresistive probes). It was found that gastric pressures showed inaccurately low values as compared to IVP and direct pressure measurements, which could potentially lead to incorrect management protocols [43].

Other methods that are used to estimate IAP include rectal and uterine pressures [3, 12, 18]. Both these routes use a fluid-filled balloon catheter which bring into question measurement accuracy. They are also more difficult to perform, require more manipulation than previous

techniques, and cannot be used when there is an active bleed, infection, or diarrhea [12]. These techniques are mostly experimental and have no validation in the ICU setting. Inferior vena cava pressure (IVCP) monitoring, also mostly experimental, has shown promise to accurately and continuously estimate IAP [12, 18, 19]. However, a large human clinical trial conducted by De Keulenaer [44] showed mixed results with femoral vein pressure not indicative of IAP unless pressures are above 20 mmHg. Although this technique can provide continuous monitoring while avoiding interference with urine output and NG feeding, it follows with a number of significant disadvantages. Insertion of the catheter is time consuming with confirmation of its placement needed via x-ray [12]. The risk of disseminated sepsis by catheter-related bloodstream infections also limits the use of this invasive procedure, with health providers opting to choose quicker, easier, and safer methods.

Piezoresistive pressure sensors have garnered attention for their continuous monitoring and excellent sensitivity to fluctuations in pressure. They have also been used to compare and validate alternate techniques and procedures [12, 25, 43, 45]. In a human clinical study by Otto et al. [45], two different piezoresistive probes, Coach®-system (CPRM, MIPM, Mamendorf, Germany) and Accurate++®-probe (APRM, MIPM, Mamendorf, Germany), have shown promise with no probe-related complications arising with direct monitoring of IAP. However, zeroing of the CPRM device cannot be performed in-vivo and must be accomplished prior to placement. Furthermore, the CPRM could only measure pressure in 3 of 10 patients and the APRM in 7 of 10 patients due to probe-related malfunctions or difficulties. This brings into question the dependability of such devices in the acute care setting and may require further modification prior to its use. In the current study a novel pressure reading device was used (MY01 pressure sensor) (NXTSens Inc., Montreal, Canada), which is based on capacitive MEMS technology with wireless capability. Preliminary

studies have shown the validity of this device as well as the accuracy as compared to other pressure-reading systems [46]. It provides an injectable indwelling sensor connected to an external reader and is also able to transmit information real-time to mobile platforms via Bluetooth. This single use insert-and-forget device does not need to be zeroed and can provide continuous monitoring of real-time pressures in an already busy environment. The findings suggest that continuous monitoring of intra-abdominal pressure can be achieved in a quick, easy, and effective manner. Additionally, the placement of the MY01 sensor retroperitoneally allows for a minimally invasive measure of IAP while reducing the probability of major organ perforation or vascular injury as compared with already available and validated techniques. The MY01 sensor provides excellent capabilities of pressure measurement in-vivo. Although the injectable device can be inserted with minimal training, it is more invasive than most current techniques. However, the benefits of continuous monitoring with the convenience of a less labour-intensive method provides significant advantages over other techniques.

This study also shows that the saline-infusion model of the rat abdomen is an economical and easily reproducible way of studying IAH/ACS. We found consistency with the amount of saline infused into each abdomen and were able to keep IAP at levels consistent with ACS. Furthermore, we were able to show that body position of the animals, whether supine or prone, did not significantly influence pressure readings. Larger animals, especially porcine models, have been favourable for their relevant anatomical and physiological parameters but are more expensive as models. This study did not look at the effect of raised IAP on the various organ systems. Future studies in rodents as well as larger animals should look to correlate patterns of raised IAP on different systems in hopes of quantifying a gold-standard objective cut-off for surgical decompression. Furthermore, comparing RP and IP monitoring in a porcine model is warranted to

ensure that there indeed exists a less invasive yet equally accurate method for direct pressure monitoring of the abdomen.

4.5 CONCLUSION

Retroperitoneal pressures closely correlated with intraperitoneal pressures. Retroperitoneal pressure measurements are congruent with intraperitoneal pressure measurements in this abdominal compartment syndrome model. Results also show that pressures are similar uniquely with this device regardless of animal position. The use of a split abdominal cast was effective at mimicking decreased wall compliance and keeping infusion levels consistent. The close correlation between RP and IP measurements provides promising evidence that an accurate and less invasive method can be used to track intrabdominal rises in pressure in a continuous fashion. Such evidence should lead to future studies investigating larger animal models followed by human patients with suspected abdominal compartment syndrome.

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CHAPTER 5

GENERAL DISCUSSION AND CONCLUSION

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5.1 GENERAL DISCUSSION

The importance of investigating ACS has been well established amongst practitioners. Currently, there is no defined decision algorithm and no gold standard for diagnosis. ACS is a surgical emergency that if left untreated long enough, tissue death will occur and possible infection with high likelihood of amputation. Rhabdomyolysis or muscle breakdown after injury can further lead to acute renal failure, which in already sick or comorbid patients can very quickly result in death. A fasciotomy is the only known treatment for ACS and is a morbid procedure with a separate set of complications. Given the increased litigation of a missed ACS, surgeons may err on the side of caution and perform a prophylactic fasciotomy. In addition to the classical six P's, a seventh P, "PRESSURE" should also be included as it has shown to be a significant aid in diagnosing ACS.

Compartment pressure monitoring has been researched extensively yet the available technologies being used rely on redundant methods that are unreliable, operator-dependent, and lack clinical validity. The Stryker needle had shown promise as a portable tool but has since been taken off the market. The MY01 sensor is a wireless continuous pressure sensor that consists of MEMS technology and was found to be 670% more precise than other available sensors. This provides a valuable opportunity to study compartment syndrome further in order to better diagnose and treat it. Although human studies cannot be achieved due to ethical considerations, different models and techniques in various animals have been used in studying compartment syndrome.

The porcine hindlimb model of ACS is preferred by most surgeons given the anatomical and physiological similarities to humans. The most popular techniques used are the balloon catheter technique as well as tourniquet technique. In the current experiment, a balloon catheter

was used in one hind limb and tourniquet on the alternate limb. The two techniques were performed at the same time given that systemic sequalae were not being investigated. Studying both techniques at the same time also decreases the number of animals used. The use of a thoracic trocar to create a pathway for balloon catheter insertion was found to be relatively simple and straightforward. However, insertion of the trocar may compromise compartment integrity leading to incorrect readings of true compartment pressure. Nonetheless, spontaneous rises in pressure consistent with that seen in ACS. Although both methods resulted in increased ICP, the tourniquet technique consistently yielded higher compartment pressures indicating a more severe injury. Upon gross inspection after open fasciotomy, pig fascia was seemingly thick compared to that of human and may even be multi-layered.

In the rat-hind limb model, a tourniquet was used in one limb while the other served as control for baseline measurements. The tourniquet was inflated to 300mmHg for a period of three hours. During the observation period no spontaneous increase in pressure was seen. Upon dissection, the fascia of the rat hindlimb was discovered to be extremely thin and extensible, possibly being the reason for no elevation in compartment pressure. Given this significant anatomical difference, the use of a rat hind limb model to investigate compartment pressure increase may not be the most optimal.

Currently the most sensitive and specific way to measure pressure in the abdomen is through direct intra-peritoneal monitoring yet this remains extremely invasive. As mentioned in Chapter 4, the objective of the rat abdominal ACS model was to see whether retroperitoneal monitoring provides a less invasive yet just as accurate way of measuring abdominal pressure. This was achieved by infusing saline into the abdomen of the animal while placing a sensor both intraperitoneally and retroperitoneally. Danger levels associated with an abdominal compartment

syndrome were successfully reached and monitored. Most significantly, retroperitoneal pressure mirrored intraperitoneal pressure within five mmHg for all rats studied. Although continuous pressure monitoring was successful, the model necessitated the use of a soft cast around the abdomen due to its compliant nature. Once again, the anatomical differences seen between animal and man complicate the translatability and must be considered prior to human experimentation.

5.2 CONCLUSION

The MY01 continuous pressure sensor successfully monitored ICP in vivo as seen in the three models explored above. However, significant anatomical differences exist when comparing animal models to humans and should be accounted for. With the aid of continuous ICP monitoring, future experiments looking at various factors such as histological grade of muscle damage, serum biomarkers or fasciotomy length may be explored. Intraperitoneal versus retroperitoneal monitoring in a porcine abdominal ACS model should also be completed prior to experimentation in humans. Although the scope of this research is acute in nature, future studies looking at chronically implanted sensors could also provide an avenue worthy of exploration.