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Animal models in compartment syndrome: a review of existing literature

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Abstract

Objective: Extremity compartment syndrome (ECS) is a morbid condition resulting in permanent myoneural damage. Currently, the diagnosis of compartment syndrome relies on clinical symptoms and/or intracompartment pressure measurements, both of which are poor predictors of ECS. Animal models have been used to better define cellular mechanisms, diagnosis, and treatment of ECS. However, no standardized model exists. The purpose of this study was to identify existing animal research on extremity compartment syndrome to summarize the current state of the literature and to identify weaknesses that could be improved with additional research.

Methods: A MEDLINE database search and reverse inclusion protocol were utilized. We included all animal models of ECS.

Results: Forty-one studies were included. Dogs were the most commonly used model species, followed by pigs and rats. Most studies sought to better define the pathophysiology of compartment syndrome. Other studies evaluated experimental diagnostic modalities or potential treatments. The most common compartment syndrome model was intracompartment infusion, followed by tourniquet and intracompartment balloon models. Few models incorporated additional soft tissue or osseous injury. Only 65.9% of the reviewed studies confirmed that their model created myoneural injury similar to extremity compartment syndrome.

Conclusions: Study purpose, methodology, and outcome measures varied widely across included studies. A standardized definition for animal compartment syndrome would direct more consistent research in this field. Few animal models have investigated the pathophysiologic relationship between traumatic injury and the development of compartment syndrome. A validated, clinically relevant animal model of extremity compartment syndrome would spur improvement in diagnosis and therapeutic interventions.

Keywords: animal model, compartment syndrome, ischemia, muscle injury, reperfusion, review

1. Introduction

Acute extremity compartment syndrome is a highly morbid condition associated with infection, contractures, fracture nonunion, chronic pain syndromes, and poor patient reported outcomes. Compartment syndrome is rare with an estimated incidence of 7.3 per 100,000 males and 0.7 per 100,000 females. However, the true incidence of compartment syndrome is unknown, as most clinical studies use fasciotomy as a proxy for diagnosis. The rarity, acuity, and lack of gold standard diagnosis for acute extremity compartment syndrome have limited effective clinical study of the condition.[1]

The basic pathophysiology of compartment syndrome involves decreased tissue perfusion and subsequent cellular hypoxia caused by supra-physiologic pressure within a closed osteofascial space. Hypoxic conditions within the compartment drive inflammation and microvascular dysfunction which propagate injury, ultimately resulting in permanent, limb-threatening myoneural damage.[2,3] Unfortunately, the cellular mechanisms that drive compartment syndrome remain incompletely understood.[1]

Clinical symptoms are a poor diagnostic predictor of extremity compartment syndrome. To date, researchers have largely focused on intracompartmental pressure as a diagnostic tool for compartment syndrome. Both animal and clinical studies have suggested that compartment syndrome develops when the intracompartmental pressure approaches systemic diastolic blood pressure.[3,4] However, other studies have demonstrated that high absolute compartment pressures and/or narrowed delta pressures have poor sensitivity for predicting compartment syndrome clinically. Currently, no consensus pressure measurement exists for diagnosing compartment syndrome. Furthermore, there have been minimal additional therapies or adjuncts for treatment of compartment syndrome developed outside of fasciotomy, the gold-standard treatment for the condition.[5] Overall, few recent advances have been made in diagnosing or treating compartment syndrome, again highlighting the need for a more thorough understanding of the cellular mechanisms driving its development to improve clinical treatment of the condition. In line with this opinion, a recent clinical practice

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summary identified major gaps in the current understanding of compartment syndrome and highlighted the need for better research.

Given its rarity and the diagnostic challenges associated with extremity compartment syndrome in humans, animal models provide an attractive option for advancing our understanding of the condition. Currently, no standardized, clinically relevant animal model of extremity compartment syndrome exists.[1] The purpose of this review was to identify existing animal research on extremity compartment syndrome to summarize the current state of the literature and identify weaknesses that could be improved with additional research.

2. Methods

A MEDLINE (PubMed) search of the literature was performed from inception to June 2021. The following search strategy was used to generate citations for manual review: "disease models, animal" OR "animal models" AND "compartment syndrome" NOT "abdominal compartment syndrome" NOT "chronic disease." Abstracts of the electronic search results were reviewed by 2 reviewers (DCO, CM) and included in the review if the study was confirmed to be an animal model of acute extremity compartment syndrome after full-text manuscript review. Review articles, human studies, animal models that did not involve extremity compartment syndrome, cadaveric studies, editorials, and chronic compartment syndrome research were excluded. Publications without full-text articles available electronically were also excluded from the review.

Inclusion of studies was by consensus. If there was a discrepancy between reviewers, a third reviewer (JMH) was consulted to make the final determination. To supplement the electronic database search, a reverse inclusion protocol was performed. A single author (DCO) evaluated the references of publications included from database search to identify additional relevant publications. In addition, review articles identified by the database search were manually evaluated. For included studies, data were abstracted by three of the study authors (DCO, EB, CM) into Excel (Microsoft, Redmond, Washington). Abstracted data was available to all authors during study creation for creation of tables and manuscript preparation.

3. Results

The database search identified 71 unique publications. Thirty-eight articles were excluded during initial review of abstracts. Reasons for exclusion included: animal models that did not involve acute extremity compartment syndrome (n=23), human studies (n=7), cadaveric studies (n=3), review articles (n=2), publication in language other than English (n=2), and editorial (n=1). One article that was included from abstract review was excluded due to lack of availability of an electronic full-text publication. Thus, 32 articles were included from the initial database source. The reverse inclusion protocol identified 11 additional publications that met inclusion criteria. Of these, 9 publications were included in the final review. Two studies were excluded due to lack of availability of an electronic full-text publication.

Forty-one studies were included in the final review (Tables 1-4).[1–41] A total of 865 animals were included with an average of 22.2 animals per study. Dogs (31.7%) were the most used model species, followed by pigs (26.8%) and rats (24.4%). In terms of the purpose of the included studies, 18 (43.9%) studies focused on the pathophysiology of compartment syndrome, 10 (24.4%) evaluated experimental diagnostic modalities, and 13 (31.7%) investigated potential treatments. Most studies used an intracompartmental infusion model (58.5%) to create compartment syndrome, though tourniquet (14.6%) and intracompartmental balloon (9.8%) models were also common. Very few models incorporated additional soft tissue (9.8%) or osseous injury (7.3%) outside of the damage created by pressurizing the extremity compartment. Only 65.9% of the reviewed studies confirmed that their model created myoneural injury similar to that of extremity compartment syndrome.

4. Discussion

4.1. Model type

There were a wide variety of model types identified in this review. Dogs, pigs, and rats were the most commonly used species. No consensus exists with respect to which species is preferable for compartment syndrome research.[1] Prior authors have noted that different species vary in their anatomic similarity to the human extremity. Kalns et al[12] suggest that the pig lower leg has inelastic fascia that is intolerant to large amounts of swelling, similar to that of humans, while the rat extremity tolerates large amounts of swelling without increases in compartment pressure. Similarly, rats have a lower ischemia tolerance than dogs or humans. Despite differences in the anatomy and/or physiology of different animals used in the study, multiple authors in this review have demonstrated similar findings using the same methodology in both rat and large animal models.[5,29,41] We could not find definitive evidence that anatomic differences associated with small animal models adversely affected compartment syndrome

Table 1

Descriptive characteristics of compartment syndrome studies included in review

Animal type (%)	
Dog	31.7 (13/41)
Pig	26.8 (11/41)
Rat	24.4 (10/41)
Rabbit	14.6 (6/41)
Multiple*	2.4 (1/41)
Number of animals	865
Mean animals per study (mean, SD)	22.2 (20.5)
Compartment syndrome model (%)	
Intracompartmental infusion	58.5 (24/41)
Tourniquet or blood pressure cuff	14.6 (6/41)
Intracompartmental balloon	9.8 (4/41)
Arterial occlusion	2.4 (1/41)
Other†	14.6 (6/41)
Study type (%)	
Pathophysiology	43.9 (18/41)
Diagnostic	24.4 (10/41)
Therapeutic	31.7 (13/41)
Studies including additional soft tissue injury (%)	9.8 (4/41)
Studies including fracture (%)	7.3 (3/41)
Studies confirming compartment syndrome-like muscle damage (%)	65.9 (27/41)

All studies were reviewed for basic model characteristics. Rats, dogs, and pigs were the most studied animals. The majority of studies used an intracompartmental infusion to generate compartment syndrome. Approximately 59% of studies were targeted at either diagnostic or therapeutic applications. Only 66% of studies confirmed the creation of compartment syndrome-like muscle damage by their model postprocedurally. Few studies investigated compartment syndrome in the setting of additional bony or soft tissue injury.

* Hansen et al (8) included both pigs and mice.

† Other study models includes studies that used fracture, multiple models, pressure chambers, circumferential burns, and a combined tourniquet and infusion model.

Table 2

Pathophysiology studies (n = 18)

Study	Animal	N	Model type	Duration CS	Reported compartment pressure	Reperfusion period	Confirmation of CS	Outcome measures	Author conclusions
Sheridan et al, 1975[6]	Rabbit	22	Intracompartmental balloon catheter	24 hours	20-150 mm Hg	24 hours	Yes, histology	Histologic analysis of muscle Fractional blood flow analysis	Elevated compartment pressure produces ischemia and resultant necrosis of skeletal muscle. Inflammatory infiltrate noted at partial perfusion (60 mm Hg) but not with absence of perfusion (70 mm Hg).
Hargens et al, 1981[7]	Dog	28	Plasma infusion	8 hours	30, 60, 100 mm Hg	40 hours	Yes, histology	Muscle necrosis (Tc stannous pyrophosphate uptake)	Significant muscle necrosis produced at a pressure as low as 30 mm Hg after an 8-hour period.
Heppenstall et al, 1986[8]	Dog	10	Thigh tourniquet vs plasma infusion	3 hours	ΔP = 0; Tourniquet = 350mm Hg	2 hours	Yes, muscle biopsy for mitochondrial / myofibrillar abnormalities	Intracellular pH ATP/ADP Phosphocreatine	Phosphocreatine levels comparable in the ischemia period but less during recovery in CS group. ADP and pH levels less in the ischemia and recovery period in CS. Increased intramitochondrial inclusions in CS.
Heppenstall et al, 1989[9]	Dog	20	Plasma infusion plus muscle contusion	6 hours	ΔP = 0,10,20,30 mm Hg	24 hours	Yes, electron microscopy	Phosphocreatine to inorganic phosphate ratio Intracellular pH	Lower delta pressures result in larger decreases in intracellular phosphocreatine ratio and pH.
Heckman et al, 1993[3]	Dog	16	Plasma infusion	8 hours	30 mm Hg; ΔP = 20, 10, and 0 mm Hg	2 weeks	Yes, histology and electron microscopy	Histology for necrosis, inflammation, edema, fibrosis and muscle regeneration	Compartment syndrome in dogs occurs at delta pressure less than 10 mm Hg.
Matava et al, 1994[4]	Dog	20	Plasma infusion	8 hours	ΔP = 0,10,20,30 mm Hg	0-14 days	Yes, histology	Histologic scoring Electron microscopy Muscle contractility	Lower ΔP associated with more muscle edema and less contractility. Histologic damage higher in groups with higher compartment pressures.
Gunal et al, 1996[10]	Dog	7	Intraosseous infusion of contrast dye	NR	>35 mm Hg	No	No	Compartment pressure, volume of infusion	Intraosseous infusion can create elevated compartment pressures which are dependent on the volume of the infusion.
Bernot et al, 1996[11]	Dog	42	Plasma infusion in postischemic vs nonischemic limbs	8 hours	ΔP = 40, 30, 20, and 10 mm Hg	No	No	Phosphocreatine to inorganic phosphate ratio	Postischemic muscle is less tolerant to elevated compartment pressures than nonischemic muscle. Recommend fasciotomy at ΔP < 40 mm Hg.
Sadasivan et al, 1997[2]	Dog	22	Pressure chamber; neutropenic vs xanthin oxidase deficient vs normal animals	2 hours	60-90 mm Hg	30 minutes	No	Myeloperoxidase activity Xanthine oxidase activity Microvascular permeability Vascular resistance	Neutropenia prevents microvascular dysfunction and neutrophilic muscle infiltrates in experimental compartment syndrome. Xanthine oxidase depletion had no effect.
Kalns et al, 2011[12]	Pig	9	Intracompartmental balloon catheter	5 and 6 hours	30 mm Hg greater than MAP	8 hours	Yes, histology	Histologic scoring ΔP during reperfusion Serum myoglobin	Spontaneous increase in compartment pressure after balloon deflation was observed in all 6-hour animals. Histologic tissue damaged increased in 6 hours injury. Serum myoglobin increased in animals with low ΔP during reperfusion period.
Kalns et al, 2011[13]	Pig	15	Intracompartmental balloon catheter	5 and 6 hours	30 mm Hg greater than MAP	8 hours at sea level vs 8 hours at altitude	Yes, histology	Histologic scoring ΔP during reperfusion Pro-inflammatory cytokine levels	Reperfusion at altitude did not increase the incidence of compartment syndrome by histology despite causing increases in some pro-inflammatory cytokine levels.
Lawendy et al, 2011[1]	Rat	10	Saline infusion	45 minutes	30-40 mm Hg	<5 minutes	Yes, EB/BB ratio	Intravital microscopy EB/BB ratio Leukocyte rolling/adherence	Early compartment syndrome characterized by microvascular dysfunction and inflammation.
Criswell et al, 2012[14]	Rat	70	Blood pressure cuff	3 hours	120-140 mm Hg	2-35 days	Yes, histology	Histologic and functional muscle recovery after CS type injury	Proposed CS model demonstrates histologic muscle, neuromuscular junction, and vascular injury compatible with clinically observed CS. Characterized regeneration process following CS.
Altay et al, 2013[15]	Rabbit	20	Open vs closed fracture	NR	Compartment pressure = outcome variable	NR	No	Intracompartmental pressure following fracture	No difference in intra-compartmental pressure between open and closed fractures. Both groups experienced increased ICP over first 24 hours and subsequent decrease from 24-48 hours.
Zhou et al, 2014[16]	Rat	113	Blood pressure cuff	3 hours	120-140 mm Hg	0-28 days	Yes, histology and functional analysis	Histology In vivo functional analysis Total RNA PCR Muscle weights	Demonstrated differences in cellular and functional muscle recovery between young, adult and aged rats, with young rats recovering most robustly.
Oyster et al, 2015[17]	Rat	40	Rubber band tourniquet and neonatal blood pressure cuff	3 hours	261 mm Hg	3-28 days	Yes, histology	ICP during reperfusion Histology CD68/CD31/DAPI/dystrophin immunohistochemistry Functional analysis	Characterized injury pattern and recovery from CS-like injury over 28 days. Injured muscles recovered 59% of strength at 28 days postinjury.
Lawendy et al, 2015[18]	Rat	50	Saline infusion in leukopenic vs normal animals	45-180 minutes	30-40 mm Hg	NR	Yes, EB/BB ratio	EB/BB ratio Leukocyte activation Capillary perfusion	CS induced muscle injury decreased in leukopenic animals vs normal controls.
Lawendy et al, 2016[19]	Rat	15	Saline infusion	2 hours	30-40 mm Hg	45 minutes	No	Liver microcirculation, leukocyte activation, cell death, and systemic TNF-alpha	Limb compartment syndrome results in systemic inflammation and injury to remote organs.

ΔP = diastolic blood pressure—compartment pressure; BB = bisbenzimide; CS = compartment syndrome; EB = ethidium bromide; ICP = intracompartmental pressure; MAP = mean arterial pressure; NR = not recorded; OxyHb = oxyhemoglobin; SBP = systolic blood pressure; VEGF = vascular endothelial growth factor.

Table 3

Therapeutic studies (n = 13)

Study	Animal	N	Model type	Duration CS	Reported compartment pressure	Reperfusion period	Confirmation of CS	Treatment	Outcome measures	Author conclusions
Strauss et al, 1983[20]	Dog	37	Plasma infusion	8 hours	30, 60, 100 mm Hg	40 hours	Yes, histology	Hyperbaric oxygen	Muscle necrosis (Tc stannous pyrophosphate uptake)	Intermittent hyperbaric oxygen exposure greatly reduced muscle necrosis at 30, 60, and 100 mm Hg.
Strauss et al, 1986[21]	Dog	18	Plasma infusion	8 hours	100 mm Hg	51 hours	Yes, histology	Immediate vs delayed hyperbaric oxygen	Histology Techneitum-99 uptake	Hyperbaric oxygen reduces muscle necrosis and edema, even when delayed 2 hours
Better et al, 1991[22]	Dog	7	Plasma infusion	1 hour	100 mm Hg	NR	Yes, histology and angiography	Intravenous mannitol (treatment) vs intravenous saline (control)	Magnitude of spontaneous decrease in ICP after 1 hour	Mannitol decreased intra-compartmental pressure by 28 mm Hg compared with normal saline
Krieger et al, 2005[23]	Pig	5	Circumferential burn	2-4 hours	Not controlled	NR	No	Enzymatic debridement vs escharotomy	ICP	Enzymatic debridement reduces intracompartmental pressures relative to fasciotomy at 4 hours
Odland et al, 2005[24]	Pig	3	Albumin infusion	8 hours	30 mm Hg > MAP	2 hours	Yes, histology	Compartment ultra-filtration	Intramuscular pressure Serum and ultrafiltrate enzyme assays Cellular dimensions, cellular injury	Ultra-filtration reduced intramuscular pressure, increased muscle perfusion, and decreased severity of cellular injury
Manjoo et al, 2010[25]	Rat	24	Saline infusion	45–90 minutes	30 mm Hg	Minimal	Yes, EB/BB ratio	Indomethacin at time of CS and 30 minutes after start of CS	EB/BB ratio Microvascular perfusion Caspase activity	Indomethacin reduced percentage of damaged cells and improved microvascular perfusion. Changes in caspase activity were not significant between groups.
Daly et al, 2011[26]	Rabbit	10	Saline infusion plus soft tissue crush injury	90 minutes	~120mm Hg	1 and 3 months	Yes, systemic CK; histologic confirmation at 7 days	Porcine small intestinal mucosa extra-cellular matrix implanted at 7 days post CS	Gross histology and immunohistochemistry at 7 days, 1 month and 3 months	Animals treated with extra-cellular matrix demonstrated myogenesis within tissue defects associated with compartment syndrome while controls did not.
Frey et al, 2012[27]	Rabbit	22	Tourniquet, muscle injury, osteotomy	90 minutes	>30mm Hg	40 days	No	Intracompartmental application of VEGF	Dorsiflexion muscle force Histology Histomorphometrics	VEGF treatment resulted in increased muscle histologically and increased dorsiflexion force relative to controls in CS model.
Wilkin et al, 2014[28]	Pig	22	Serum infusion	6 hours	10mm Hg > MAP	7 and 21 days	Yes, histology	Wet to dry vs wound vacuum dressing for 7 days	Histology Muscle weight	Wound vacuum treatment resulted in decreased amount of normal muscle fibers at 7 and 21 days post-CS relative to wet to dry dressing
Lawendy et al, 2014[29]	Rat	16	Saline infusion	2 hours	30 mm Hg	45 minutes	Yes, EB/BB ratio	Novel carbon monoxide releasing molecule	Systemic leukocyte count, capillary perfusion, TNF alpha, tissue injury (EB/BB ratio)	Elevated ICP resulted in microvascular perfusion deficits, increased tissue injury and leukocyte count, and progressive rise in systemic TNF alpha which were decreased by administration of carbon monoxide releasing molecule
Erturk et al, 2017[30]	Rabbit	20	Fracture	NR	Not controlled	NR	No	Intramedullary fixation vs external circular fixator	ICP Fracture union	ICP was higher in the intramedullary fixation group compared with the external fixator group at 30, 36 and 42 hours postoperatively. No differences in fracture union between groups.
Bihari et al, 2018[5]	Pig	12	Saline infusion	6 hours	40-65 mm Hg	3 hours	Yes, EB/BB ratio	Novel carbon monoxide releasing molecule	Systemic leukocyte count, capillary perfusion, TNF alpha, tissue injury (EB/BB ratio)	Confirmed findings of Lawendy et al, 2014[29] in a porcine model of compartment syndrome
Yosef et al, 2020[31]	Rat	NR	Blood pressure cuff	3 hours	120-140 mm Hg	4-28 days	Yes, histology and functional analysis	N-Acetyl L-cysteine (treatment) vs phosphate buffered saline (control)	In vivo muscle function Histologic evaluation of muscle reactive oxygenation species, fibrosis, vascularization and regeneration	Treatment with N-Acetyl L-cysteine improved muscle function and decreased fibrosis relative to controls at 28 days postinjury

ΔP = diastolic blood pressure—compartment pressure; BB = bisbenzimide; CS = compartment syndrome; EB = ethidium bromide; ICP = intracompartmental pressure; MAP = mean arterial pressure; NR = not recorded; OxyHb = oxyhemoglobin; SBP = systolic blood pressure; VEGF = vascular endothelial growth factor.

Table 4

Diagnostic studies (n = 10)

Study	Animal	N	Model type	Duration CS	Reported compartment pressure	Reperfusion period	Confirmation of CS	Diagnostic Modality	Outcome measures	Author conclusions
Garr et al, 1999[32]	Pig	9	Albumin infusion	20 minutes past loss of muscle twitch	10-40 mm Hg	10 minutes	No	Near-infrared spectroscopy	OxyHb saturation Perfusion pressure (PP) Muscle twitch	Animals lost dorsiflexion at mean ICP 43.1 mm Hg, PP 13.6 mm Hg, OxyHb sat 19.8%. Inverse correlation between ICP and OxyHb saturation. OxyHb saturation was a more consistent predictor of twitch loss than PP.
Garabekyan et al, 2009[33]	Pig	7	Albumin infusion	NR	0-100 mm Hg	NR	No	Ultrasound measurement of fascial displacement	Correlation of fascial displacement measured on ultrasound with ICP	Fascial displacement as measured by ultrasound is greater in CS than in controls over clinically relevant elevations in ICP
Doro et al, 2014[34]	Dog	12	Lactated Ringers Infusion	8 hours	74 mm Hg	14 days	Yes, histology	Intramuscular glucose concentration	Intramuscular glucose Partial pressure of oxygen Histology	Intramuscular glucose can identify muscle ischemia rapidly in CS
Cathcart et al, 2014[35]	Pig	31	Infusion vsBlunt trauma plus infusion	70 minutes	ΔP = 40, 30, 20, 10, 0; ICP = MAP, ICP = SBP, ICP = SBP+10	10 minutes	No	Near infrared spectroscopy (NIRS)	NIRS value (% oxygenation) Intra-compartmental perfusion pressure	NIRS detected decreased oxygenation at every TIPP decrease and detected increased oxygenation after fasciotomy
Tian et al, 2016[36]	Rabbit	20	Tourniquet	2 hours	Not controlled	NR	No	Invasive arterial blood pressure monitoring system	Correlation of ICP reading between study monitor and Whiteside's apparatus	Sufficient agreement between study monitoring system and Whiteside's apparatus to allow for study monitoring system use clinically
Budsberg et al, 2016[37]	Pig	6	Intracompartmental balloon catheter	6 hours	30 mm Hg > MAP	8 hours	Yes, histology	Near-infrared spectroscopy, serum biomarkers	Near-infrared spectroscopy, serum biomarkers, histologic scoring	Near-infrared spectroscopy is a reliable predictor of intracompartmental perfusion pressure. Serum myoglobin and creatine kinase increase predictably following fasciotomy. Pro-inflammatory cytokines did not increase after fasciotomy.
Weick et al, 2016[38]	Dog	15	Thigh tourniquet vs infusion	0-8 hours	Tourniquet = 300mm Hg; CS from ΔP > 20 to ΔP = < 0	NR	No	Polarographic tissue oxygen electrode	Muscle oxygenation (PmO2); ICP	Suggest tissue oxygen electrode is a viable tool for measuring real time muscle oxygenation in setting of CS.
Martinez et al, 2017[39]	Rat	15	Iliac artery clamp	0.5-6 hours	NR	4 days	Yes, histology*	Phonomyography	Phonomyography vs ischemia time Nerve and muscle histology	Phonomyographic output decreases in response to ischemia compared with controls from 30 minutes to 4 hours of ischemia. No statistical difference between groups at 6 hours.
Bloch et al, 2018[40]	Pig	3	Blood infusion	NR	0-40 mm Hg	NR	No	Compression sonography	Sonography vs invasively measured compartment pressure	Compression sonography may have utility as noninvasive diagnostic modality for CS
Hansen et al, 2021[41]	Multiple	7	Tourniquet or arterial ligation	60-160 minutes	Not controlled	NR	No	Hemodynamic detection device	Doppler ultrasound ICP Hemodynamic detection device	Hemodynamic detection device correlated well with compartment pressures and doppler ultrasound. Hemodynamic detection device may be useful in diagnosing CS noninvasively.

ΔP = diastolic blood pressure—compartment pressure; BB = bisbenzimide; CS = compartment syndrome; EB = ethidium bromide; ICP = intracompartmental pressure; MAP = mean arterial pressure; NR = not recorded; OxyHb = oxyhemoglobin; SBP = systolic blood pressure; VEGF = vascular endothelial growth factor.

* Not all animals in study developed muscle damage consistent with compartment syndrome suggesting inconsistent model.

research outcomes. While large animals may provide better anatomic similarity relative to humans, they are associated with significant additional research cost and it is our opinion that authors must weigh the benefits of anatomic similarity with their over-arching research goals when selecting a species.

With respect to the means of generating compartment syndrome, most included publications used an intracompartmental infusion technique. Other relatively common methods were ischemia-reperfusion using a thigh tourniquet or blood pressure cuff, direct external compression of the studied compartment using a tourniquet or blood pressure cuff, and intracompartmental balloon placement. Both intracompartmental infusion and balloon models have the advantage of creating pressure directly within the compartment to be studied. Conversely, both types of tourniquet model rely on creating ischemia from an external source. We did not find definitive evidence to suggest superiority of any model for compartment syndrome generation in this review, as different models of generating compartment syndrome were rarely compared. Only one study directly compared intracompartmental infusion vs thigh tourniquet for generating compartment syndrome. This study suggested that the 2 models have similar metabolic profiles during ischemia but that metabolic injury is more persistent during reperfusion in an infusion model compared with a thigh tourniquet.[8] Beyond the fact that few models have been directly compared, over one-third of studies did not demonstrate that their compartment syndrome model reproduced cellular level and/or functional findings consistent with extremity compartment syndrome. Based on limited available data, it is our opinion that intracompartmental techniques, such as infusion or balloon catheter models, more specifically mimic extremity compartment syndrome relative to tourniquet-based techniques, which could represent any type of ischemia-reperfusion injury. Furthermore, we would recommend that future research confirm creation of compartment syndrome-like injury as a means of strengthening the veracity of future study conclusions.

Perhaps the most striking finding of the current review is the rarity of soft tissue or osseous injury adjuncts to the above-mentioned means of generating increased compartment pressure. Fracture (and associated soft tissue injury) is the most common cause of extremity compartment syndrome. However, only 3 (7.3%) studies included in the review involved fracture.[15,27,30] Of those, only 1 publication studied a combination of fracture (simulated by osteotomy) and elevated compartment pressures using a thigh tourniquet.[27] Similarly, only 4 studies included in the review involved additional soft tissue injury outside of the model used to generate elevated compartment pressures.[9,26,27,35] Minimal data exists regarding the influence of soft tissue or bony injury on the cellular level mechanisms driving compartment syndrome. Daly et al[26] tested compartment syndrome models that included infusion alone, soft tissue injury alone, and infusion plus soft tissue injury. In pilot testing, they state that the combination of soft tissue injury and infusion most reliably produced histologic findings consistent with extremity compartment syndrome, though their pilot results were not published for review.[26] Bernot et al[11] demonstrated that prior ischemia rendered skeletal muscle less tolerant to elevated compartment pressures. Past research demonstrating important pathophysiologic roles for both inflammation and microvascular dysfunction in extremity compartment syndrome models would further suggest that additional sources of injury may contribute to the overall pathophysiology of the condition.[1,2,5,14,18,29] To date, insufficient animal research has been performed to characterize the relationship between external injury and elevated compartment pressure. As such, we would highlight this area as having high potential for future research.

4.2. Compartment pressure

Studies identified by the review reported a wide range of intracompartmental pressure (0 to > 100 mm Hg). Many studies used compartment pressures based on absolute values between 30 and 60 mm Hg or delta pressures approaching 0 mm Hg, both of which are similar to clinical criteria for pressure-based diagnosis of compartment syndrome in humans. However, the range of pressures identified by the review is far outside the typical range seen in clinical compartment syndrome. It is rare that human compartment pressures exceed 50 mm Hg clinically and, even in documented cases of compartment syndrome, reported absolute compartment pressures range from 45 to 75 mm Hg. The ideal compartment pressure for animal models of compartment syndrome is unknown. Despite a significant amount of early research into the effects of intracompartmental pressure on muscle tissue, Heckman et al[3] noted that methodologic variations across animal models of compartment syndrome have resulted in lack of consensus in recommended pressure thresholds. Prior animal research has demonstrated that the nature of muscle injury varies as intracompartmental pressure rises. In fact, the earliest publication identified in the review demonstrated that inflammatory necrosis was observed at lower compartment pressures while ischemic necrosis predominated at compartment pressures from 70 to 150 mm Hg.[6] Based on this finding, many included studies modeled levels of intracompartmental pressure that may result in different pathophysiology and cellular injury pattern than is observed in clinical compartment syndrome, though this hypothesis has not been rigorously tested in recent research. More research is needed to fully characterize pathophysiologic changes at varying levels of elevated intracompartmental pressure. When designing future work, authors should be thoughtful when choosing compartment pressures, balancing the need for a reproducible model with an understanding of the level of intracompartmental pressure typically observed in clinical practice.

4.3. Pathophysiology

Eighteen studies investigating the pathophysiology of compartment syndrome were identified by the review. Earlier studies focused on identifying pressure thresholds for ischemic injury in muscle.[3,4,6–9] More recent studies have employed a variety of study designs. Several authors demonstrated the role of inflammation and/microvascular dysfunction in compartment syndrome development.[1,2,18,19] Two publications compared the effect of different durations of elevated compartment pressures on skeletal muscle injury.[12,13] Three studies characterized the timeline of injury and recovery in compartment syndrome over several weeks.[12,16,17] Finally, 1 study demonstrated that open and closed fractures have similar intracompartmental pressures from 0 to 48 hours postinjury.[15]

Based on the results of the review, we have identified several areas for future research. First, as discussed above, there has been minimal research into the interaction of elevated compartment pressure with other modes of soft tissue or osseous injury. It is likely that the initial traumatic insult contributes to the pathophysiology of extremity compartment syndrome, particularly with respect to promoting inflammation and microvascular injury. However, the

exact mechanisms underlying this interaction have not been characterized. Second, there are few studies using immunohistochemistry or gene expression analyses to further characterize pathways of dysfunction in compartment syndrome. This is likely because most of the pathophysiology studies identified by the review were published over 10 years ago. Only 7 of the 18 studies were published since 2011 and only 1 of the 18 studies has been published within the last 5 years. We believe that more sophisticated cellular and genetic level analyses could further advance our understanding of compartment syndrome pathophysiology. Third, no recovery model following compartment syndrome using an intracompartmental infusion technique at clinically relevant compartment pressures currently exists. While prior publications have characterized the cellular level injury and healing process following a compartment syndrome-type injury, these models involved tourniquets for the initiation of compartment syndrome. Recharacterizing injury and recovery patterns in a more clinically relevant animal model using direct, intracompartmental pressure may provide more useful information for treating extremity compartment syndrome secondary to fracture or crush injury.

4.4. Therapeutics

The review identified 13 therapeutic studies (Table 3). These studies covered a wide array of potential therapeutics over several decades. No single therapeutic appeared in more than 2 studies. While the conclusions of most studies identified in the review were generally positive, no single therapeutic intervention was widely studied by multiple groups. Overall, the research on therapeutic treatment options outside of fasciotomy is limited. It is possible that improving our understanding of the pathophysiology of compartment syndrome may lead to new, more promising therapeutic targets for animal research.

4.5. Diagnostics

Ten diagnostic studies were included in the review. Three studies measured noninvasive or alternative means of measuring intracompartmental pressure.[33,35,37] However, prior research has demonstrated consistently poor diagnostic accuracy of compartment pressure measurements for detecting compartment syndrome in the clinical setting. As all these studies use correlation with intracompartmental pressure as their validation metric, it is unclear whether any of these diagnostic tools can provide additional utility toward compartment syndrome diagnosis in the clinical setting. Three studies evaluated near-infrared spectroscopy with promising results.[32,35,37] Unfortunately, since that time, a large multicenter study demonstrated that near-infrared spectroscopy was difficult to reliably utilize clinically. Other studies used methods of directly measuring tissue oxygenation and/or glucose, again with promising results.[34,38,39,41] However, these modalities have not been widely adopted clinically. Overall, no animal model for diagnosis identified in the review outside of intracompartmental pressure monitoring has been successfully translated to clinical use.

5. Conclusions

Study purpose, methodology, and outcome measures varied widely across included studies. A standard definition for animal compartment syndrome would direct more consistent research in this field. Additional research is needed to further our understanding of the pathophysiology of compartment syndrome. Few animal models have investigated the pathophysiologic relationship between traumatic injury and the development of compartment syndrome. Once a clinically relevant animal model of extremity compartment syndrome has been developed and validated, researchers can move toward developing better diagnostic tests and therapeutic interventions to better mitigate compartment syndrome development.

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