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 intra-compartmental 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
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. 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). 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. Prior authors have noted that different species vary in their anatomic similarity to the human extremity. Kalns et al12 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. 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 | 2.2 (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 | 2.2 (1/41) |
| Other† | 2.2 (1/41) |
| 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 postprocedure. 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 | Reperpusion 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 | 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). Significant muscle necrosis produced at a pressure as low as 30 mm Hg after an 8-hour period. Phosphoacetate levels comparable in ischemia period but less during recovery in CS group. ADP and pH levels less in ischemia and recovery period. Increased intracompartmental inclusions in CS. |
| Hargens et al, 1981[7] | Dog | 28 | Plasma infusion | 8 hours | 30, 60, 100 mm Hg | 40 hours | Yes, histology | Muscle necrosis (Tc stannous phosphate uptake) | Lower P associated with more muscle edema and less contractility. Histologic damage higher in groups with higher compartment pressures. Intraosseous infusion can create elevated compartment pressures which are dependent on the volume of the infusion. Postischemic muscle is less tolerant to elevated compartment pressures than nonischemic muscle. Recommend fasciectomy at P < 40 mm Hg. Neutropenia prevents microvascular dysfunction and neutrophil muscle infiltrates in experimental compartment syndrome. Xanthine oxidase depletion had no effect. |
| Heppenstall et al, 1986[8] | Dog | 10 | Thigh tourniquet vs plasma infusion | 3 hours | ΔP = 0; Tourniquet = 250 mm Hg | 2 hours | Yes, muscle biopsy for mitochondrial / myofibrillar abnormalities | Histology for necrosis, inflammation, edema, fibrosis and muscle regeneration | Compartment syndrome in dogs occurs at ΔP less than 10 mm Hg. |
| 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 | Phosphoacetate to inorganic phosphate ratio Intracellular pH | Lower ΔP associated with more muscle edema and less contractility. Histologic damage higher in groups with higher compartment pressures. |
| Matava et al, 1994[10] | Dog | 20 | Plasma infusion | 8 hours | ΔP = 0.10,20,30 mm Hg | 0-14 days | Yes, histology and electron microscopy | Histologic scoring ΔP during reperfusion Muscle contractility | Histologic damage in animals with low ΔP | |
| Gual et al, 1996[11] | Dog | 7 | Intravenous infusion of contrast dye | NR | >35 mm Hg | No | No | No | No | |
| Bernot et al, 1996[12] | Dog | 42 | Plasma infusion in postischemic vs nonischemic limbs | 8 hours | ΔP = 40, 30, 20, and 10 mm Hg | No | No | No | Lower P associated with more muscle edema and less contractility. Histologic damage higher in groups with higher compartment pressures. |
| Saddawian et al, 1999[13] | Dog | 22 | Pressure chamber; neutropenic vs xanthine oxidase deficient vs normal animals | 2 hours | 60-90 mm Hg | 30 minutes | No | Myeloperoxidase activity Xanthine oxidase activity Microvascular permeability Vascular resistance | Intraosseous infusion can create elevated compartment pressures which are dependent on the volume of the infusion. Postischemic muscle is less tolerant to elevated compartment pressures than nonischemic muscle. Recommend fasciectomy at P < 40 mm Hg. Neutropenia prevents microvascular dysfunction and neutrophil muscle infiltrates in experimental compartment syndrome. Xanthine oxidase depletion had no effect. |
| Kahs et al, 2011[14] | 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 diffusion 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. |
| Kahs et al, 2011[14] | 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 Intraosseous microscopy EB/BB ratio Leukocyte rolling/adherence | Reperpusion at altitude did not increase the incidence of compartment syndrome by histology despite causing increases in pro-inflammatory cytokine levels. Early compartment syndrome characterized by microvascular dysfunction and inflammation. |
| Lawendy et al, 2011[15] | Rat | 10 | Saline infusion | 45 minutes | 30-40 mm Hg | <5 minutes | Yes, EB/BB ratio | 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. |
| Orsini et al, 2012[16] | Rat | 70 | Blood pressure cuff | 3 hours | 120-140 mm Hg | 2-35 days | Yes, EB/BB ratio | Leukocyte rolling/adherence | Early compartment syndrome characterized by microvascular dysfunction and inflammation. |
| Alpay et al, 2013[17] | Rabbit | 20 | Open vs closed fracture | NR | Compartment pressure-outcome variable | NR | No | No | 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. Demonstrated differences in cellular and functional muscle recovery between young, adult and aged rats, with young rats recovering most robustly. |
| Zhou et al, 2014[18] | Rat | 113 | Blood pressure cuff | 3 hours | 120-140 mm Hg | 0-28 days | Yes, histology and functional analysis | Total RNA:PRO Muscle weights 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 50% of strength at 28 days postinjury. |
| Cryer et al, 2015[19] | Rat | 40 | Rubber band tourniquet and nebulal blood pressure cuff | 3 hours | 261 mm Hg | 3-28 days | Yes, histology | Histology and functional analysis | Characterized injury pattern and recovery from CS-like injury over 28 days. Injured muscles recovered 50% of strength at 28 days postinjury. |
| Lawendy et al, 2015[20] | Rat | 50 | Saline infusion in leukopenic vs normal animals | 45-180 minutes | 30-40 mm Hg | NR | Yes, EB/BB ratio | Leukocyte activation | CS induced muscle injury decreased in leukopenic animals vs normal controls. |
| Lawendy et al, 2015[21] | Rat | 15 | Saline infusion | 2 hours | 30-40 mm Hg | 45 minutes | No | Leukocyte activation Capillary perfusion Liver microcirculation, leukocyte activation, cell death, and systemic TNF-alpha | CS induced muscle injury decreased in leukopenic animals vs normal controls. |

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.
| Study            | Animal | N  | Model type                      | Duration CS | Reparfusion pressure | 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                                                           | 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 hyperbaric oxygen                                                   | Hyperbaric oxygen reduces muscle necrosis and edema, even when delayed diagnosis by 2 hours |
| Betor et al, 1991[22] | Dog    | 7  | Plasma infusion                 | 1 hour      | 100 mm Hg            | NR                 | Yes, histology and angiography                                             | Intravenous saline (control)                                                 | 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   | NR                   | NR                 | Enzymatic debridement vs escharotomy                                       | IOP                                                                             | Enzymatic debridement reduces intra-compartmental pressures relative to fasciotomy at 4 hours |
| Olnd et al, 2005[24] | Pig    | 3  | Albumin infusion                | 8 hours     | 30 mm Hg > MAP       | 2 hours            | Yes, histology                                                             | Intravenous mannitol                                                        | Ultrafiltration reduced 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                  | 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 | ~120 mm Hg           | 1 and 3 months      | Yes, systemic OK; histologic confirmation at 7 days                         | Gross histology and immunohistochemistry at 7 days, 1 month and 3 months      | Animals treated with extracellular 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 | >30 mm Hg            | 40 days            | No                                                                           | Intracompartmental application of VEGF                                       | VEGF treatment resulted in increased muscle histologically and increased donoflonic force relative to control in CS model. |
| Wilkin et al, 2014[28] | Pig    | 22 | Serum infusion                  | 6 hours     | 10 mm Hg > MAP       | 7 and 21 days       | Yes, 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. |
| Lavender et al, 2014[29] | Rat    | 16 | Saline infusion                 | 2 hours     | 30 mm Hg            | 45 minutes          | Yes, EB/BB ratio                                                          | Novel carbon monoxide releasing molecule                                    | 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                         | IOP                                                                     | IOP 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. |
| Bhai et al, 2018[31] | Pig    | 12 | Saline infusion                 | 6 hours     | 40-65 mm Hg          | 3 hours            | Yes, EB/BB ratio                                                          | Novel carbon monoxide releasing molecule                                    | Confirmed findings of Lawender et al, 2014[29] in a porcine model of compartment syndrome. Treatment with N-Acetyl L-cysteine improved muscle function and decreased fibrosis relative to controls at 28 days postIjury. |
| Yosef et al, 2020[32] | 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)      | VEGF = vascular endothelial growth factor. |
| 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 dorsi flexion 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. Intra muscular glucose can identify muscle ischemia rapidly in CS. |
| 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                       | NIRS detected decreased oxygenation at every TIP decrease and detected increased oxygenation after fasciotomy. |
| Calhoun et al, 2014[35]     | Pig    | 31   | Infusion w/Blunt trauma plus infusion | 70 minutes  | \(\Delta P = 40, 30, 20, 10, 0; ICP = MAP, ICP = SBP, ICP = SBP + 10\) | 10 minutes        | No                 | Near infrared spectroscopy (NIRS) | Intra-compartmental perfusion pressure | Sufficient agreement between study monitoring system and Whiteside's apparatus to allow for study monitoring system use clinically. |
| 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 | 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. |
| 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 | Suggest tissue oxygen electrode is a valuable tool for measuring real time muscle oxygenation in setting of CS: Phonomography 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. |
| Weick et al, 2016[38]       | Dog    | 15   | Thigh tourniquet vs infusion | 0-8 hours   | Tourniquet = 300 mm Hg; CS from \(\Delta P = 20\) to \(\Delta P = < 0\) | NR                | No                 | Polarographic tissue oxygen electrode | Muscle oxygenation (Pm20), ICP | Compression sonography may have utility as a noninvasive diagnostic modality for CS: Hemodynamic detection device correlated well with compartment pressures and doppler ultrasound. Hemodynamic detection device may be useful in diagnosing CS noninvasively. |
| Martinez et al, 2017[39]    | Rat    | 15   | Iliac artery clamp          | 0.5-6 hours | NR                                          | 4 days            | Yes, histology     | Phonometry                            | Phonometry vs ischemia time, Nerve and muscle histology                     | Compression sonography may have utility as a noninvasive diagnostic modality for CS: Hemodynamic detection device correlated well with compartment pressures and doppler ultrasound. Hemodynamic detection device may be useful in diagnosing CS noninvasively. |
| Bloch et al, 2018[40]       | Pig    | 3    | Blood infusion              | NR          | 0-40 mm Hg                                 | NR                | No                 | Compression sonography                | Sonography vs invasively measured compartment pressure | |
| 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 | |

\(\Delta P = \text{diastolic blood pressure} - \text{compartment pressure}; \text{BB} = \text{bisbenzimide}; \text{CS} = \text{compartment syndrome}; \text{EB} = \text{ethidium bromide}; \text{ICP} = \text{intracompartmental pressure}; \text{MAP} = \text{mean arterial pressure}; \text{NR} = \text{not recorded}; \text{OxyHb} = \text{oxyhemoglobin}; \text{SBP} = \text{systolic blood pressure}; \text{VEGF} = \text{vascular endothelial growth factor}. \)

\(^*\) 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 overarching 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 al26 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 al11 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 pathophysiologic 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 al19 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 pathophysiologic 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. 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. 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. 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 pathophysiology 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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