JAMA Surgery | Review

Diagnostic Modalities for Acute Compartment Syndrome of the Extremities
A Systematic Review

Sharri J. Mortensen, MD; Molly M. Vora, BSc; Amin Mohamadi, MD, MPH; Casey L. Wright, BA; Philip Hanna, MD; Aron Lechtig, MD; Jonathan Egan, MEng; Patrick M. Williamson, BSc; John J. Wixted, MD; Seward B. Rutkove, MD; Ara Nazarian, PhD

IMPORTANCE Acute compartment syndrome (ACS) can cause catastrophic tissue damage leading to permanent muscle and nerve loss. Acute compartment syndrome is a clinical diagnosis, with intracompartmental pressure (ICP) used in equivocal cases. There are no reliable diagnostic methods. The clinical evaluation is impossible to standardize, and the threshold for ICP has been known to be unreliable; thus, guidelines for diagnosis can result in overtreatment or delayed diagnosis.

OBJECTIVE To present and review the advantages and disadvantages of each diagnostic modality and identify gaps that need to be addressed in the future and to review the most used and appropriate animal and human ACS models.

EVIDENCE REVIEW We included clinical studies and animal models investigating diagnostic modalities for ACS of the extremities. A MEDLINE and Web of Science search was performed. The protocol for the study was registered on PROSPERO (CRD42017079266). We assessed the quality of the clinical studies with Newcastle-Ottawa scale and reported level of evidence for each article.

FINDINGS Fifty-one articles were included in this study, reporting on 38 noninvasive and 35 invasive modalities. Near-infrared spectroscopy and direct ICP measurement using a Stryker device were the most common, respectively. Cadaveric studies used saline infusions to create an ACS model. Most studies with human participants included injured patients with acquired ACS or at risk of developing ACS. In healthy human participants, tourniquets formed the most commonly used ACS model. Application of tourniquets and infusion of saline or albumin were the most used ACS models among animal studies.

CONCLUSIONS AND RELEVANCE This article reports on the most common as well as many new and modified diagnostic modalities, which can serve as inspiration for future investigations to develop more effective and efficient diagnostic techniques for ACS. Future studies on diagnostic modalities should include the development of tools for continuous assessment of ICP to better identify the earliest alterations suggestive of impending ACS. With the advent of such technologies, it may be possible to develop far less aggressive and more effective approaches for early detection of ACS.

JAMA Surg. doi:10.1001/jamasurg.2019.1050
Published online May 1, 2019.

Author Affiliations: Center for Advanced Orthopaedic Studies, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts (Mortensen, Vora, Mohamadi, Wright, Hanna, Lechtig, Egan, Williamson, Nazarian); Carl J. Shapiro Department of Orthopaedic Surgery, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts (Wixted); Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts (Rutkove); Department of Orthopaedic Surgery, Yerevan State Medical University, Yerevan, Armenia (Nazarian).

Corresponding Author: Ara Nazarian, PhD, Center for Advanced Orthopaedic Studies, 330 Brookline Ave, RN115, Boston, MA 02215 (anazaria@bidmc.harvard.edu).

Acute compartment syndrome (ACS) is a devastating musculoskeletal disorder in clinical practice. The mean incidence is estimated to be 3.1 per 100 000 people per year, with a strong male predominance of 7.3 per 100 000 men compared with 0.7 per 100 000 women.[1] Acute compartment syndrome typically occurs in trauma settings; it occurs in 1% to 9% of lower extremity fractures, with severe limb contusion, limb ischemia, revascularization after arterial obstruction, and burn among other common causes. Increased pressure within a muscle compartment leading to reduced capillary blood flow is commonly recognized as the main mechanism behind development of ACS.[1] In addition, the accumulation of waste products along with the lack of oxygenated blood can result in nerve irritation and severe pain. Acute compartment syndrome initially presents as intense pain that appears to be out of proportion to the severity of the injury.[2] Patients may have palpable tightness, progressive paresthesia, and increased pain on passive stretch. The diagnosis of ACS is largely based on clinical assessment, with intracompartmental pressure (ICP) measurements as supportive data in equivocal cases. The most common clinical approach to treating high-risk patients is serial clinical examination and close monitoring of patients at high risk. The major downside of relying on clinical features only is that by the time all symptoms have developed, the limb may already have had severe, sometimes irreversible, tissue damage. The most reliable symptoms that have been identified are increasing pain and pain on passive stretching of the muscle within the affected compartment.[3] However, these symptoms are subjective, rely heavily on clinical expertise, and are impossible to standardize. This is especially true in patients who are either unconscious, sedated, noncooperative, or those with a regional block or any inadequate analgesia.

The standard modality to measure ICP is via insertion of a pressure monitor device into the muscle compartment. The most commonly used device is produced by Stryker (Stryker Surgical). High ICP pressures can cause irreversible tissue necrosis within 6 to 10 hours and therefore demand acute surgical treatment.[4] While this modality can be useful when applied by trained physicians, it is highly user dependent, and an absolute compartment pressure with the current threshold of 30 mm Hg is not universally accepted.

The goal of this systematic review is to identify the existing modalities for diagnosing ACS, review the advantages and disadvantages of each modality, and identify gaps that need to be addressed. Furthermore, the article aims to review the different animal and human models of ACS that can be used to help develop improved diagnostic methods.

Key Points

Question What are the existing diagnostic modalities and research models for acute compartment syndrome (ACS)?

Findings In this systematic review of 51 studies, near-infrared spectroscopy and direct intracompartmental pressure measurement using a Stryker device were the most commonly used methods, but all modalities lacked a reliable threshold. Of the most commonly used models, cadaveric studies used saline infusions; most studies with human patients included injured patients with acquired ACS or at risk of developing ACS; in healthy human patients, tourniquets formed the most commonly used ACS model; and application of tourniquets and infusion of saline or albumin among animal studies.

Meaning Future studies on diagnostic modalities should include continuous assessment tools to better identify the earliest signs of ACS and thereby establish a reliable threshold.

Methods

A MEDLINE (PubMed) search of the English literature extending from inception to September 2017 was performed using the following search strategy: ("Diagnosis"[Mesh] OR "diagnosis"[Subheading] OR "Diagnosis, Computer-Assisted"[Mesh] OR "Ultrasonography"[Mesh] OR "diagnostic imaging"[Subheading]) OR ("Pressure"[Mesh] OR "Transducers, Pressure"[Mesh]) AND ("Humans"[Mesh] OR "Disease Models, Animal"[Mesh]) AND "Compartment Syndromes"[Mesh] AND English[lang] NOT "Intra-Abdominal Hypertension"[Mesh] NOT "Chronic Disease"[Mesh] NOT "Treatment Outcome"[Mesh]. The MEDLINE search strategy later was adopted for searching Web of Science. Moreover, the references of included studies as well as previous reviews[2,5] were manually searched to identify articles that did not appear in the original search. However, no additional studies were identified through cross-reference checking. The protocol of this systematic review was registered prior to data collection at the PROSPERO register (CRD42017079266). The institutional review board at Beth Israel Deaconess Medical Center waived approval from this study because the data collection was previous studies in which informed consent has already been obtained by the trial investigators.

All studies involving human, animal, and cadaveric models, evaluating ACS of extremities and published in the English language, were included. Exclusion criteria were chronic compartment syndrome, noncompartment syndrome models, ex vivo studies, not original studies, or studies not published in full text. Of the 2601 studies, 51 articles were included in this review (**Figure 1**). Two independent reviews (A.M. and M.M.V.) performed all screening, and data abstraction were done by 3 authors (S.J.M., M.M.V., C.L.W.) and independently verified by a fourth one (A.M.). Two independent reviewers (S.J.M. and A.M.) graded the level of evidence of each article based on Oxford Centre for Evidence-Based Medicine evaluation,[6] and methodologic quality of the clinical studies were assessed using Newcastle-Ottawa Scale.[7]

Results

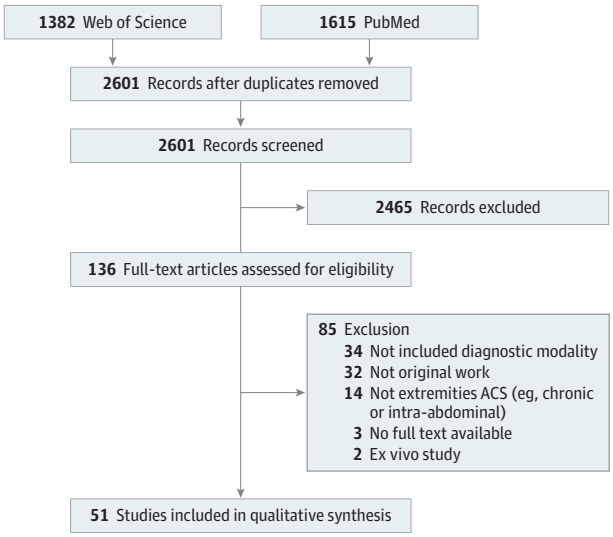
Characteristics

Fifty-one articles were included, dating from 1975 to 2017. The final articles included 33 clinical studies and 1 with both human participants and rabbit subjects (**Table 1**).[8-41] Furthermore, 15 animal models and 2 cadaveric studies were included in this review (**Table 2**).[42-58] This study includes 852 human participants and 319 animals, out of which there were 27 dogs (specifically beagles), 53 pigs, 118 rabbits, and 121 rats. Thirty articles included a control group or control contralateral extremity.

Diagnostic Modalities

We found 38 noninvasive modalities, of which near-infrared spectroscopy (NIRS) was the most common (n = 12). Of the 35 invasive

Figure 1. PRISMA Flow Diagram



ACS indicates acute compartment syndrome.

modalities included, direct ICP measurement using a Stryker device was the most commonly used approach (n = 8). Other invasive modalities included the Whiteside method (n = 7), slit catheter (n = 2), and invasive arterial blood pressure monitoring (n = 3). Some studies did not fully define their modalities and stated an ICP measurement technique without further clarification. Of other noninvasive modalities, the studies included ultrasonic pulsed phase locked loop (PPLL; n = 5), magnetic resonance imaging (n = 4), computed tomography (n = 3), contrast-enhanced ultrasonography (CEUS, n = 2), and tissue hardness (n = 2), among others. Most of these modalities were shown to be able to successfully identify ACS; however, discrepancies exist for threshold and reliability in the clinical setting.

ACS Model

Among the human participant studies, 25 of 31 studies included patients with existing injuries who either acquired ACS or were at risk of developing ACS (eg, due to injury). Moreover, tourniquets appeared to be the preferred method for creating a reversible ACS model in healthy human participants. The 2 cadaveric studies used a saline infusion model to create ACS. Use of tourniquet and infusion of saline or albumin were the most commonly used ACS models in the animal studies. Other models included balloon catheter, pressure chamber, and induction of injuries. All of these models were able to successfully create an ACS model; however, some were not extensively studied and properly validated.

Discussion

To avoid irreversible tissue damage, early and appropriate diagnosis of ACS is required. Despite efforts in this field, there continues to be a need for a more reliable tool to diagnose ACS. This review highlights the diagnostic modalities available, as well as the different research models of ACS.

Human ACS Model

Most of the human studies included patients with injuries/trauma and either verified ACS, suspicion of ACS, or at risk of developing ACS. However, in healthy volunteers, the clinical studies used tourniquets or pressure cuffs to create a model of high ICP resembling that seen in ACS. Although most ACS cases are the result of trauma rather than ischemia reperfusion, an ACS model can only be simulated in humans effectively by using circumferential compression and pressure elevation. Yet it has not been properly validated, and it is unlikely that a realistic perfusion impairment in ACS can be simulated with this approach. Furthermore, not all participants can tolerate the high tourniquet pressures needed to create this model of high ICP. It is still unclear how factors, such as age, comorbidities, and individual muscle mass, affect and possibly confound the ICP. There are several essential weaknesses with a tourniquet model for simulation of ACS in humans and may potentially impose a risk of ACS to healthy volunteers. Studies using this technique should take these limitations under consideration and include an invasive direct ICP measurement to validate their models.

Animal ACS Model

Tourniquets were used frequently in the animal models alongside the infusion techniques to increase the ICP. Both animal models have been studied extensively and are therefore preferred by several investigators.[44-46,48,50,53-55,57-60] Rodent studies usually include relatively larger numbers of animals and also include the advantage of lower cost and maintenance. However, the skeletal muscle of a rat is more sensitive to ischemia than those of a dog or human.[61-63] Therefore, differences in the response to ischemia between various animal models may lead to flawed conclusions and should be taken into consideration. Furthermore, similar to the human tourniquet model of ACS, the animal models might not simulate a true perfusion impairment such as that occurring in ACS. A possible benefit of the infusion model vs the tourniquet model is that both limbs of the animal can be used for a paired analysis if needed. Release of a tourniquet results in systemic secretion of metabolites, rhabdomyolysis, and fluid shifts,[64] and may compound the systemic toxicity if bilaterally released, which should specially be taken into account when studying biomarkers for the purpose of ACS diagnostic. The infusion model allows use of bilateral limb, enabling each animal to act as its own control. Daly et al[49] reported on an animal model of ACS, which includes a combination of crush injury and increased ICP by saline infusion in rabbits.[49] While this model needs to be verified and validated, it appears to be effective because it includes an element of injury/trauma, which is the most common risk factor for developing ACS.

We included all available original studies meeting our inclusion criteria to explore different diagnostic modalities for ACS. Several modalities recur in many of the studies such as the Stryker device and NIRS. The following subsection includes the most commonly reported modalities.

Invasive Diagnostic Modalities

The Stryker ICP device is portable and relatively easy to use (**Figure 2**A). Measurements of the compartment pressure are successfully obtained as an adjunct to clinical examination, although it requires some technical learning to accurately use the device.[22] Absolute compartment pressures from 30 to 45 mm Hg have been

Table 1. Diagnostic Modalities and Acute Compartment Syndromes in Human Studies

Source	Population	Study Group, No.	Control Group, No.	Compartments Evaluated	ACS Model	Diagnostic Techniques	Level of Evidence	Newcastle-Ottawa Scale
Chambers et al,[8] 2011	Human	1	NA	Medial compartment of the foot	Nontraumatic injury	MRI; Stryker device	V	NA (case report)
Jensen et al,[9] 1986	Human	1	NA	All 4 compartments of the lower leg	Iatrogenic hematoma	CT	V	NA (case report)
Jiang et al,[10] 2016	Human	1	NA	All 4 compartments of the lower leg	Injury	MRI; CTA	V	NA (case report)
Wang et al,[11] 2016	Human	1	NA	All 4 compartments of the lower leg	Injury	CT	V	NA (case report)
Bariteau et al,[12] 2011	Human	7	NA	All 4 compartments of the lower leg	Injury	NIRS	II	5
Blick et al,[13] 1986	Human	18	180	All 4 compartments of the lower leg	Injury	Whitesides infusion technique	III	7
Boonstra et al,[14] 2012	Human	1	NA	Anterior tibial compartment	Postsurgery	Whitesides infusion technique	V	NA (case report)
De Franciscis et al,[15] 2016	Human	7	212	All 4 compartments of the lower leg	Acute ischemia owing to embolism/thrombosis	Clinical; ICP ≥30, 40-55, or ≥55 mm Hg	II	7
Geis et al,[16] 2012	Human	8	NA	Lower limb and upper extremity	Injury	CEUS	II	6
Goyal et al,[17] 2017	Human	32	NA	Deep posterior compartment of the leg	Injury	Modified Whitesides' technique	III	6
Katz et al,[18] 2008	Human	11	160	All 4 compartments of the lower leg and foot	Injury	Infrared imaging	II	8
Kenny et al,[19] 2013	Human	1	NA	Supraspinatus and infraspinatus	Injury	Stryker device and diastolic BP	V	NA (case report)
Lee et al,[20] 2013	Human	15	15 Contralateral	Anterior tibial compartment	External pressure chamber	NIRS; ultrasonic PPLL slit catheter for direct IMP	III	7
Lynch et al,[21] 2009	Human	23	23 Contralateral	Anterior tibial compartment	Pressure cuff	Ultrasonic PPLL	III	7
McQueen et al,[22] 1996	Human	116	NA	Anterior tibial compartment	Injury	Slit catheter	II	7
Mitas et al,[23] 2014	Human	13	42	Unspecified tibial compartment	Embolism of the femoral artery	Stryker device; biomarkers	II	7
Nygren et al,[24] 2014	Human	20 (40 Limbs)	NA	Anterior tibial compartment	Pneumatic tourniquets and/or exercise	NIRS	III	6
Ogunlusi et al,[25] 2005	Human	3	49	Anterior and deep posterior compartment of the leg	Injury	Whitesides' infusion technique	III	7
Ozkan et al,[26] 2015	Human	43	NA	All compartments of the upper extremity	Injury (burn)	Clinical	IV	7
Phillips et al,[27] 1987	Human	11	12	Forearm and anterior tibial compartment	Forearm injury (injured patients) and pneumatic antishock garment (healthy control)	Vibrometer with different tuning forks and Wick catheter technique	III	7
Reisman et al,[28] 2013	Human	20	20 Baseline	Anterior tibial compartment	Tourniquet	NIRS	III	7
Roskosky et al,[29] 2014	Human	50	50	Anterior tibial compartment	Injury	NIRS	IV	5
Schmidt et al,[30] 2017	Human	24	167	Anterior and deep posterior compartment of the leg	Injury	Twin Star ECS; PMFC catheter; ECS monitoring unit; and NIRS	II	7
Sellei et al,[31] 2014	Human	8	8 Contralateral	Anterior tibial compartment	Tourniquet	CEUS	III	7
Shuler et al,[32] 2010	Human	14	14 Contralateral	All 4 compartments of the lower leg	Injury	NIRS; Stryker device with a side port needle	III	6

(continued)

Table 1. Diagnostic Modalities and Acute Compartment Syndromes in Human Studies (continued)

Source	Population	Study Group, No.	Control Group, No.	Compartments Evaluated	ACS Model	Diagnostic Techniques	Level of Evidence	Newcastle-Ottawa Scale
Steinberg et al,[33] 2011	Human	52	52	All 4 compartments of the lower leg	Parallel tourniquets	Quantitative tissue hardness with NCSE device; Synthes compartment pressure monitoring system	II	7
Suzuki et al,[34] 2005	Human	8 (9 Thighs)	0	All 3 compartments of the thigh	Injury	Whitesides' infusion technique	III	5
Tobias et al,[35] 2007	Human	1	NA	All 4 compartments of the lower leg	After cardiac surgery	NIRS; undefined IMP	V	NA (case report)
Whitney et al,[36] 2014	Human	46 (48 Fractures)	NA	All 4 compartments of the lower leg	Injury	Stryker device	II	7
Wiemann et al,[37] 2006	Human	3	14	Anterior tibial compartment	Tourniquet (control); injury (study group)	Ultrasonic PPLL; Stryker device with slit catheters	II	7
Yilmaz et al,[38] 2014	Human	5	NA	All 4 compartments of the lower leg	Multifactorial	MRI	IV	NA (case series)
Shuler et al,[39] 2009	Human	26	25	All 4 compartments of the lower leg	Injury	NIRS	II	8
Joseph et al,[40] 2006	Human and amputated legs	20 Adults; 189 children; 3 amputated limbs	20 Adults; 189 children; contralateral	Forearm on humans, anterior tibial compartment in the amputated limbs	A fluid bag; amputated legs with ICP increased by saline infusion; healthy control without ACS	Tissue hardness; Stryker device on the fluid bag and amputated legs	III	7
Tian et al,[41] 2016	Human and rabbit	20 Rabbits, 30 healthy humans, 11 humans with ACS	20 Rabbits, 30 healthy humans, 11 humans with ACS	Anterior tibial compartment in rabbits and healthy humans, all extremities in ACS humans	Tourniquet (rabbit); injury (human)	Whitesides' technique; invasive arterial blood pressure monitor	III	7

Abbreviations: ACS, acute compartment syndrome; BP, blood pressure; CEUS; contrast-enhanced ultrasonography; CTA, computed tomography angiography; ECS, extremity compartment syndrome; ICP, intracompartmental pressure; IMP, intramuscular pressure; MRI, magnetic resonance angiography; NA, not applicable; NIRS, near-infrared spectroscopy; PMFC, pressure monitoring fluid collection; PPLL, pulse phase locked loop.

advocated to warrant fasciotomy.[2] These diagnostic pressure thresholds have low specificity and have been debated extensively owing to the concern of overtreatment. Several studies have shown that these thresholds are too unreliable to be used as indicators for the need for fasciotomy, thus subjecting patients to an unnecessary surgical treatment with its concurrent risks and disfigurement.[65] Some of the potential complications associated with fasciotomy include one or two 20-cm to 30-cm length scars, infections, secondary procedures to close the wound, impairment of calf muscle function, and most commonly, chronic venous insufficiency.[2] Controversy still exists regarding the use of absolute compartment pressure vs change in pressure (the difference between diastolic blood pressure and compartment pressure) as an objective diagnostic test. In 1996, McQueen et al[22] studied the use of continuous ICP monitoring with a slit catheter in addition to the diastolic pressure of each patient with tibial diaphyseal fracture before and after surgery. They found that fasciotomy is only indicated if the change in pressure falls to less than 30 mm Hg. Thus, a change in pressure greater than 30 mm Hg, even in the presence of relatively high absolute compartment pressures, only necessitates observation with continuous monitoring. Despite encouraging results,[4,22] with 1 study reporting a sensitivity of 94% and a specificity of 98%,[4] continuous pressure monitoring has not become a standard diagnostic measurement. Continuous ICP monitoring is possible with the Stryker device by attaching a reliable catheter to an arterial transducer system; such an approach could be easily used at most level 1 trauma centers in the United States.[3,66] Continuous pressure monitoring allows for a better understanding of the pressure changes and may be important for detecting trends of increasing ICP prior to the development of clinical ACS. However, the standard ICP measurement is usually performed as a 1-time analysis only. Furthermore, similar to other invasive diagnostic modalities, the Stryker device cannot be used for home monitoring after discharge following trauma. This would be valuable because ACS can develop in the days following an acute injury and may be detected too late, when the patient returns to the hospital with an already infarcted compartment.

There are many other devices available for ICP measurement, using catheters such as slit catheters, wick catheters, or simple needle manometry. The Wick catheter method is illustrated in Figure 2B. Most of these devices are expensive and may not be available in underfunded hospitals. The Whitesides infusion technique[67] is another invasive diagnostic modality. Although not in use where digital devices are available, it is still used in underdeveloped countries. The materials needed for this technique include a mercury manom-

Table 2. Diagnostic Modalities and Acute Compartment Syndromes in Cadaveric and Animal Studies[a]

Source	Study Population	Study Group, No.	Control Group, No.	Compartments Evaluated	ACS Model	Diagnostic Techniques
Lynch et al,[42] 2004	Cadaver	6	NA	Anterior tibial compartment	Saline infusion	Ultrasonic PPLL; coach pressure measurement system
Sellei et al,[43] 2015	Cadaver	6	6 Baseline	Anterior tibial compartment	Saline infusion	Ultrasonography, pressure-related; invasive pressure measurement using a Codman intracranial pressure monitor
Doro et al,[44] 2014	Dog	12	12 Contralateral	Craniolateral compartment of the leg	Lactated Ringer's solution with 100-mg/dL glucose infusion; tourniquet on the control limb; dissolved oxygen probe insertion into the compartment	A side-port 18-gauge needle with a standard pressure transducer (not further defined); blood glucose
Weick et al,[45] 2016	Dog	15	NA	Anterolateral compartment of the leg	Hydroxyethyl starch colloid fluid infusion on one limp; tourniquet on the other	Straight needle connected to a pressure transducer (not further defined); polarographic tissue oxygen electrode
Garabekyan et al,[46] 2009	Pig	6	6 Contralateral	Anterior tibial compartment	Albumin infusion	Ultrasonic PPLL
Altay et al,[47] 2013	Pig	31	31 Contralateral	All compartment of the lower leg	Injury	Stryker device with side-ported 18-gauge needle
Babinkov et al,[48] 2000	Pig	7	7 Contralateral	Anterior compartment of the lower leg	Tourniquet	A modified device; pressure at which the liquid overcomes tissue resistance and enters the tissue through a needle injected along muscle fibers (compensation method)
Daly et al,[49] 2011	Pig	9	9 Contralateral	Anterolateral compartment of the leg	Saline infusion alone; saline infusion w/ crush; crush technique alone	16-Gauge side portal needle connected to an arterial blood pressure monitor (not further defined)
Greenberg et al,[50] 1988	Rabbit	20	NA	Anterior tibial compartment	Tourniquet	MRI
Sheridan and Matsen[51] 1975	Rabbit	16	NA	Anterior and posterior tibial compartment	Balloon catheter	Intracompartmental balloons were placed and pressure from them registered
Kearns et al,[52] 2010	Rabbit	10	10 Contralateral	Anterior tibial compartment	Pressure chamber/CS simulation chamber	Chamber pressure; arterial pressure
Lawendy et al,[53] 2011	Rabbit	18	18 Contralateral	Anterior tibial compartment	Saline infusion	Electronic compartmental pressure monitoring system inserted with a 14-gauge angio-catheter
Oyster et al,[54] 2015	Rabbit	34	NA	Anterior tibial compartment	Tourniquet and neonatal pressure cuffs	Implantable transmitter
Zhou et al,[55] 2014	Rat	38	19	Cremaster muscle	Pressure cuff	Pressure managed with the pressure cuff
Budsberg et al,[56] 2016	Rat	5	5	Anterior and posterior compartment of the hindlimb	Balloon catheter, internal compression	NIRS
Cathcart et al,[57] 2014	Rat	40	40 Contralateral	Anterior compartment of the hindlimb	Albumin infusion; trauma	NIRS
Garr et al,[58] 1999	Rat	38	38 Baseline	Anterior compartment of the hindlimb	Albumin infusion	NIRS; two 18-gauge needles attached to pressure transducers

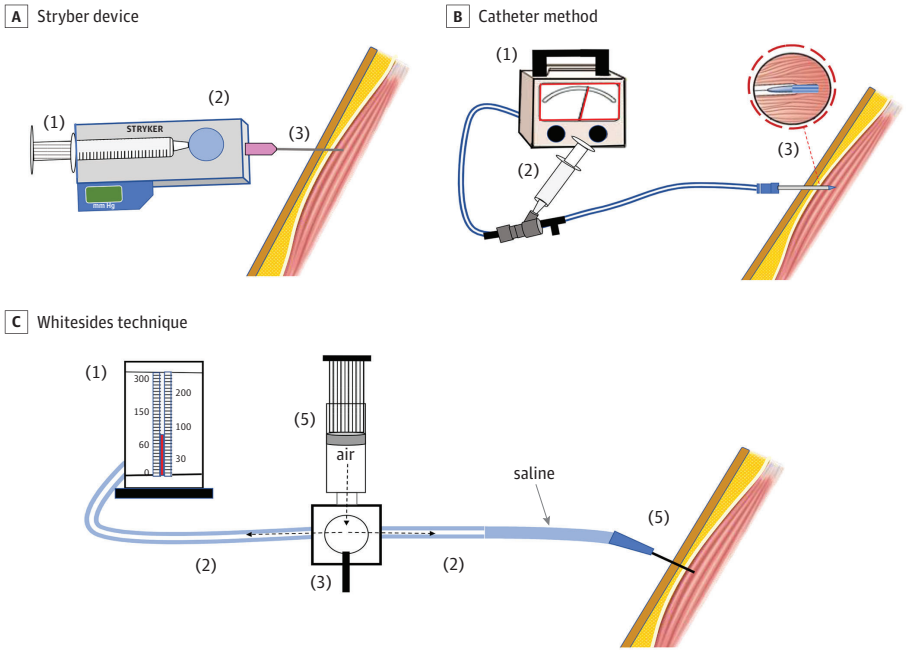
Abbreviations: ACS, acute compartment syndrome; CS, compartment syndrome; MRI, magnetic resonance imaging; NA, not applicable; NIRS, near-infrared spectroscopy; PPLL, pulse phase locked loop.

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

[a] All of these studies have a level of evidence of V.

eter, 2 intravenous extension tubes, an 18-gauge needle, a 20-cc syringe, a 3-way stopcock, and a bag of normal saline (Figure 2C). The Whitesides apparatus is simple and can easily be assembled with these materials that are available at any hospital.[68] However, there are studies that find the Whitesides method to be inaccurate and not appropriate for clinical use.[69] Nevertheless, there are other

Figure 2. Invasive Modalities



A, The Stryker device with (1) prefilled syringe, (2) diaphragm chamber, and (3) side-port needle. B, The catheter method with (1) pressure transducer and recorder, (2) 3-way stopcock, and (3) Wick catheter. Before insertion, the catheter is filled with 20 units per mL saline and calibrated to zero hydrostatic fluid pressure after removing excess saline from the fibers in the catheter. C, The Whitesides technique with (1) mercury manometer, (2) extension tube, (3) 3-way stopcock, (4) 20-cc syringe with 15-mL air, and (5) 18-gauge needle. The method is done under antiseptic conditions; the second extension tube is filled with sterile saline until about half of the length of the tube. With the stopcock off, the needle is inserted into the compartment, after which the stopcock is turned so both sides with the extension tubes are open to the syringe. The air is then injected slowly until the saline meniscus begins to move, and the pressure at this point represents the intracompartmental pressure.

similarly low-cost methods that use widely available materials, such as the intervenous arterial catheter manometer method. This method has been shown to be more accurate compared with the Stryker and Whitesides apparatus.[70]

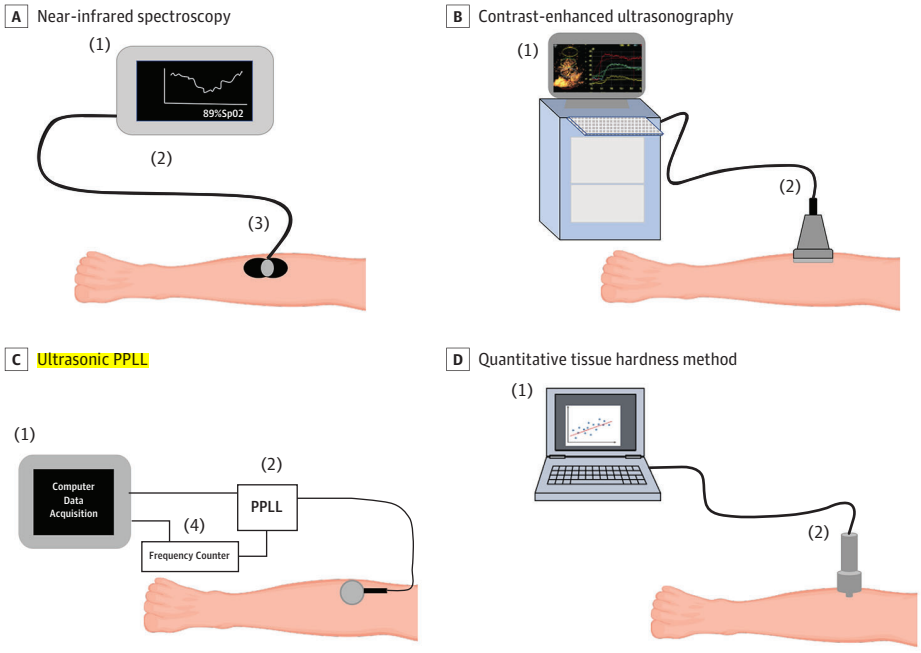
Noninvasive Diagnostic Modalities

Because pressure-induced ischemia of the muscle tissue underlines the pathophysiology of ACS, monitoring muscle tissue oxygenation appears to be a logical diagnostic approach. Whereas direct pressure measurement reflects the ICP, which may or may not result in muscle ischemia, tissue oxygenation measurement with NIRS reflects the underlying pathophysiology of muscle ischemia and necrosis. This technology was first used in 1977 by Jöbsis[71] to monitor cerebral and myocardial oxygenation. There are many studies investigating its use in the diagnosis of ACS. Figure 3A illustrates an example of the setup of NIRS. However, despite the promising advantages of NIRS, it includes several limitations such as its limited maximum penetration depth of 30 to 40 mm. Although this is the biggest critique of NIRS, a 2014 study by Roskosky et al[29] found subcutaneous tissue rarely extends beyond 30 to 40 mm and is therefore unlikely to affect NIRS measurements. Other limitations include variables that could affect the penetration and reflection of the radiated infrared light signal (eg, melanin), the lack of an appropriate threshold that is diagnostic of ACS, and the effects of hypotension and hypoxia in trauma. Some of these issues have been addressed by using the bilateral uninjured leg compartments as controls.[72] However, without a definite and objective tissue oxygenation threshold for ACS, this method cannot be implemented in a clinical setting. A case report from 2011 reported on the use of NIRS as a continuous monitoring device, which was able to detect perfusion changes in real time.[73] Further studies need to establish an appropriate threshold through continuous measurement of intramuscular tissue oxygenation of a compartment during controlled simulation of ACS.

The ultrasonic PPLL is being studied as a potential modality for diagnosing ACS.[37,42] In 1998, Ueno et al[74] developed this technique as a noninvasive method to monitor intracranial pressure. This modality involves an ultrasonic device that uses PPLL to measure the micromovement of the fascia wall (Figure 3B). As the ICP increases in ACS, it causes small fascial displacements, which this device can detect and continuously monitor.[37] Similar to other diagnostic procedures, a major limitation of this technique is the lack of a diagnostic threshold. However, relative changes in serial PPLL recordings have shown good sensitivity and specificity in detecting changes in ICP.[21] While it requires further investigation, the ultrasonic PPLL is a promising noninvasive method for the early diagnosis of ACS.

Several studies have investigated CEUS for diagnosis of ACS[16,31] (Figure 3C). This method can be used to examine muscle perfusion

Figure 3. Noninvasive Modalities



A, Near-infrared spectroscopy (NIRS) with (1) spectrophotometer monitor, (2) optical fiber cable, and (3) optical sensor containing light an emission probe and a light detection probe. B, Ultrasonic pulsed phase locked loop (PPLL) with (1) computer data acquisition, (2) PPLL, (3) ultrasonic transducer, and (4) frequency counter. C, Contrast-enhanced ultrasonography (CEUS) with (1) ultrasonography machine and (2) transducer. D, Quantitative tissue hardness method with (1) computer and (2) probe containing a nonmovable pressure probe in the middle of a movable spring-loaded platform. The probe is pressed on the desired compartment, and the pressure is measured as the probe is pushed into the extremity. When the movable platform shifts, the space between the probe tip to the platform represents the depth of compression. This is plotted in association with the incremental pressures in the probe, creating a linear regression analysis representing a quantitative measurement of hardness.

in an affected limb. Limitations include the need for an experienced ultrasonography examiner, sensitivity to movement artifacts, and an undetermined threshold for diagnosis.[31] Further research is needed to determine how CEUS is affected by factors such as soft tissue as well as chronic diseases such as diabetes and arterial diseases.[31] Comparison with an uninjured contralateral limb is likely necessary to overcome many of these limitations. One big disadvantage of this method is that it cannot be used for continuous monitoring.

Measurement of tissue hardness has also been explored as a diagnostic modality for compartment syndrome. Different devices have been developed for this purpose, such as the noninvasive compartment evaluator (EBI Medical Systems) and the noninvasive compartment syndrome evaluator. This modality includes a manually held device, which is not optimal for continuous monitoring (Figure 3D). Steinberg et al[33] found a sensitivity of 97% and specificity of 66% to 81% when using this modality. However, other studies have demonstrated variability in measurements based on age, testing location, active muscle contraction, and dominance of the limb.[40] These factors are significant limitations, and there is a need for great improvements before this method can be considered.

Molecular Biomarkers for ACS Diagnosis

A review of diagnostic techniques of ACS by Shadgan et al[75] identified serum molecular markers, among other things, as a promising technique for early detection of ACS. Although molecular biomarkers may be used to diagnose ACS, many studies have been unable to identify sensitive and specific biomarkers that increase within a timely fashion following the development of compartment syndrome. While myoglobin rises within 30 minutes of muscle injury and creatinine kinase within 2 hours, they are not specific for skeletal muscle injury and are late indicators of muscle damage. Doro et al[44] found that intramuscular glucose and oxygen tension decline significantly within 15 minutes of the onset of compartment syndrome, which allows for the possibility to detect ACS prior to the onset of irreversible damage. Although this is a promising biomarker, the technique requires further development. A few of its limitations include inability to detect glucose readings less than 40 mg/dL (to convert to millimoles per liter, multiply by 0.0555), and a lengthy calibration process that may take several hours. Furthermore, in many cases, the patients at risk for ACS are patients with trauma or burn, where systemic molecular biomarkers might be affected for multiple other reasons than the increasing compartment pressure of the limb. Additionally, continuous monitoring is necessary to detect changes in biomarkers rather than comparing single time measurements and to establish a threshold, which is currently lacking. For the purposes of our study, we chose not to include the reported molecular biomarkers from some of the studies in our results owing to inaccuracy and inconsistent reporting in the literature.

Limitations

As with any systematic review, our results are as good as the data that they are based on. Furthermore, owing to inconsistent reporting of the diagnostic performance for each modality and wide variety of ACS models, we were not able to perform a meta-analysis. Additionally, we were only able to assess methodologic quality of the clinical studies owing to lack of a well-accepted tool for nonclinical studies; however, we graded the level of evidence assessment for all studies to provide a general overview regarding available evidence in this topic.

Conclusions

This work reviews the literature on ACS diagnostic modalities to facilitate and inspire further research on effective ACS models and diagnostic modalities. For animal models, larger animals are preferred for ACS studies, although smaller animals (eg, rodents) offer the possibility of studying more animals owing to accessibility. Tourniquets and saline infusion are the 2 most commonly used methods and are both well examined. However, 1 study included both crush injury and saline injection to create a more accurate model that stimulates the most common ACS circumstance, which is seen after injury/trauma.

Furthermore, many new and modified diagnostic modalities are used that can serve as inspiration for future guidelines for diagnosis. The NIRS is the most used noninvasive modality and has the potential for continuous monitoring of the perfusion changes in a compartment; however, further studies are needed to verify this capability and establish a threshold. The PPLL has shown great potential and might be a preferred noninvasive modality in the future. However, it is still in the early stages of investigation, and a reliable threshold needs to be established for this method as well. The Stryker pressure device is the most used invasive modality and the gold standard diagnostic tool to assist a clinical suspicion. All 3 of these modalities are limited by availability, user dependency, and most importantly, lack of a reliable diagnostic threshold. Continuous measurement of the compartment pressure and the diastolic blood pressure, to calculate change in pressure, has shown successful results in numerous studies for several years. It seems to be the most reliable technique and with a definite threshold, but it has not yet been extensively studied or implemented in the clinical setting. Moreover, it is still debatable whether the absolute compartment pressure or the change in pressure is the most appropriate diagnostic quantity. Nonetheless, we encourage all future studies to also include continuous monitoring; as such, a multimodal approach will provide more information for establishing a proper threshold for ACS onset. Future studies should also consider and include modalities that can be used for monitoring at home (eg, following trauma) because ACS can progress after discharge and requires prompt evaluation and treatment.

ARTICLE INFORMATION

Accepted for Publication: November 5, 2018.

Published Online: May 1, 2019. doi:10.1001/jamasurg.2019.1050

Author Contributions: The principal investigator Dr Nazarian and the first author Dr Mortensen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Mortensen and Mohamadi and Ms Vora contributed equally to the work as first authors. Drs Wixted, Rutkove and Nazarian contributed equally as senior authors.
Concept and design: Mortensen, Vora, Mohamadi, Hanna, Lechtig, Egan, Williamson, Wixted, Rutkove, Nazarian.
Acquisition, analysis, or interpretation of data: Mortensen, Vora, Mohamadi, Wright, Egan, Nazarian.
Drafting of the manuscript: Mortensen, Vora, Mohamadi, Wright, Lechtig, Williamson, Rutkove, Nazarian.
Critical revision of the manuscript for important intellectual content: Mortensen, Mohamadi, Wright, Hanna, Lechtig, Egan, Wixted, Rutkove, Nazarian.
Statistical analysis: Mortensen, Vora, Mohamadi.
Administrative, technical, or material support: Mohamadi, Lechtig, Egan, Williamson, Wixted, Rutkove.
Supervision: Mortensen, Hanna, Rutkove, Nazarian.

Conflict of Interest Disclosures: None reported.

REFERENCES

1. McQueen MM, Gaston P, Court-Brown CM. Acute compartment syndrome: who is at risk? *J Bone Joint Surg Br*. 2000;82(2):200-203. doi:10.1302/0301-620X.82B2 .9799

2. von Keudell AG, Weaver MJ, Appleton PT, et al. Diagnosis and treatment of acute extremity compartment syndrome. *Lancet*. 2015;386 (10000):1299-1310. doi:10.1016/S0140-6736(15) 00277-9

3. McQueen MM, Christie J, Court-Brown CM. Acute compartment syndrome in tibial diaphyseal fractures. *J Bone Joint Surg Br*. 1996;78(1):95-98. doi:10.1302/0301-620X.78B1.0780095

4. McQueen MM, Duckworth AD, Aitken SA, Court-Brown CM. The estimated sensitivity and specificity of compartment pressure monitoring for acute compartment syndrome. *J Bone Joint Surg Am*. 2013;95(8):673-677. doi:10.2106/JBJS.K.01731

5. Shadgan B, Menon M, O'Brien PJ, Reid WD. Diagnostic techniques in acute compartment syndrome of the leg. *J Orthop Trauma*. 2008;22(8): 581-587. doi:10.1097/BOT.0b013e318183136d

6. OCEBM Levels of Evidence Working Group; Durieux N, Pasleau F, Howick J. The Oxford 2011 Levels of Evidence: group. http://www.cebm.net/index.aspx?o=1025. Published 2011. Accessed February 26, 2018.

7. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed May 29, 2018.

8. Chambers L, Hame SL, Levine B. Acute exertional medial compartment syndrome of the foot after playing basketball. *Skeletal Radiol*. 2011; 40(7):931-935. doi:10.1007/s00256-011-1157-8

9. Jensen IW, Olsen A. Compartmental syndrome diagnosed by computed tomography. *J R Soc Med*. 1986;79(5):300-301. doi:10.1177/014107688607900512

10. Jiang L-F, Li H, Xin Z-F, Wu L-D. Computed tomography angiography and magnetic resonance imaging performance of acute segmental single compartment syndrome following an Achilles tendon repair: a case report and literature review. *Chin J Traumatol*. 2016;19(5):290-294. doi:10.1016/j.cjtee.2016.03.005

11. Wang S-M, Kim M. Compartment syndrome after varicose vein surgery evidenced by CT images. *Int J Low Extrem Wounds*. 2016;15(1):71-73. doi:10.1177/1534734614555003

12. Bariteau JT, Beutel BG, Kamal R, Hayda R, Born C. The use of near-infrared spectrometry for the diagnosis of lower-extremity compartment syndrome. *Orthopedics*. 2011;34(3):178-178. doi:10.3928/01477447-20110124-12

13. Blick SS, Brumback RJ, Poka A, Burgess AR, Ebraheim NA. Compartment syndrome in open tibial fractures. *J Bone Joint Surg Am*. 1986;68(9): 1348-1353. doi:10.2106/00004623-198668090-00007

14. Boonstra RH, Haverkamp D, Campo MM, van der Vis HM. Acute compartment syndrome of the thigh following total knee arthroplasty. *Knee*. 2012;19(2):151-153. doi:10.1016/j.knee.2011.02.007

15. de Franciscis S, De Caridi G, Massara M, et al. Biomarkers in post-reperfusion syndrome after acute lower limb ischaemia. *Int Wound J*. 2016;13 (5):854-859. doi:10.1111/iwj.12392

16. Geis S, Gehmert S, Lamby P, et al. Contrast enhanced ultrasound (CEUS) and time intensity curve (TIC) analysis in compartment syndrome: first results. *Clin Hemorheol Microcirc*. 2012;50(1-2):1-11. doi:10.3233/CH-2011-1438

17. Goyal S, Naik MA, Tripathy SK, Rao SK. Functional outcome of tibial fracture with acute compartment syndrome and correlation to deep posterior compartment pressure. *World J Orthop*. 2017;8(5):385-393. doi:10.5312/wjo.v8.i5.385

18. Katz LM, Nauriyal V, Nagaraj S, et al. Infrared imaging of trauma patients for detection of acute compartment syndrome of the leg. *Crit Care Med*. 2008;36(6):1756-1761. doi:10.1097/CCM.0b013e318174d800

19. Kenny RM, Beiser CW, Patel A. Supraspinatus and infraspinatus compartment syndrome following scapular fracture. *Int J Shoulder Surg*. 2013;7(1):28-31. doi:10.4103/0973-6042.109891

20. Lee SH, Padilla M, Lynch JE, Hargens AR. Noninvasive measurements of pressure for detecting compartment syndromes. *J Orthop Rheumatol*. 2013;1(1):5. doi:10.13188/2334-2846.1000005

21. Lynch JE, Lynch JK, Cole SL, Carter JA, Hargens AR. Noninvasive monitoring of elevated intramuscular pressure in a model compartment syndrome via quantitative fascial motion. *J Orthop Res*. 2009;27(4):489-494. doi:10.1002/jor.20778

22. McQueen MM, Court-Brown CM. Compartment monitoring in tibial fractures: the pressure threshold for decompression. *J Bone Joint Surg Br*. 1996;78(1):99-104. doi:10.1302/0301-620X.78B1.0780099

23. Mitas P, Vejrazka M, Hruby J, et al. Prediction of compartment syndrome based on analysis of biochemical parameters. *Ann Vasc Surg*. 2014;28(1):170-177. doi:10.1016/j.avsg.2012.12.006

24. Nygren A, Rennerfelt K, Zhang Q. Detection of changes in muscle oxygen saturation in the human leg: a comparison of two near-infrared spectroscopy devices. *J Clin Monit Comput*. 2014;28(1):57-62. doi:10.1007/s10877-013-9494-x

25. Ogunlusi JD, Oginni LM, Ikem IC. Compartmental pressure in adults with tibial fracture. *Int Orthop*. 2005;29(2):130-133. doi:10.1007/s00264-004-0630-6

26. Özkan A, Şentürk S, Tosun Z. Fasciotomy procedures on acute compartment syndromes of the upper extremity related to burns. *Electron J Gen Med*. 2015;12(4):326–333. doi:10.15197/ejgm.01410

27. Phillips JH, Mackinnon SE, Beatty SE, Dellon AL, O'Brien JP. Vibratory sensory testing in acute compartment syndromes: a clinical and experimental study. *Plast Reconstr Surg*. 1987;79(5):796-801. doi:10.1097/00006534-198705000-00020

28. Reisman WM, Shuler MS, Kinsey TL, et al. Relationship between near infrared spectroscopy and intra-compartmental pressures. *J Emerg Med*. 2013;44(2):292-298. doi:10.1016/j.jemermed.2012.06.018

29. Roskosky M, Robinson G, Reisman W, Ziran B, Shuler MS, Freedman B. Subcutaneous depth in a traumatized lower extremity. *J Trauma Acute Care Surg*. 2014;77(3)(suppl 2):S190-S193. doi:10.1097/TA.0000000000000323

30. Schmidt AH, Bosse MJ, Frey KP, et al; METRC. Predicting Acute Compartment Syndrome (PACS): the role of continuous monitoring. *J Orthop Trauma*. 2017;31(suppl 1):S40-S47. doi:10.1097/BOT.0000000000000796

31. Sellei RM, Waehling A, Weber CD, et al. Contrast enhanced ultrasound (CEUS) reliably detects critical perfusion changes in compartmental muscle: a model in healthy volunteers. *Eur J Trauma Emerg Surg*. 2014;40(5):535-539. doi:10.1007/s00068-014-0443-2

32. Shuler MS, Reisman WM, Kinsey TL, et al. Correlation between muscle oxygenation and compartment pressures in acute compartment syndrome of the leg. *J Bone Joint Surg Am*. 2010;92(4):863-870. doi:10.2106/JBJS.I.00816

33. Steinberg B, Riel R, Armitage M, Berrey H. Quantitative muscle hardness as a noninvasive means for detecting patients at risk of compartment syndromes. *Physiol Meas*. 2011;32(4):433-444. doi:10.1088/0967-3334/32/4/005

34. Suzuki T, Moirmura N, Kawai K, Sugiyama M. Arterial injury associated with acute compartment syndrome of the thigh following blunt trauma. *Injury*. 2005;36(1):151-159. doi:10.1016/j.injury.2004.03.022

35. Tobias JD, Hoernschemeyer DG. Near-infrared spectroscopy identifies compartment syndrome in an infant. *J Pediatr Orthop*. 2007;27(3):311-313. doi:10.1097/BPO.0b013e3180326591

36. Whitney A, O'Toole RV, Hui E, et al. Do one-time intracompartmental pressure measurements have a high false-positive rate in diagnosing compartment syndrome? *J Trauma Acute Care Surg*. 2014;76(2):479-483. doi:10.1097/TA.0b013e3182aaa63e

37. Wiemann JM, Ueno T, Leek BT, Yost WT, Schwartz AK, Hargens AR. Noninvasive measurements of intramuscular pressure using pulsed phase-locked loop ultrasound for detecting compartment syndromes: a preliminary report. *J Orthop Trauma*. 2006;20(7):458-463. doi:10.1097/00005131-200608000-00002

38. Yılmaz TF, Toprak H, Bilsel K, Ozdemir H, Aralasmak A, Alkan A. MRI findings in crural compartment syndrome: a case series. *Emerg Radiol*. 2014;21(1):93-97. doi:10.1007/s10140-013-1156-2

39. Shuler MS, Reisman WM, Whitesides TE Jr, et al. Near-infrared spectroscopy in lower extremity trauma. *J Bone Joint Surg Am*. 2009;91(6):1360-1368. doi:10.2106/JBJS.H.00347

40. Joseph B, Varghese RA, Mulpuri K, Paravatty S, Kamath S, Nagaraja N. Measurement of tissue hardness: can this be a method of diagnosing compartment syndrome noninvasively in children? *J Pediatr Orthop B*. 2006;15(6):443-448. doi:10.1097/01.bpb.0000236226.21949.5c

41. Tian S, Lu Y, Liu J, Zhu Y, Cui Y, Lu J. Comparison of 2 available methods with Bland-Altman analysis for measuring intracompartmental pressure. *Am J Emerg Med*. 2016;34(9):1765-1771. doi:10.1016/j.ajem.2016.06.010

42. Lynch JE, Heyman JS, Hargens AR. Ultrasonic device for the noninvasive diagnosis of compartment syndrome. *Physiol Meas*. 2004;25(1):1-9.

43. Sellei RM, Hingmann SJ, Weber C, et al. Assessment of elevated compartment pressures by pressure-related ultrasound: a cadaveric model. *Eur J Trauma Emerg Surg*. 2015;41(6):639-645. doi:10.1007/s00068-014-0449-9

44. Doro CJ, Sitzman TJ, O'Toole RV. Can intramuscular glucose levels diagnose compartment syndrome? *J Trauma Acute Care Surg*. 2014;76(2):474-478. doi:10.1097/TA.0b013e3182a9ccd1

45. Weick JW, Kang H, Lee L, et al. Direct measurement of tissue oxygenation as a method of diagnosis of acute compartment syndrome. *J Orthop Trauma*. 2016;30(11):585-591. doi:10.1097/BOT.0000000000000651

46. Garabekyan T, Murphey GC, Macias BR, Lynch JE, Hargens AR. New noninvasive ultrasound technique for monitoring perfusion pressure in a porcine model of acute compartment syndrome. *J Orthop Trauma*. 2009;23(3):186-193. doi:10.1097/BOT.0b013e31819901db

47. Altay MA, Ertürk C, Altay N, et al. Comparison of intracompartmental pressures in a rabbit model of open and closed tibial fractures: an experimental study. *Bone Joint J*. 2013;95-B(1):111-114. doi:10.1302/0301-620X.95B1.29504

48. Babinkov VI, Khitrov NK, Cherkashina ZA. Effect of early fasciotomy on intramuscular pressure and electrical excitability of muscles in experimental compartment syndrome. *Bull Exp Biol Med*. 2000;130(9):857-860. doi:10.1023/A:1015358027188

49. Daly KA, Wolf M, Johnson SA, Badylak SF. A rabbit model of peripheral compartment syndrome with associated rhabdomyolysis and a regenerative medicine approach for treatment. *Tissue Eng Part C Methods*. 2011;17(6):631-640. doi:10.1089/ten.tec.2010.0699

50. Greenberg BM, Masem M, Ragozzino M, Schoenfeld DA, May JW Jr. The role of magnetic resonance imaging in assessing elevated intracompartmental pressure in the rabbit hindlimb. *Plast Reconstr Surg*. 1988;82(4):678-687. doi:10.1097/00006534-198810000-00021

51. Sheridan GW, Matsen FA III. An animal model of the compartmental syndrome. *Clin Orthop Relat Res*. 1975;(113):36-42. doi:10.1097/00003086-197511000-00006

52. Kearns SR, O'Briain DE, Sheehan KM, Kelly C, Bouchier-Hayes D. N-acetylcysteine protects striated muscle in a model of compartment syndrome. *Clin Orthop Relat Res*. 2010;468(8):2251-2259. doi:10.1007/s11999-010-1287-7

53. Lawendy A-R, Sanders DW, Bihari A, Parry N, Gray D, Badhwar A. Compartment syndrome-induced microvascular dysfunction: an experimental rodent model. *Can J Surg*. 2011;54(3):194-200. doi:10.1503/cjs.048309

54. Oyster N, Witt M, Gharaibeh B, Poddar M, Schneppendahl J, Huard J. Characterization of a compartment syndrome-like injury model. *Muscle Nerve*. 2015;51(5):750-758. doi:10.1002/mus.24461

55. Zhou Y, Lovell D, Bethea M, et al. Age-dependent changes cooperatively impact skeletal muscle regeneration after compartment syndrome injury. *Am J Pathol*. 2014;184(8):2225-2236. doi:10.1016/j.ajpath.2014.03.018

56. Budsberg SC, Shuler MS, Hansen M, Uhl E, Freedman BA. Comparison of NIRS, serum biomarkers, and muscle damage in a porcine balloon compression model of acute compartment syndrome. *J Trauma Acute Care Surg*. 2016;81(5):876-881. doi:10.1097/TA.0000000000001225

57. Cathcart CC, Shuler MS, Freedman BA, Reno LR, Budsberg SC. Correlation of near-infrared spectroscopy and direct pressure monitoring in an acute porcine compartmental syndrome model. *J Orthop Trauma*. 2014;28(6):365-369. doi:10.1097/BOT.0b013e3182a75ceb

58. Garr JL, Gentilello LM, Cole PA, Mock CN, Matsen FA III. Monitoring for compartmental syndrome using near-infrared spectroscopy: a noninvasive, continuous, transcutaneous

monitoring technique. *J Trauma*. 1999;46(4):613-616. doi:10.1097/00005373-199904000-00009

59. Heckman MM, Whitesides TE Jr, Grewe SR, Judd RL, Miller M, Lawrence JH III. Histologic determination of the ischemic threshold of muscle in the canine compartment syndrome model. *J Orthop Trauma*. 1993;7(3):199-210. doi:10.1097/00005131-199306000-00001

60. Hargens AR, Akeson WH, Mubarak SJ, et al. Fluid balance within the canine anterolateral compartment and its relationship to compartment syndromes. *J Bone Joint Surg Am*. 1978;60(4):499-505. doi:10.2106/00004623-197860040-00012

61. Sapega AA, Heppenstall RB, Chance B, Park YS, Sokolow D. Optimizing tourniquet application and release times in extremity surgery: a biochemical and ultrastructural study. *J Bone Joint Surg Am*. 1985;67(2):303-314. doi:10.2106/00004623-198567020-00018

62. Newman RJ. Metabolic effects of tourniquet ischaemia studied by nuclear magnetic resonance spectroscopy. *J Bone Joint Surg Br*. 1984;66(3):434-440. doi:10.1302/0301-620X.66B3.6725357

63. Riquelme A, Avellanal M, Vigil D, Salinero E, Vaquero J. Ischemia-reperfusion challenge in human skeletal muscle: study in knee arthroplasty surgery. *J Anesth Clin Res*. 2011;2(12). doi:10.4172/2155-6148.1000178

64. Townsend HS, Goodman SB, Schurman DJ, Hackel A, Brock-Utne JG. Tourniquet release: systemic and metabolic effects. *Acta Anaesthesiol Scand*. 1996;40(10):1234-1237. doi:10.1111/j.1399-6576.1996.tb05556.x

65. Janzing HMJ, Broos PLO. Routine monitoring of compartment pressure in patients with tibial fractures: beware of overtreatment! *Injury*. 2001;32(5):415-421. doi:10.1016/S0020-1383(01)00005-5

66. McQueen M. How to monitor compartment pressures. *Tech Orthop*. 1996;11(1):99-101. doi:10.1097/00013611-199601110-00015

67. Whitesides TE, Haney TC, Morimoto K, Harada H. Tissue pressure measurements as a determinant for the need of fasciotomy. *Clin Orthop Relat Res*. 1975;(113):43-51. doi:10.1097/00003086-197511000-00007

68. Sangwan SS, Marya KM, Devgan A, Siwach RC, Kundu ZS, Gupta PK. Critical evaluation of compartment pressure measurement by saline manometer in peripheral hospital setup. *Trop Doct*. 2003;33(2):100-103. doi:10.1177/004947550303300216

69. Moed BR, Thorderson PK. Measurement of intracompartmental pressure: a comparison of the slit catheter, side-ported needle, and simple needle. *J Bone Joint Surg Am*. 1993;75(2):231-235. doi:10.2106/00004623-199302000-00010

70. Boody AR, Wongworawat MD. Accuracy in the measurement of compartment pressures: a comparison of three commonly used devices. *J Bone Joint Surg Am*. 2005;87(11):2415-2422. doi:10.2106/JBJS.D.02826

71. Jöbsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science*. 1977;198(4323):1264-1267. doi:10.1126/science.929199

72. Jackson K II, Cole A, Potter BK, Shuler M, Kinsey T, Freedman B. Identification of optimal control compartments for serial near-infrared spectroscopy assessment of lower extremity compartmental perfusion. *J Surg Orthop Adv*. 2013;22(1):2-9. doi:10.3113/JSOA.2013.0002

73. Shuler MS, Reisman WM, Cole AL, Whitesides TE Jr, Moore TJ. Near-infrared spectroscopy in acute compartment syndrome: case report. *Injury*. 2011;42(12):1506-1508. doi:10.1016/j.injury.2011.03.022

74. Ueno T, Ballard RE, Shuer LM, Cantrell JH, Yost WT, Hargens AR. Noninvasive measurement of pulsatile intracranial pressure using ultrasound. *Acta Neurochir Suppl*. 1998;71:66-69.

75. Shadgan B, Menon M, Sanders D, et al. Current thinking about acute compartment syndrome of the lower extremity. *Can J Surg*. 2010;53(5):329-334.