Muscle Microvascular Blood Flow, Oxygenation, pH, and Perfusion Pressure Decrease in Simulated Acute Compartment Syndrome

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Background: The current gold standard for diagnosing acute compartment syndrome (ACS) is an assessment of clinical signs, invasive measurement of intramuscular pressure (IMP), and measurement of local perfusion pressure. However, IMP measurements have several shortcomings, including pain, risk of infection, risk of technique error, plugging of the catheter tip, lack of consensus on the diagnostic pressure threshold, and lack of specificity and sensitivity. The objective of this study was to evaluate muscle hemodynamics, oxygenation, and pH as diagnostic parameters in a human model of ACS. We hypothesized that as IMP increases, muscle microvascular blood flow, oxygenation, and pH decrease in the anterior compartment of a leg at heart level and that they decrease significantly more when the leg is elevated further.

Methods: An external pneumatic leg pressure chamber, combined with a venous stasis thigh cuff, was used to increase IMP and simulate ACS. Eight healthy subjects (5 males and 3 females; mean age, 26 years) had photoplethysmography and near-infrared spectroscopy-pH sensors placed over the middle aspect of the tibialis anterior muscle of the right (experimental) and left (control) legs. Leg chamber pressure conditions (40, 50, and 60 mm Hg) were applied in a randomized order after baseline measurements were taken. Data were collected continuously for each 11-minute pressure condition, with an 11-minute recovery period after each condition, and the average of the last 6 minutes was used for data analyses. The same protocol was repeated with each subject's legs elevated 12 cm above heart level. Data were analyzed using repeated-measures analysis of variance (ANOVA).

Results: As IMP increased, muscle microvascular blood flow ($p = 0.01$), oxygenation ($p < 0.001$), and pH ($p < 0.001$) all decreased significantly in the experimental leg compared with the control leg. At all IMP levels, leg elevation significantly decreased muscle oxygenation ($p = 0.013$) and perfusion pressure ($p = 0.03$) compared with the control leg at heart level.

Conclusions: These results indicate that muscle microvascular blood flow, oxygenation, pH, and perfusion pressure decrease significantly as IMP increases in a human model of ACS.

Clinical Relevance: This study identifies hemodynamic and metabolic parameters as potential noninvasive diagnostic tools for ACS.

Acute compartment syndrome (ACS) occurs when intramuscular pressure (IMP) increases and compromises muscle microvascular blood flow. The highest

rate of ACS occurs in leg muscles, typically following tibial fracture or blunt trauma (for example, from a motor-vehicle accident)^{1,2}. Clinical signs of ACS are high IMP and pain,

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paresthesia, paresis, pink skin pigmentation, decreased perfusion pressure, and the presence of a distal pulse³. If diagnosis and treatment are delayed, ACS may produce sensory deficits, paralysis, infection, and a Volkmann contracture, possibly leading to limb amputation.

Presence of these clinical signs, elevated IMP, and decreased perfusion pressure are the current gold standard for diagnosing ACS². However, several shortcomings are associated with the current technology used for IMP measurements, such as the risk of infection, risk of technique error, pain, plugging of the catheter tip, lack of consensus on the diagnostic pressure threshold, and lack of sensitivity and specificity. There is no difference in clinical outcome for patients at or above and those below the currently used threshold (≥ 30 mm Hg) for IMP^{4,5}.

Perfusion pressure (Δp), calculated as the difference between mean arterial pressure (MAP) and IMP, is a more reliable measure of ACS than absolute IMP values are^{2,6,7}. Previous studies documented that leg elevation decreases both perfusion pressure and muscle tolerance to ischemia during elevated IMP, yielding neuromuscular dysfunction in a human model⁸⁻¹⁰. A previous study comparing absolute IMP and perfusion pressure demonstrated that perfusion pressure of <30 mm Hg is a useful clinical parameter for ACS diagnosis².

It is important to identify quick and noninvasive means to measure parameters such as muscle microvascular blood flow, oxygenation, and pH that can act as surrogate markers for perfusion pressure. Near-infrared spectroscopy and photoplethysmography have previously been evaluated but have not been implemented clinically. One study showed that muscle oxygenation decreased significantly with external compression of the limb, but there was significant subject-to-subject variability¹¹. It is important for light-based near-infrared spectroscopy measurement techniques to include a strategy to control for skin pigmentation and subcutaneous fat, which can confound the near-infrared spectroscopy measurements¹². Recent advances in near-infrared spectroscopy technology, including removal of subject-to-subject variability due to skin pigmentation and fat thickness, provide reliable and sensitive local muscle hemodynamic measurements as validated during standard physiological protocols of hypovolemia¹³.

Assessments of bone microvascular blood flow using photoplethysmography demonstrated a 33% reduction with cold exposure and an 83% reduction during arterial occlusion¹⁴. Zhang and colleagues^{15,16} identified a significant decrease in post-exercise muscle blood flow using photoplethysmography following a period of abnormally elevated IMP. However, photoplethysmography probes are extremely sensitive to interference from ambient light as well as variability in sensor placement. Optimized placement of photoplethysmography sensors and minimization of interference by ambient light can produce reliable and robust microvascular blood-flow measurements.

This study was designed to evaluate muscle hemodynamics, oxygenation, and pH as diagnostic parameters in a model of ACS using photoplethysmography and near-infrared spectroscopy technology. We hypothesized that as calcu-

lated IMP increases, muscle microvascular blood flow, oxygenation, and pH will decrease in a leg at heart level and will decrease significantly more when the leg is elevated further.

Materials and Methods

We used a validated model of ACS as employed by Styf and Wiger¹⁷ and others^{11,18}, combining venous stasis and external compression. This traditional ACS model uses venous stasis induced by a thigh cuff, external compression of the limb with a plaster of Paris cast, and limb elevation to 35 cm above heart level. Previous research using this ACS model found a decrease in perfusion pressure of 26 mm Hg within the anterior compartment. Leg elevation further decreased tissue tolerance to the decreased perfusion pressure¹⁷. Lee and coworkers¹¹ demonstrated that this ACS model is safe and consistent, with muscle oxygenation decreasing linearly with increasing chamber pressure of 0 to 70 mm Hg.

An external pneumatic leg pressure chamber¹¹, combined with a venous stasis thigh cuff⁷, was used to increase IMP and simulate ACS. The external pneumatic leg pressure chamber model uses a $12 \times 36 \times 12$ -in ($30 \times 91 \times 30$ -cm) chamber with an opening sealed by a neoprene sleeve with a resistive layer that fits around the subject's thigh. Air is pumped into the chamber to compress the subject's leg, and pressure is monitored using a gauge attached to the chamber. This model is similar to the ACS model used by Lee et al.¹¹.

Microvascular blood flow was measured noninvasively using photoplethysmography, which consists of a light-emitting diode and a photodetector¹⁴. When the light-emitting diode illuminates an area of the skin, the photodetector records the amount of attenuation of the reflected light because a portion of the light is absorbed and scattered by the underlying tissue. This attenuation, recorded in volts, corresponds with blood flow¹⁶. The photoplethysmography probe used in our study was secured with tape to allow maximum contact with the skin and was shielded from ambient light with gauze and aluminum foil. Muscle oxygenation and pH were measured noninvasively using the factory-calibrated near-infrared spectroscopy-pH device (CareGuide; Sotera Wireless)¹². Subjects with a wide variety of skin pigmentation were included in this study, and sufficient signal was obtained by the near-infrared spectroscopy-pH probe in all subjects.

Eight healthy subjects, 5 men and 3 women (mean age, 26 years), were recruited for this study with approval from the institutional review board at the University of California, San Diego. The mean arterial blood pressure (MAP $\pm$ standard error of the mean) taken at baseline with the subjects supine, was 86.4 ± 5.4 mm Hg. Written and informed consent was obtained from each subject prior to enrollment in the study. Photoplethysmography and near-infrared spectroscopy-pH sensors were placed over the middle aspect of the tibialis anterior muscle of the right anterior compartment, and a thigh blood pressure cuff was placed around the right thigh, approximately 10 cm above the knee. The experimental (left) leg was then placed in the pressure chamber with a neoprene

sleeve sealing the chamber to the subject's thigh. The contralateral leg, which had no external pressure or thigh cuff, was used as the control and had a near-infrared spectroscopy-pH sensor placed on the tibialis anterior. This leg was placed outside the pressure chamber at the same height as the experimental leg.

Baseline measurements were collected on both the photoplethysmography and near-infrared spectroscopy-pH devices. Leg chamber pressure conditions (40, 50, and 60 mm Hg) were then applied in a randomized order for 11 minutes with a thigh tourniquet pressure of 65 mm Hg to induce venous stasis. The 11-minute interval for the elevated pressure conditions and recovery periods was selected on the basis of preliminary experiments documenting that 5 minutes of pressure application was adequate to reach steady-state muscle microvascular blood flow, muscle oxygenation, and pH. In addition, 5 minutes of recovery was found to be sufficient for these variables to return to baseline values. Data were collected continuously for each 11-minute pressure condition, and the average of the last 6 minutes was used for data analyses. An 11-minute recovery period with ambient chamber pressure and a deflated thigh cuff followed each pressure condition. The protocol was then repeated on a different day on each subject, as described above, but with the subject's experimental leg and control leg elevated 12 cm above heart level. Blood pressure was measured for each subject on both ankles at baseline and on the right arm during the last 2 minutes of each pressure condition and was used to calculate local perfusion pressure in each subject. Mean arterial pressure was calculated from blood pressure measurements from the right ankle obtained with the leg supine and elevated 12 cm above heart level ($MAP = \text{diastolic pressure} + 1/3 \times [\text{systolic pressure} - \text{diastolic pressure}]$). IMP was calculated as $11.05 + 1.11 \times \text{chamber pressure}$, a linear relationship that was established by previous research using a similar ACS model¹¹.

Statistical Analyses

Power analysis of preliminary oxygenation data indicated that a sample size of 8 would produce a power of 0.8 and an alpha of 0.5. Data were analyzed using repeated-measures analysis of variance (ANOVA), with main effects being the leg (experimental and control legs), pressure (baseline of 0; 40, 50, and 60; and recovery or 0 mm Hg), and position (leg at heart level and leg elevated 12 cm further). After detecting a significant main effect, pairwise comparisons were conducted to determine a specific difference between pressure conditions. A *p* value of <0.05 indicated significance. All data are presented as the mean $\pm$ standard error of the mean.

Results

The IMP in the experimental leg was calculated to be 55.4, 66.5, and 77.6 mm Hg at an external chamber pressure of 40, 50, and 60 mm Hg, respectively. Muscle microvascular blood flow, oxygenation, and pH did not significantly change in the control leg at any of the pressure conditions when the leg was at heart level or elevated further. However, there was an immediate decrease in muscle microvascular blood flow, oxygenation, and pH with the application of external pneumatic pressure and venous stasis. All measures reached a steady state by the fifth minute of each condition. The leg (control compared with experimental leg) had a significant effect; as IMP increased, muscle microvascular blood flow ($p = 0.01$) (Fig. 1), oxygenation ($p < 0.001$) (Fig. 2), and pH ($p < 0.001$) (Fig. 3) all decreased significantly in the experimental leg compared with the control leg.

There was a significant effect of external pressure on microvascular blood flow. Mean microvascular blood flow decreased from 1.48 ± 0.13 V at baseline (0 mm Hg) to 1.26 ± 0.23 , 0.97 ± 0.24 , and 0.76 ± 0.24 V at external pressures of 40, 50, and 60 mm Hg, respectively ($p < 0.001$). Microvascular blood flow decreased as chamber pressure increased from 0 to

Fig. 1
Box plots showing the mean microvascular blood flow as measured by photoplethysmography of the supine legs and elevated legs at each pressure condition. An asterisk (*) indicates a significant decrease in microvascular blood flow as external pressure increased from 0 to 50 and 60 mm Hg, a pound sign (#) indicates a significant decrease in microvascular blood flow from 40 to 50 and 60 mm Hg, and a dagger (†) indicates a further decrease in microvascular blood flow from 50 to 60 mm Hg. The top and bottom of a box represent the 25th and 75th percentiles, the whiskers represent the 10th and 90th percentiles, and the dots represent outliers.

Fig. 2

Box plots showing the mean muscle oxygenation of the supine legs and elevated legs at each pressure condition. An asterisk (*) indicates a significant decrease in muscle oxygenation as external pressure increased from 0 to 40, 50, and 60 mm Hg; a pound sign (#) indicates a further significant decrease in muscle oxygenation from 40 to 50 and 60 mm Hg; a dagger (†) indicates a significant decrease in muscle oxygenation from 50 to 60 mm Hg; and a plus sign (+) indicates a significant decrease in muscle oxygenation in the leg elevated 12 cm above heart level compared with the supine leg. The top and bottom of a box represent the 25th and 75th percentiles, the whiskers represent the 10th and 90th percentiles, and the dots represent outliers.

50 mm Hg ($p = 0.003$) and further at 60 mm Hg ($p = 0.001$). Microvascular blood flow decreased significantly from 40 to 50 mm Hg ($p = 0.009$) (Fig. 1). Significant decreases in blood flow were also observed from 40 to 60 mm Hg ($p = 0.006$) and from 50 to 60 mm Hg ($p = 0.018$). Oxygenation significantly decreased in the experimental leg from $76.4\% \pm 1.0\%$ at baseline (0 mm Hg) to $69.0\% \pm 1.7\%$, $65.3\% \pm 3.4\%$, and $59.7\% \pm 4.5\%$ at external pressures of 40, 50, and 60 mm Hg, respectively ($p < 0.001$). Oxygenation decreased significantly as chamber pressure increased from 0 to 40 ($p = 0.02$), 50 ($p = 0.008$), and 60 ($p = 0.001$) mm Hg (Fig. 2). Significant decreases in oxygenation were also observed from 40 to 50 ($p = 0.02$) and 60 ($p = 0.001$) mm Hg, and from 50 to 60 mm Hg

($p = 0.03$). Muscle pH significantly decreased from 7.48 ± 0 at baseline (0 mm Hg) to 7.38 ± 0.04 , 7.37 ± 0.04 , and 7.31 ± 0.04 at external pressures of 40, 50, and 60 mm Hg, respectively ($p < 0.001$) (Fig. 3). The pH decreased significantly as chamber pressure increased from 0 to 40 ($p = 0.021$), 50 ($p = 0.002$), and 60 ($p < 0.001$) mm Hg. The decreases from 40 to 50 ($p = 0.046$) and 60 ($p = 0.010$) as well as 50 to 60 ($p = 0.009$) mm Hg were also significant.

There was a significant effect of leg elevation on muscle oxygenation as measured by near-infrared spectroscopy. As IMP increased, leg elevation significantly decreased muscle oxygenation compared with the leg at heart level ($p = 0.013$) (Fig. 2). Specifically, mean muscle oxygenation in the elevated

Fig. 3

Box plots showing the mean muscle pH of the supine legs and elevated legs at each pressure condition. An asterisk (*) denotes a significant decrease in muscle pH as external pressure increased from 0 to 40, 50, and 60 mm Hg; a pound sign (#) indicates a significant decrease in pH from 40 to 50 and 60 mm Hg; and a dagger (†) indicates a further significant decrease in pH from 50 to 60 mm Hg. The top and bottom of a box represent the 25th and 75th percentiles, the whiskers represent the 10th and 90th percentiles, and the dots represent outliers.

Fig. 4
Box plots showing the mean perfusion pressure of the supine legs and elevated legs. An asterisk (*) indicates a significant decrease in perfusion pressure in the leg elevated 12 cm above heart level compared with the supine leg. The top and bottom of a box represent the 25th and 75th percentiles, the whiskers represent the 10th and 90th percentiles, and the dots represent outliers.

leg decreased from $73.0\% \pm 1.9\%$ at baseline (0 mm Hg) to $66.6\% \pm 1.5\%$, $55.7\% \pm 4.4\%$, and $44.8\% \pm 4.5\%$ at external pressures of 40, 50, and 60 mm Hg, respectively. In addition, there was a significant effect of leg elevation on perfusion pressure. At all external pressures, there was a significant decrease in perfusion pressure as IMP increased in the elevated leg (12 cm above heart level) compared with the supine leg ($p = 0.03$) (Fig. 4). However, muscle pH and microvascular blood flow did not decrease significantly more in the elevated leg than in the leg at heart level (Figs. 1 and 3).

Discussion

Our results indicate that muscle microvascular blood flow, oxygenation, and pH all decrease significantly as IMP increases in a human model of ACS. Our results support previous findings that near-infrared spectroscopy measures of muscle oxygenation decrease with increased IMP and decreased local perfusion pressure in animal and human models^{11,19-21}.

Various studies have reported that increasing tissue pressures decrease blood flow to the muscle^{6,22}. This decrease in blood flow could be caused either by active closure of small arterioles or by passive collapse of soft-walled capillaries when tissue pressure rises above intracapillary pressure⁶. As IMP increases, as with simulated ACS, and exceeds 30 mm Hg, the intracapillary pressure is not sufficiently high to maintain muscle blood flow^{22,23}. Our results support this proposition as muscle oxygenation decreases significantly with increasing IMP.

Perfusion pressure is proposed as a more relevant and diagnostic parameter than absolute IMP values are in diagnosing ACS^{2,6,7}. Research performed with photoplethysmography using

the venous stasis model of ACS found that perfusion pressure decreased from 42 to 17 mm Hg in a leg elevated 32 cm above heart level and from 65 to 43 mm Hg with the leg supine²⁴. Our data support previous propositions that leg elevation decreases perfusion pressure and tissue tolerance to ischemia during elevated IMP. For example, the present results demonstrate that leg elevation significantly decreased perfusion pressure and significantly exacerbated muscle oxygenation decrements during elevated IMP. This further decrease in muscle oxygenation can be explained by a decrease in local perfusion pressure to the muscle, ischemia, and increased IMP¹⁰.

Compartment syndrome or vascular injury interferes with the normal hyperperfusion of the site of an injury, causing hypoperfusion. This hypoperfusion lowers muscle oxygenation as measured with near-infrared spectroscopy during ACS of the leg²¹. In addition, invasively verified IMP elevations, using an external compression model, significantly decrease muscle oxygenation as measured with near-infrared spectroscopy¹¹. However, the near-infrared spectroscopy device used had a probe that was difficult to secure to and maintain contact with the skin. There was also subject-to-subject variation observed using alternative near-infrared spectroscopy techniques¹¹. The near-infrared spectroscopy-pH device used in the present study accommodates for each subject's skin pigmentation and fat thickness, and it reached steady state within 5 minutes of each pressure condition, reducing subject-to-subject variability²⁵. Compared with the prior study²⁵, in our study we controlled for confounding effects of reactive hyperemia by allowing the near-infrared spectroscopy measures to reach steady state during the 11-minute interval between pressure conditions.

Accumulation of cellular lactic acid and carbon dioxide during muscle activity decreases interstitial pH, which is proposed to signal vasodilation in vascular smooth muscle cells in response to acidosis²⁶. For example, at rest, the average invasively measured skeletal muscle interstitial pH in human subjects is 7.38; however, after intense exercise, the pH drops to 7.04²⁷. Moreover, the magnitude of the decrease in pH is linearly associated with exercise intensity. Our study documents a similar, progressive muscle acidosis as the pH decreases with increasing IMP. The mechanism for such a decrease in pH with tourniquet-induced ischemia is proposed to be a function of decreased phosphocreatine and increased inorganic phosphate levels²⁸. In addition to the decrease in phosphocreatine with tourniquet-induced ischemia, there is a rapid decline in the levels of adenosine triphosphate in the presence of compartment syndrome⁷, as simulated by our model. This explains the significant decrease in pH with increasing IMP in our study.

Zhang and coworkers²⁴ found that mean microvascular blood flow to the tibialis anterior muscle decreased by 50% in a leg elevated 32 cm above heart level compared with 42% in a supine leg. While our data follow this trend, there was no further significant decrease in blood flow with leg elevation. It is possible that maximal reduction in blood flow was achieved with external compression in addition to venous stasis of the limb at heart level and therefore blood flow did not decrease further with limb elevation. Alternatively, it is possible that the

12-cm elevation used in our study was not sufficient to further decrease blood flow significantly in the control leg when elevated, as compared with the supine leg.

While our study identifies valid parameters and methods for identifying a decrease in microvascular blood flow, oxygenation, and pH with increasing IMP, it has some limitations. We were only able to elevate the leg 12 cm above heart level because of chamber dimensions and leg orientation, which may have limited the amount of decrease in perfusion pressure, and therefore the amount of decrease in oxygenation and pH, achieved. We were also unable to simultaneously gather measurements on the photoplethysmography and near-infrared spectroscopy-pH probes because of interference. This was overcome by lengthening the protocol to allow for sequential rather than parallel measures during each measurement condition. The current model is able to elevate IMP to 30 mm Hg or more and compromise perfusion to the tibialis anterior adequately to decrease oxygenation and pH of the muscle. Using a standardized human model of ACS, we were able to calculate perfusion pressure on the basis of an accepted formula for ACS, reflecting adequate simulation of early ACS in our subjects. However, the current study is a model of ACS and future studies involving patients with suspected acute and chronic compartment syndrome are necessary to further evaluate these noninvasive methods. Another point of interest for future studies is modifying the photoplethysmography and near-infrared spectroscopy-pH probes to study ACS in other compartments of the lower limb as well as ACS in the upper limb.

The strengths of the study include its noninvasive, continuous monitoring of muscle microvascular blood flow, oxygenation, and pH throughout the study in human subjects,

including the 11-minute recovery periods. Our study identifies metabolic and hemodynamic parameters as potential diagnostic tools for ACS.

The current gold standard for diagnosis of ACS is IMP measurement, along with perfusion pressure calculation, after thorough evaluation of clinical signs. However, the limitations of these methods—including pain, risk of infection, risk of technique error, plugging of the catheter tip, lack of consensus on the diagnostic pressure threshold, and lack of specificity and sensitivity—warrant new methods to diagnose ACS more accurately and noninvasively. Our study identifies reliable parameters such as muscle microvascular blood flow, oxygenation, and pH measured noninvasively that may aid diagnosis of ACS. ■

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References

- Hargens AR, Mubarak SJ. Current concepts in the pathophysiology, evaluation, and diagnosis of compartment syndrome. *Hand Clin*. 1998 Aug;14(3):371-83.
- McQueen MM, Court-Brown CM. Compartment monitoring in tibial fractures. The pressure threshold for decompression. *J Bone Joint Surg Br*. 1996 Jan;78(1):99-104.
- McQueen MM, Gaston P, Court-Brown CM. Acute compartment syndrome. Who is at risk? *J Bone Joint Surg Br*. 2000 Mar;82(2):200-3.
- Tiidos PM. Is intramuscular pressure a valid diagnostic criterion for chronic exertional compartment syndrome? *Clin J Sport Med*. 2014 Jan;24(1):87-8.
- White TO, Howell GE, Will EM, Court-Brown CM, McQueen MM. Elevated intramuscular compartment pressures do not influence outcome after tibial fracture. *J Trauma*. 2003 Dec;55(6):1133-8.
- Ashton H. The effect of increased tissue pressure on blood flow. *Clin Orthop Relat Res*. 1975 Nov-Dec;113:15-26.
- Heppenstall RB, Scott R, Sapega A, Park YS, Chance B. A comparative study of the tolerance of skeletal muscle to ischemia. Tourniquet application compared with acute compartment syndrome. *J Bone Joint Surg Am*. 1986 Jul;68(6):820-8.
- Matsen FA 3rd, Krugmire RB Jr, King RV, Nicolas Andry Award. Increased tissue pressure and its effects on muscle oxygenation in level and elevated human limbs. *Clin Orthop Relat Res*. 1979 Oct;144:311-20.
- Whitesides TE, Haney TC, Morimoto K, Harada H. Tissue pressure measurements as a determinant for the need of fasciotomy. *Clin Orthop Relat Res*. 1975 Nov-Dec;113:43-51.
- Wiger P, Zhang Q, Styf J. The effects of limb elevation and increased intramuscular pressure on nerve and muscle function in the human leg. *Eur J Appl Physiol*. 2000 Sep;83(1):84-8.
- Lee SH, Padilla M, Lynch JE, Hargens AR. Noninvasive measurements of pressure for detecting compartment syndromes. *J Orthop Rheumatol*. 2013 Dec 21;1(1):5.
- Ellerby GEC, Smith CP, Zou F, Scott P, Soller BR. Validation of a spectroscopic sensor for the continuous, noninvasive measurement of muscle oxygen saturation and pH. *Physiol Meas*. 2013 Aug;34(8):859-71. Epub 2013 Jul 17.
- Soller BR, Yang Y, Soyemi OO, Ryan KL, Rickards CA, Walz JM, Heard SO, Convertino VA. Noninvasively determined muscle oxygen saturation is an early indicator of central hypovolemia in humans. *J Appl Physiol* (1985). 2008 Feb;104(2):475-81. Epub 2007 Nov 15.
- Mateus J, Hargens AR. Photoplethysmography for non-invasive in vivo measurement of bone hemodynamics. *Physiol Meas*. 2012 Jun;33(6):1027-42. Epub 2012 May 4.
- Zhang Q, Styf J. Abnormally elevated intramuscular pressure impairs muscle blood flow at rest after exercise. *Scand J Med Sci Sports*. 2004 Aug;14(4):215-20.
- Zhang Q, Lindberg LG, Kadefors R, Styf J. A non-invasive measure of changes in blood flow in the human anterior tibial muscle. *Eur J Appl Physiol*. 2001 May;84(5):448-52.
- Styf J, Wiger P. Abnormally increased intramuscular pressure in human legs: comparison of two experimental models. *J Trauma*. 1998 Jul;45(1):133-9.
- Reneman RS, Slaaf DW, Lindbom L, Tangelder GJ, Arfors KE. Muscle blood flow disturbances produced by simultaneously elevated venous and total muscle tissue pressure. *Microvasc Res*. 1980 Nov;20(3):307-18.
- 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 Jun;28(6):365-9.
- Garr JL, Gentilello LM, Cole PA, Mock CN, Matsen FA 3rd. Monitoring for compartmental syndrome using near-infrared spectroscopy: a noninvasive, continuous, transcutaneous monitoring technique. *J Trauma*. 1999 Apr;46(4):613-6; discussion 617-8.

- 21.** Shuler MS, Reisman WM, Kinsey TL, Whitesides TE Jr, Hammerberg EM, Davila MG, Moore TJ. Correlation between muscle oxygenation and compartment pressures in acute compartment syndrome of the leg. *J Bone Joint Surg Am.* 2010 Apr;92(4):863-70.
- 22.** Hargens AR, Akeson WH, Mubarak SJ, Owen CA, Evans KL, Garetto LP, Gonsalves MR, Schmidt DA. Fluid balance within the canine anterolateral compartment and its relationship to compartment syndromes. *J Bone Joint Surg Am.* 1978 Jun;60(4):499-505.
- 23.** Hallböök T, Månsson B, Nilsén R. A strain gauge plethysmograph with electrical calibration. *Scand J Clin Lab Invest.* 1970 Jun;25(4):413-8.
- 24.** Zhang Q, Styf J, Lindberg LG. Effects of limb elevation and increased intramuscular pressure on human tibialis anterior muscle blood flow. *Eur J Appl Physiol.* 2001 Oct;85(6):567-71.
- 25.** Soller BR, Zou F, Ryan KL, Rickards CA, Ward K, Convertino VA. Lightweight noninvasive trauma monitor for early indication of central hypovolemia and tissue acidosis: a review. *J Trauma Acute Care Surg.* 2012 Aug;73(2)(Suppl 1):S106-11.
- 26.** Aalkjaer C, Peng HL. pH and smooth muscle. *Acta Physiol Scand.* 1997 Dec;161(4):557-66.
- 27.** Street D, Bangsbo J, Juel C. Interstitial pH in human skeletal muscle during and after dynamic graded exercise. *J Physiol.* 2001 Dec 15;537(Pt 3):993-8.
- 28.** Newman RJ. Metabolic effects of tourniquet ischaemia studied by nuclear magnetic resonance spectroscopy. *J Bone Joint Surg Br.* 1984 May;66(3):434-40.