2009

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Recommended Citation

Lynch, J. E., Lynch, J. K., Cole, S. L., Carter, J. A., & Hargens, A. R. (2009). Noninvasive monitoring of elevated intramuscular pressure in a model compartment syndrome via quantitative fascial motion. Journal of Orthopaedic Research, 27(4), 489-494.

Noninvasive Monitoring of Elevated Intramuscular Pressure in a Model Compartment Syndrome via Quantitative Fascial Motion

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Received 2 April 2008; accepted 25 August 2008
Published online 31 October 2008 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jor.20778

ABSTRACT: Compartment syndromes, conditions of elevated intramuscular pressure (IMP) resulting from trauma or chronic overuse, frequently require invasive IMP monitoring for accurate diagnosis. Our objective was to test a noninvasive ultrasound technique for estimating IMP based on fascial displacement waveforms from arterial blood pressure pulses. IMP was increased in the legs of 23 healthy adult subjects up to 80 mmHg using two blood pressure cuffs covering the region from the knee to the ankle. Receiver operator characteristic curves and recursive partitioning were used to determine the sensitivity and specificity of diagnosing elevated IMP using fascial displacement. For one curve, in which several ultrasonic measurement parameters were used along with subject body mass index and blood pressure, the sensitivity and specificity for diagnosing normal IMP (below 30 mmHg) from elevated IMP (30 mmHg and up) was 0.61 and 0.94, respectively. Recursive partitioning, in which IMP was divided into three ranges (normal $<$30 mmHg, midrange of 30–40 mmHg, and elevated $\geq$50 mmHg), resulted in improved diagnostic sensitivity (0.77) with almost no change in specificity (0.93). © 2008 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res 27:489–494, 2009

Keywords: compartment syndrome; intramuscular pressure; noninvasive diagnosis; Volkmann's contracture; crush injury

Compartment syndrome is a condition in which high pressure within a closed fascial space (muscle compartment) reduces capillary blood perfusion below the level necessary for tissue viability. Compartment syndromes develop in skeletal muscles that are enclosed by relatively noncompliant, osseofascial boundaries, where a buildup of pressure is not easily dissipated.[1] In acute cases, this pressure buildup may result from tibial fracture, blunt trauma resulting in interstitial edema, hemorrhage, postischemic muscle fiber swelling, or venous obstruction caused by burns or compartment volume constriction (e.g., a tight cast). Chronic cases may be caused by repeated strenuous exercise. Treatment of acute compartment syndrome relies on early recognition and prompt fasciotomy to prevent Volkmann's contracture.[2–4] In chronic cases, symptoms may disappear with rest, although in many cases fasciotomy is also required to relieve symptoms.

Compartment syndrome can often be diagnosed on the basis of clinical examination, but recognition can be difficult in cases of severe trauma where the patient is unable to convey early symptoms of pain. An important adjunct to clinical diagnosis is direct measurement of intramuscular pressure (IMP) by insertion of a catheter into the muscle at risk, for example, the use of a slit catheter to provide continuous IMP measurement.[5] Most clinicians accept direct IMP measurement as the gold standard for diagnosis. However, due to the invasive nature of the measurement and because considerable disagreement exists over the appropriate threshold pressure for diagnosis of compartment syndrome, some clinicians are reluctant to perform direct IMP measurement in all cases.

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Inaccuracy in the current methods of compartment syndrome diagnosis often leads to delays in treatment. Recent studies showed that near-infrared spectroscopy (NIRS) can be effective for diagnosis of chronic compartment syndrome. These studies demonstrated a significant inverse correlation between IMP and oxyhemoglobin level; when IMP reaches critical values some form of shock often accompanies trauma, which leads to low oxygen tissue saturation globally. Low global oxygen saturation can lead to misdiagnosis of acute compartment syndrome. Also, NIRS has trouble measuring oxygen saturation in deep muscle compartments, as the infrared signal can only penetrate 2–3 cm into tissue.[6–9]

In chronic exertional compartment syndrome, magnetic resonance imaging has shown increased T2 signal intensity with anterior compartment pressures.[10–12] However, magnetic resonance imaging (MRI) use is usually limited to radiology departments. A lower cost, portable alternative is noninvasive measurements of tissue hardness using a tonometer-type device. Initial results indicated low diagnostic sensitivity and specificity (68% sensitivity and 96% specificity).[13] A more recent study showed improved performance, but diagnosis is limited to superficial compartments.[14]

Noninvasive ultrasonic measurements of muscle compartment motion provide a promising alternative. Lynch and coworkers[15] first described the technique, in which the ultrasonic pulsed phased locked loop (PPLL) was used to measure micron-level tissue displacements caused by saline infusion into a cadaver model. The expansion of the muscle compartment with saline infusion was related to the nonlinear pressure–volume curve. Further work on human subjects showed that the ultrasonic PPLL could detect arterial pulsations in the compartment, and that automated waveform analysis could be used to estimate IMP without calibration.[16] In

this study, the harmonic content of the arterial pulse waveform was used to determine pressure, and the ratio of the fundamental waveform frequency to the first harmonic (harmonic ratio) correlated to IMP with an R^2 value of 0.89.

Previous work on harmonic analysis of intracranial pressure waveforms suggested that the harmonic ratio is related to tissue compliance, and is therefore an indirect measure of pressure.[17–21] In a follow-up study in pigs, in which plasma infusion to the anterior compartment was used to increase IMP, harmonic ratio correlated poorly with pressure,[22] suggesting that the relationship between compliance and pressure varies with compartment type and species. In this same study, the amplitude of the arterial pulse waveform was more directly related to IMP than harmonic ratio. The relationship was nonlinear, with pulse amplitude initially increasing with IMP until it approached the mean arterial pressure. This trend is consistent with findings from Kim and associates,[23] who measured the displacement of the arterial wall using a 2D ultrasonic imaging array when the wall was compressed using a blood pressure cuff. Displacement increased with external pressure, which was attributed to a reduction in transluminal pressure on the arterial wall. By reducing transluminal pressure, the external pressure reduced arterial compliance, resulting in increased displacement, as long as the external pressure was less than arterial pressure. As external pressure approaches mean arterial pressure, blood flow is occluded and displacement begins to decrease.

In the previous pig study, fascial displacement remained elevated over baseline even when pressure exceeded 100 mmHg, so that fascial displacement could be used to distinguish elevated pressures (30 mmHg and up) from normal pressures with fair sensitivity 74% and specificity 75%.[22] In this study, fascial displacement and other ultrasound echo parameters were monitored in a human model of elevated IMP with respect to body mass index (BMI) and mean arterial pressure. We hypothesized that ultrasonic measurements of fascial displacement can be used to detect elevated IMP in this model with high sensitivity and specificity.

MATERIALS AND METHODS

This study was conducted under an institutional review board-approved protocol in which IMP was increased in the anterior compartment of the leg in 23 healthy adult subjects (14 males, 9 female, average weight 75 ± 16 kg) by applying one 21 cm-wide blood pressure cuff and one 15-cm cuff over the leg, covering the entire length from the tibial tuberosity to a position proximal to the malleolus flair of the ankle. A wide cuff was previously found to increase IMP uniformly from superficial fascia down to bone[24,25] with IMP approximately equal to cuff pressure.[26] About half the subjects were 18–22-year-old student-athletes; the other half ranged in age from 25 to 70, with varying degrees of physical fitness.

In each subject, a baseline cuff-pressure reading at 0 mmHg was taken, then cuff pressure was increased from 20 to 80 mmHg in 10 mmHg steps. At each step, the cuff pressure was maintained for 1 min while ultrasonically monitoring fascial displacement. Fascial displacement was measured in the cuffed leg and the contralateral control leg using 1 MHz, unfocused ultrasonic transducers, 1.72 cm in diameter. The transducers were placed over the anterior compartment, about 4 cm distal to the bottom of the tibial tuberosity and 1–2 cm outside the tibia. In the cuff leg, the cuff was placed over the transducer prior to pressurizing the cuff.

At each pressure setting, adjustments were made to the transducer position and the receiver depth to obtain a strong echo at a depth around 3–4 cm, which corresponds to the depth of the interosseous membrane and the inner fascia wall of the anterior compartment. Once a strong echo was obtained, the transducer was taped in place, and the position of the four largest echoes within the 4-cm sample depth of the ultrasonic receiver was tracked using a digital pulsed phase locked loop (dPPLL) algorithm. The dPPLL is a new implementation of the PPLL that measures phase changes of an ultrasonic echo, converting the change into a time-of-flight measurement.[27–29] In this implementation, provided on the Emergency Non-invasive Tissue and Compartment Tester (EN-TACT^{TM}, Luna Innovations, Inc., Roanoke, VA), phase measurements are converted into displacement by assuming that ultrasonic velocity is constant. This assumption has not been conclusively validated, but a published report supports the claim.[30]

Displacement and echo backscatter waveforms were obtained at a sample rate equal to the ultrasonic pulse repetition rate of 1 ms. These waveforms follow the cardiac cycle (Fig. 1). From each waveform, the amplitude and harmonic ratio were extracted once per second, after shifting the starting point of the waveform 1000 samples and performing an autocorrelation routine to filter out nonpulsatile motion artifacts such as those caused by inflation of the blood pressure cuff or muscle fasiculations. After filtering out nonpulsatile waveforms, the fast Fourier transform of the signal was taken, and the amplitude of the fundamental frequency was used to estimate fascial displacement and backscatter amplitude.

Although amplitude measurements are most often performed in the time domain, frequency domain amplitude measurements correlate well to time domain measurements of amplitude and are less noisy.[31] The frequency domain measurement also provides data used in analyzing harmonic content. Numerous waveform analysis techniques have been proposed for measuring harmonic content, but for this application the ratio of the fundamental frequency amplitude to root mean squared sum of the next four harmonics was used.

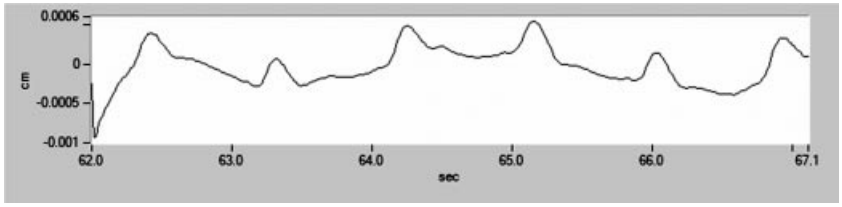

Figure 1. Tissue displacement waveform displayed over a 5-s interval.

Data were recorded for 2 min at each cuff pressure, yielding a maximum of 120 data points per pressure. At each pressure, the data point that represented the 90th quantile reading was used for analysis to eliminate possible outliers due to patient movement or other transient effects that passed through the autocorrelation filter. Use of a median value would also filter outliers from the measurement. However, the recorded values often had a bimodal distribution with multiple echoes, and the system sometimes tracked motion from a tissue boundary that did not correspond to the fascial wall. Use of the 90th quantile reading ensured that the reading was chosen from the fascial wall while eliminating the occasional outlier.

Four ultrasonic parameters were measured: fascial displacement amplitude, displacement harmonic ratio, echo backscatter amplitude, and backscatter harmonic ratio. To assess the relationship between each of the four parameters and cuff pressure, an analysis of variance (ANOVA) followed by contrast analysis was performed using JMP v5.1.1. The multifactor ANOVA modeled variance for the following values: leg (control vs. cuffed), cuff pressure, BMI, mean arterial pressure, and the interaction between the variables. Next, two receiver operator characteristic (ROC) curves were constructed to assess clinical diagnostic utility. The first was constructed using a full logistic regression model in which diagnosis was based on the four parameters described above plus subject BMI and mean arterial pressure. The second was constructed using fascial displacement amplitude alone, as this parameter appeared to be most sensitive to pressure changes. Both curves were constructed using a true positive reading when the cuff pressure was $\geq$30 mmHg. Thus, all readings on the control leg were used as readings of normal IMP, as were readings on the cuffed leg taken at cuff pressures of 0 and 20 mmHg.

A diagnostic threshold of 30 mmHg was chosen to be conservative in diagnosis. As mentioned earlier, many clinicians set the threshold at 40 mmHg, while others base diagnosis on perfusion pressure (mean arterial pressure minus IMP) or use a combination of clinical signs and pressure readings. This ambiguity can be incorporated into the diagnostic decision by using recursive partitioning, which divides measured parameters into groups to find an optimal diagnostic threshold. This technique is ideal for finding borderline diagnostic groups, in which some readings are neither positive nor negative. In performing recursive partitioning, the diagnostic IMP values were divided into three groups. Ultrasonic readings obtained at cuff pressures of 0 and 20 mmHg, plus all readings on the control leg, were categorized as normal IMP. Readings obtained at cuff pressures of 30 and 40 mmHg were categorized as midrange IMP; readings obtained at cuff pressures 50 mmHg and up were categorized as elevated IMP.

For comparing ROC curves, sensitivity measurements were obtained from the recursive partitioning data using a ratio of true positive (TP) readings to the sum of true positives and false negatives (FN):

$$\text{Sensitivity} = \text{TP}/(\text{TP} + \text{FN}) \quad (1)$$

Similarly, specificity was determined using a ratio of true negative (TN) readings to the sum of true negatives and false positives (FP):

$$\text{Specificity} = \text{TN}/(\text{TN} + \text{FP}) \quad (2)$$

In the recursive partitioning analysis, midrange diagnostic readings introduced some ambiguity as to whether a reading was a true/false positive or negative. We resolved this ambiguity by providing two sets of sensitivity and specificity values. In the first set of calculations, all midrange displacement values were considered TP when the cuff pressure was 30 or 40 mmHg, while midrange displacements were considered FP or FN if the cuff pressure was either high or low. Case 2 provides an alternative scenario, where it was assumed that the use of continuous monitoring and the evaluation of clinical signs would allow a clinician to arrive at a correct diagnosis over time. The only exception was for a low displacement reading at a pressure of 30 or 40 mmHg, in which case a clinician might incorrectly assume that further monitoring was unnecessary. This was considered a false negative.

RESULTS

Each of the four ultrasonic parameters exhibited significant increases in the model compartment syndrome leg versus the control leg (Fig. 2) once pressure exceeded 50 mmHg. All four parameters increased

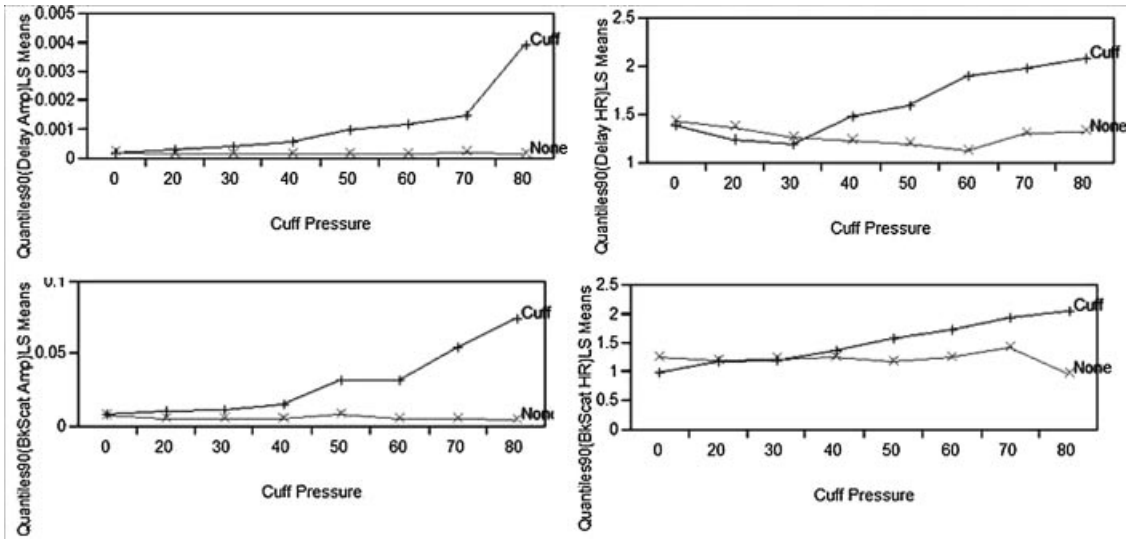

Figure 2. Comparison of the mean displacement amplitude (top left) on the cuffed leg (dark) versus the uncuffed leg (light) at each pressure level over the 23 individuals tested. Similar comparisons of the displacement harmonic ratio (top right), mean backscatter amplitude (bottom left), and mean backscatter harmonic ratio (bottom right) are also provided.

Table 1. ANOVA Model p-Values (Values in Bold are Statistically Significant ($p<0.05$))

	Displacement Amp.	Disp. Harmonic Ratio	Backscatter Amplitude	Backscatter Harm. Ratio
Leg	0.99	0.85	0.96	0.39
Cuff pressure	<**0.01**	0.06	<**0.01**	**0.02**
BMI	0.75	<**0.01**	0.83	0.60
MAP	0.72	0.72	0.67	0.54
Leg*cuff Pressure	<**0.01**	**0.01**	<**0.01**	**0.01**
Leg*BMI	0.77	0.17	0.97	0.25
Leg*MAP	0.35	0.47	0.16	0.05
Cuff Pressure*BMI	**0.05**	0.54	0.07	0.81
Cuff Pressure*MAP	0.99	0.80	0.50	0.85
BMI*MAP	0.79	0.84	0.18	0.91
Leg*cuff Pressure*BMI	**0.05**	0.52	0.30	0.89

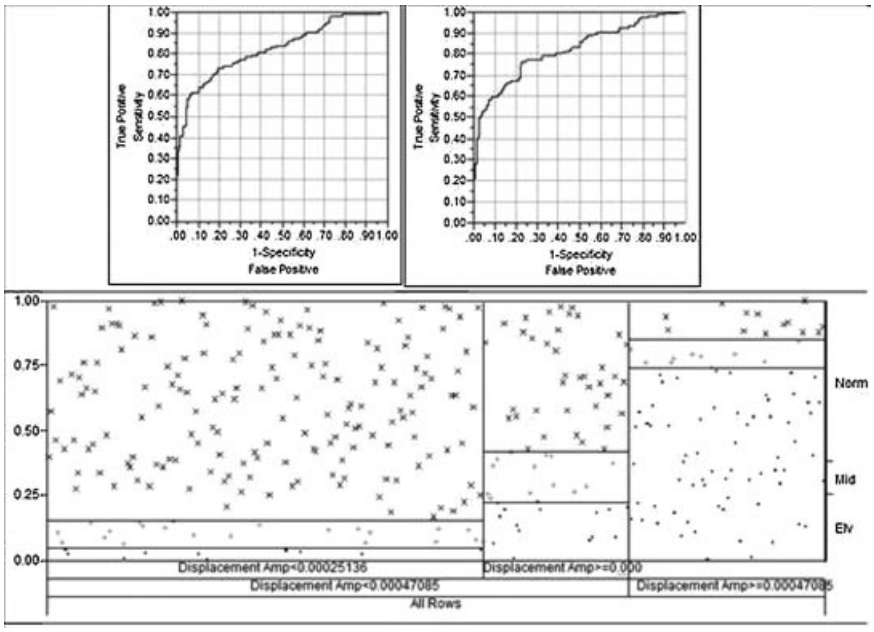

Figure 3. Sensitivity and specificity measurements using full effect model ROC curves (top left), an ROC curve based on displacement amplitude only (top right) and recursive partitioning (bottom). The area under the curve for the first ROC curve was 0.83; for the second it was 0.82.

with pressure with fascial displacement and echo backscatter amplitude exhibiting a strong, nonlinear increase at high pressures. Displacement harmonic ratio and backscatter harmonic ratio exhibited weaker linear increases.

Other sources of variation, including BMI and mean arterial pressure are shown in Table 1. The ANOVA model, which included higher order interactions between variables, showed that cuff pressure, leg, and the interaction between these two variables were the most significant sources of variation in all of the measured parameters. BMI was a significant source of variation in the displacement harmonic ratio only, while the higher order interactions between BMI, leg, and cuff pressure were significant sources of variation in the displacement amplitude.

Figure 3 provides two ROC curves with the diagnostic threshold set at a cuff pressure of 30 mmHg along with results from the recursive partitioning test. The first curve, formed using a full logistic regression of all parameters, provides only a marginal improvement in the diagnosis of elevated IMP over the use of displacement amplitude alone in the second curve. The sensitivity and specificity readings for the curves and the recursive partitioning tests are summarized in Table 2.

Table 2. Sensitivity and Specificity of Diagnosis

Model	Sensitivity	Specificity
Multiparameter	0.61	0.93
Delay only	0.75	0.77
Recursive partition: Case 1	0.66	0.73
Recursive partition: Case 2	0.77	0.94

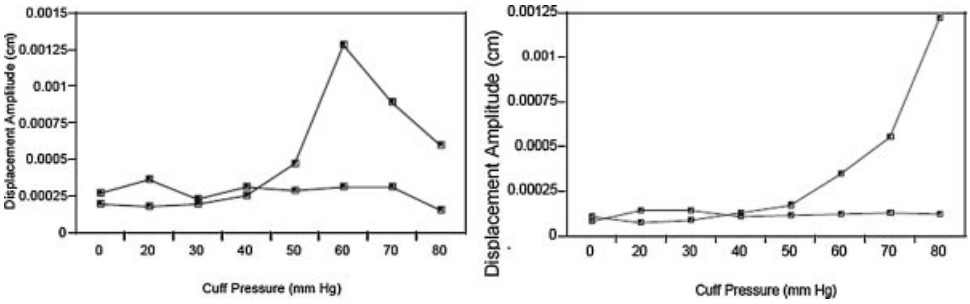

Figure 4. Example tissue displacement readings for two individuals tested. The decrease in tissue displacement at pressures of 70 and 80 mmHg that occur in the first subject (left) appear to be linked to low blood pressure, as the first subject had a blood pressure of 112/46, while the second subject had a blood pressure of 116/75.

DISCUSSION

Our results are consistent with the hypothesized relationship between fascial displacement and elevated IMP. Although the mean values for each of the ultrasonic parameters were not significantly elevated over control values until cuff pressure reached 60 mmHg, this may have been due to a few outliers, as the sensitivity and specificity readings (Table 2) were obtained with a diagnostic threshold of 30 mmHg and up corresponding to a true positive reading.

The sensitivity and specificity values are comparable to those reported for clinical signs[32] and invasive IMP measurements.[13] However, a more direct comparison to gold standard invasive IMP measurements in a clinical setting is still needed.

The sensitivity and specificity did not appear to depend on physiological characteristics such as blood pressure, age, or BMI. However, all subjects in this study had a blood pressure in the normal range. In a few of the subjects with a lower blood pressure reading, the tissue displacement was observed to decrease when IMP approached mean arterial pressure (as illustrated for two subjects in Fig. 4). This is consistent with the results from a porcine model,[22] in which tissue displacement was observed to increase with IMP until IMP approached mean arterial pressure; at that point, tissue displacement appeared to decrease. Despite this tissue-displacement decrease in the porcine model, pressure remained elevated over baseline values even when IMP = 100 mmHg. The nonlinear response of tissue displacement was more pronounced in the porcine model[22] than in our study, probably because the human subjects had a higher mean arterial pressure (96 mmHg $\pm$ 11 mmHg) than that in the pigs (81 $\pm$ 12 mmHg) and because the maximum IMP in humans was limited to 80 mmHg for safety concerns.

Based on this observation, ultrasonic measurements of tissue displacement would be a less sensitive diagnostic tool in hypotensive subjects, particularly when IMP approaches mean arterial pressure. However, in subjects with a normal blood pressure, the clinical signs of a compartment syndrome are quite pronounced at the high IMP values needed to reduce fascial displacement below baseline values. Further study is needed to determine whether clinical signs would be similarly obvious in the case of a severely hypotensive subject with high IMP.

The close relationship between fascial displacement and echo backscatter (Fig. 2) suggests that the two parameters are closely linked, most likely because changes in fascial geometry during tissue motion affect the amount of reflected ultrasonic signal. Thus, the echo backscatter waveform provides no additional diagnostic information over the fascial displacement waveform. In addition, the harmonic ratio readings followed a similar trend to the amplitude readings, and do not appear to provide additional diagnostic information beyond that already provided by displacement amplitude. The two ROC curves (Fig. 3) are consistent with this conclusion, as the full logistic regression model provided only marginal improvement in diagnostic accuracy over the ROC curve formed using fascial displacement alone.

Based on these results, noninvasive measurement of pulsatile tissue motion using ultrasound appears to have comparable diagnostic sensitivity and specificity to invasive measurements and clinical signs. However, this model study has important limitations, as it is unclear to what extent the low sensitivity is due to errors in the cuff model or due to errors in the measurement itself. A more controlled study, conducted using gold standard invasive measurements of intramuscular pressure would provide more definitive results. Ideally, this testing would be performed in a clinical setting with noninvasive measurements performed in conjunction with invasive measurements of IMP and with diagnosis by clinical signs.

ACKNOWLEDGMENTS

This study was funded by Luna Innovations Incorporated.

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