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Scholarly Report Title: Evaluation of the Change in Vascular Tone Following Brachial Plexus Nerve Block Using Amplification of Video from a Mobile Device.

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Evaluation of the change in vascular tone following brachial plexus nerve block using amplification of video from a mobile device.

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**Purpose:** To evaluate the efficacy of using an iPhone as a pulse plethysmograph in detecting changes in cutaneous perfusion and vascular tone caused by regional anesthesia in the form of clinically established brachial plexus block techniques.

**Methods:** 50 patients scheduled to undergo brachial plexus blocks as part of their planned surgeries were enrolled in this study. Bilateral iPhone contact photoplethysmography recordings and Radical 7 pulse co-oximeter measurements were made shortly prior to and for 20 minutes after the placement of the brachial plexus block. Shorter recordings were made after the completion of surgery and again once per hour for 4 hours or until the patient was discharged home. Admitted patients were further monitored at 24-hour post-block.

**Results:** Skin temperature changed significantly, however measurements made by the Radical 7 and iPhone did not show significant changes after brachial plexus block.

**Conclusions:** Although there was likely increased blood flow to the periphery as evidenced by the significant change in skin temperature, neither the Radical 7 nor the iPhone was able to detect significant changes in the plethysmograph signal. Further study is necessary to determine whether this is truly due to a failure of the iPhone or whether differences in the study protocol resulted in the blunted effect size that was also seen in the Radical 7 data.
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Glossary:

ABI – Ankle Brachial Index, IC – infraclavicular, PA – pulse area, PACU – post-anesthesia care unit, PI – Pulse Index, PPG – pulse plethysmograph, PVI – Pleth Variability Index, RT – Rise time, SC – Supraclavicular
Introduction:

The Center for Disease control and Prevention has stated that as of 2011, 8.3% of the US population has diabetes, a percentage that continues to rise. These 25.8 million people generate $116 billion in medical expenses per year with another $58 billion lost due to disability, work loss, and premature mortality (1). In addition, the number of diabetic patients in the US is expected to grow to 44.1 million in 2034 and generate $336 billion in total expenses (2). Currently, 2% of people with diabetes (520,000 patients) develop ulcers each year (3) and cause $38.3 billion in yearly healthcare expenditures (4). The major driver of the costs of care and of adverse outcomes for this group is the time required to heal; a factor that depends critically on the degree of perfusion of the injured tissue. Non-healing ulcers notoriously lead to amputations and account for 60% of all nontraumatic surgical amputations performed in the US (1). Guided interventions (e.g. surgical debridement, advanced wound care or standard wound care) can potentially prevent up to 85% of amputations (5). However, new prognostic tools for the healing potential of these wounds are sorely needed.

Currently, there are no reliable tools that can accurately guide conservative wound care versus medical or surgical intervention of diabetic ulcers. The standard of care now utilizes the ankle-brachial pressure index (ABI), a technique that assesses the difference in blood pressures between the arms and the legs to estimate perfusion. Although the ABI is able to be performed in any practice, training and experience are required to obtain accurate results, leading to significant inter-observer bias (6). Furthermore, patients with diabetes develop arterial calcifications that can prohibit ABI from identifying states of low perfusion (7,8). Especially in the setting of diabetes, the number of missed cases has led many physicians to dismiss the validity of this test. A replacement diagnostic must be found. It has to be accessible, inexpensive, minimally invasive, and ideally easy to use by minimally trained personnel or the patients themselves, potentially allowing for remote monitoring and follow up.

Given this need, numerous other experimental approaches have evolved including hyperspectral imaging, transcutaneous oxygen sensors, and laser Doppler. However, these devices require great initial investment and often extensive training. Lower extremity Doppler ultrasound can also be used but at a cost of over $700 per scan to perform is expensive as a routine measure and is still only a measure of large vessel blood flow rather than a direct measure of cutaneous perfusion. In an attempt to meet this need, we have developed an extension for a tool that most
Physicians (and patients) already own – a smartphone – and here attempt to prove its efficacy in detecting changes in blood flow. By using the phone’s flash and camera and then quantifying the changes in reflected light, one can essentially turn the device into a reflectance photoelectric pulse plethysmograph (PPG).

Photoelectric Pulse plethysmography measures the volume of blood vessels by detecting the changes in amount of light that is reflected or transmitted depending on the methodology being used. In this way it has long been known to be capable of evaluating the small vessels in sum. Multiple studies have shown that changes in the PPG signal can reflect atherosclerosis and disease state. Likewise, studies have shown that it can evaluate changes in sympathetic vascular tone. Applications in both scenarios have faced limitations due to the complexity of computational analysis that must be performed. Recently, smartphones have begun to be evaluated for their use in assessing physiologic parameters as a reflectance PPG (9,10). Indeed, many simple apps are available that can determine one’s heart rate from the phone’s flash and camera but a wealth of additional information is contained in that signal and has only just begun to be tapped.

Expanding from these smartphone approaches and the existing literature on the use of standard PPG in detecting changes in peripheral vascular tone, regional anesthesia was identified as an ideal testing setup to validate our device. Regional anesthesia blocks peripheral nerves with local anesthetics, resulting in interrupted conduction in sensory, motor and autonomic fibers, thus directly disrupting the sympathetic innervation of the blood vessels unilaterally and thereby allowing for internal control on the unaffected side. It also provides the ability to measure changes in vessel tone over a short time period without the confounding factor of significant central hemodynamic variations. For purposes of comparison, a Radical 7 pulse co-oximeter (Masimo, Irvine CA) was used to measure the pulse index (PI) and pleth variability index (PVI). These values had been previously thought to correlate with central hemodynamic changes and responsiveness to a fluid bolus but, in a recent study by Bergek et. al. in 2015(11), PI and PVI were also shown to change significantly in patients receiving regional anesthesia and thereby suggesting a peripheral component to the measures.

Student Role:
The student, Benjamin Brush, has conceived and designed this project in partnership with Dr. Kamen Vlassakov MD, Director of Regional Anesthesia at Brigham and Women’s hospital. Benjamin has generated all the funding to support this work from external competitions that he
and his team have won. Together with Isabel Restrepo and Steven Dalvin he programmed the backend analysis platform. He has personally performed the recordings for this study under the observation of Kamen Vlassakov and others in the anesthesia department at Brigham and Women’s Hospital.

**Methods:**

*iPhone:*

A mobile application (app) was designed by the author and collaborators for tracking the measurements. After entering a code in place of the patient’s name, the region of the body being measured is selected (in this instance, the hand). Once the subject’s finger is secured in place by a Velcro strap, the recording is begun by tapping a button on the screen. The phone’s light emitting diode (LED) is turned on and the camera is allowed a short lag period before any video is saved to allow for reduction of movement artifact. Video is recorded at 30 frames per second. White balance is held constant throughout the recording process. In addition to the video, a text file is generated with the average values per frame of the green channel (as has been shown to reduce motion artifact (12)). The video records until 20 minutes after the block is performed and is stopped by touching another button on the screen.

The videos are processed offline on custom Python code with the use of Numpy, SciPy (13), and MatPlotLib (14) packages. 60-second windows of raw data were conditioned with a Butterworth bandpass filter. A low cutoff of 0.15Hz, high cutoff of 10Hz and order of 1 were selected as the ideal compromise between preserving true wave-shape and minimization of baseline deviation and after reviewing published evidence (15,16) as well as conducting our own assessment of the effects of filtering parameters on the waveform (Figure 1). Local minima on the processed signal were used for isolating pulses and artifact contribution was reduced by omitting local minima values that differed by greater than 1 standard deviation from the median local minima value or which occurred more frequently than 2.5Hz (which allowed for detection up to a heart rate of 150). Average pulse amplitude, defined as the difference in the unnormalized signal between the local minima and local maxima of a given pulse, was recorded at this point across the pulses in the window.

The isolated pulses were then normalized for width and height as per Allen et al. 2005 (17) to control for varying heart rate. Normalized pulse waveforms that were not within 90% agreement with the average were discarded and this process was repeated until all waveforms were within
90% agreement. Averaged normalized waveforms were then generated for each minute of a recording. Rise time (RT) and pulse area (PA) were measured from the normalized pulse. RT was calculated from the normalized pulse signal as the time from the start of the pulse (local minima 1) to the highest point in the pulse (the local maxima). PA was calculated using trapezoidal approximation of the area under the normalized pulse curve. Averages were then calculated based on the final count of the number of pulses in a given 60-second window after removing outliers as above.

**Radical 7**

Two Radical 7 pulse co-oximeters were used simultaneously for recordings. Both devices were configured with software version 7.3.3.1. Settings for PI and PVI were set to “short”. A reusable sensor (Masimo LNCS DC-I) was then placed onto a finger. The radical 7 then recorded data for the duration of the iPhone video at a sampling frequency of about 0.5Hz. Heart rate, PI, and PVI data was offloaded to a computer using TrendCom software. Analysis of offloaded data was performed using custom python code with the above packages.

**The Recordings:**

The study was designed to include a total of 50 adult patients (age >18) otherwise receiving brachial plexus regional anesthesia at Brigham and Women’s hospital for non-emergent procedures. These participants did not have any prior history of neurological or vascular impairment to either arm (prior nerve injury, stroke, arteriovenous fistula, venous thrombosis, etc.). The study participants furthermore did not have any signs and/or symptoms of sepsis or shock. Additionally, there was no significant alteration to the skin (extensive burns, tattoo, etc.) in the assessed area.

Prior to recording, the participant was supine or with their head slightly elevated in bed for a minimum of 5 minutes. An IV was placed on the non-operative arm and a baseline blood pressure is recorded. Two Radical-7’s were used to record the pulse index (PI) and Pleth Variability Index (PVI), one attached to a finger on the left hand and one on the right hand. Likewise, one iPhone 6s (Apple, Cupertino CA; iOS version 9.2.1) was gently secured to a finger on either hand using a Velcro strap. Skin temperature was approximated with an infrared thermometer.
Recordings on the iPhones and Rad-7s were begun roughly at least 60 seconds prior to placement of the block and the patient was asked to provide a 10-point subjective measure of their pain/sensation. Standard IV sedation and analgesia with midazolam (max dose 2 mg) and fentanyl (max dose 100 mcg) were then administered and a brachial plexus block was performed under ultrasound guidance (Sonosite, Bothell, WA). Recordings continued until 20 minutes had elapsed after the first injection of perineural anesthetic or until it was necessary to stop the recordings to allow for the start of the surgery. Depending on the method of brachial plexus block used, several variations exist for the postoperative measurements (always iterations of about 3 minute recordings with Rad-7 and iPhone):

1. For patients receiving a single injection nerve block with plans for discharge the same day: following the operation, a set of short recordings was obtained once per hour as they were recovering in the post-anesthesia care unit (PACU) to a maximum of 4 hours or discharge.

2. For patients receiving a single injection nerve block that are to be admitted to the hospital, postoperative measurements were made once per hour for four hours post-operatively and then at 24 hours after the initial block was placed.

3. For patients receiving continuous nerve blocks via a perineural catheter and the patient is to be admitted, measurements were made once per hour for 4 hours after admission to the PACU and then once per day until the perineural infusion was discontinued. Measurements were made at the time of discontinuation and then once per hour thereafter for 4 hours and an additional recording 24 hours after if the patient was still in the hospital.

Results:

A total of 20 patients have been recruited to date with a mean and median age of 48 and a range of 20 – 90 years old. The patient demographics are further described in Table 1. In every subject to date full regional anesthesia was achieved prior to start of surgery and also noted at the first postoperative recording session. Two subjects had to be removed from the data when it was later discovered that they had met exclusion criteria.
Temperature:

Summative temperature information is found in Figure 3. Overall there was seen to be a significant change of about 3-4 degrees Fahrenheit between the pre- and post-block measurements in the blocked arm, with negligible change in the control arm.

PI/PVI:

As assessed by the Masimo Radical 7, the changes in PI and PVI over time after the block are depicted in Figure 4. On the side of the regional block there is an increase in PI and decrease in PVI however, the standard deviation for all time points overlaps the control side.

iPhone:

Values averaged across up to 20 trials are depicted in Figure 5 with many sections having fewer trials due to interruptions in recordings for patient care. There is no apparent difference between the block side and the control for values measured for amplitude, RT, or PA.

Discussion:

The recordings completed to date fail to demonstrate the ability of the iPhone to measure changes in amplitude, PA, or RT after brachial plexus block. Furthermore, the recordings in this study fail to replicate the Radical 7 measurements made by Bergek et al. The significant temperature change observed in the blocked hand 20 minutes after performing the block suggests that there was indeed increased flow to the hand, however, as the Radical 7 was being used as the PPG control for determining alteration in the PPG signal after a regional block, it is difficult to assess the validity of the iPhone measurements.

Our study does differ from Bergek et al. in a few significant ways. These differences are outlined in Table 2. Of particular note, axillary blocks were the predominant block type selected by anesthesiologists for subjects participating in this study rather than supraclavicular (SC) and infraclavicular (IC). The axillary block is performed with perineural injections around the terminal branches of the brachial plexus and affects the median, ulnar, radial and musculocutaneous nerves. By comparison, the supraclavicular block targets the trunks of the brachial plexus with injections.
usually affecting the superior, middle, and with spread to the inferior trunks and therefore effectively blocks the entirety of the brachial plexus. Furthermore, the current methodologies for administering axillary, SC, or IC blocks at this institution, especially after the introduction of ultrasound guidance, all involve multiple smaller volume perineural injections rather than a single large-volume injection. Consequently, time zero was specified as the time of the first injection often with minutes elapsing before the needle was removed. This allowed for a degree of imprecision (reflecting evolving clinical practice) in measuring elapsed time and might limit assessment of the changing values measured by both the Radical 7 and the iPhone. However, the great majority of the effect of the nerve block was seen by Bergek et al. to take effect within the first 5-10 minutes of the block and thus even assuming a possible 2 minutes of variance between trial start times, values beyond 12 minutes should have reached a fairly steady state along the response curve and thus later time points would still be valid measures of overall change relative to baseline.

The type and amount of anesthetic used in our study was also variable as it was determined not by protocol but by anesthesiologist discretion for the particular clinical scenario. This resulted in the use not just of mepivacaine, but also often the addition of ropivacaine. Ropivacaine has been shown, at least in mouse models, to produce a mild local vasocontriction (18) which may conceivably have an effect on the otherwise vasodilatory disruption of sympathetic tone achieved by the nerve block. However, neither clinical experience, nor uniform distal temperature rise, due to arterial hyperemia supports this notion. Further study is necessary to determine exactly how this interaction would affect the plethysmograph signal.

One interesting additional finding from these recordings and the development of the signal analysis platform is the effect of filtering parameters on the shape of the pulse signal. The effect of the low-frequency cutoff has been previously described (15), however, high frequency cutoff and filter order have not been investigated to date. Unlike many traditional PPGs which use analog filters to process the incoming signal, the raw iPhone data provided the ability to easily process the signal in a multitude of ways. We used digital equivalents to these analog filters and were able to explore the effect of the high-frequency cutoff and filter order parameters on the raw pulse shape. This was previously illustrated in figure 1 and informed our final parameter selection. From this assessment it is worth noting that a higher-order Butterworth bandpass filter significantly
altered the shape of the pulse wave, the pulse area, and specifically the location of the dicrotic notch. As filter order increased, the dicrotic notch was seen to move later in the pulse and lower down the descending limb, closer to the diastolic nadir of the pulse. This effect is similar to the waveform changes that were noted by Allen and Murray in their assessment of the effects of the low cutoff (15). Additionally, the pulse area decreased with increased filter order. Rise time remained relatively constant except at a high frequency cutoff of less than 6.67. In sum, it would seem that the ideal filter for the iPhone pulse signal recorded from the green channel is a simple 1st order bandpass filter with a low cutoff of 0.15 Hz and high cutoff of 10 Hz.

In conclusion, we determined that a band pass filter with a low frequency cutoff of 0.15 Hz and high frequency cutoff of 10 Hz provided satisfactory representation of the pulse shape while a filter order greater than 1 caused distortion of the dicrotic notch. Yet, it appears that while the iPhone was able to detect a robust pulse signal, more rigorously controlled experiments are necessary to assess the ability of the iPhone to detect changes in the plethysmographic signal after regional anesthesia. Furthermore, it would seem that sensor-type and brachial plexus block methodology may play a larger role in the Radical 7 measurement of PI and PVI than was previously anticipated, further study is needed to determine the true differences each of these variables may impart.

Acknowledgements:

We would like to thank the other anesthesiologists of the Brigham and Women Anesthesia Department who allowed us to approach their patients. We would also like to thank the Brigham and Women’s anesthesiology department for the loan of 2 Radical-7 pulse co-oximeters for the duration of this study and our local Masimo representative for the donation of the TrendCom software and transfer cable.
References:


Figure 1. The effect of high frequency cutoff (vertical axis, Hz) and Butterworth bandpass filter order (horizontal axis) on averaged wave shape. Average wave shape for the unfiltered data is shown in gray with filtered wave in black.
Figure 2. Comparison of selected Bandpass filter settings vs. Raw data signal. A) a magnified 10-sec interval for better visualization of individual waveforms to illustrate changes imposed by filtering. The green line on graphic A and B illustrates the median local minima. The red line is 1 standard deviation from the median used as a cutoff to remove artifact. B) 60-sec windows were used in actual data analysis and are seen in B. The variability in underlying signal baseline is eliminated by the bandpass filter and can be seen clearly in the latter half of the recording. C) Normalized averaged pulses from the raw data signal and the chosen bandpass parameters of low cutoff: 0.15Hz, high cutoff: 10Hz, filter order: 1.
Figure 3. Averaged temperatures pre- and post-regional nerve block with 1 standard deviation. Block side post measurements are significantly different from ipsilateral pre-block (p = 0.0032) and contralateral post block control side (p = 0.0003).

<table>
<thead>
<tr>
<th>Skin Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-Block</strong></td>
</tr>
<tr>
<td><strong>Post-Block</strong></td>
</tr>
</tbody>
</table>

*Figure 3. Averaged temperatures pre- and post-regional nerve block with 1 standard deviation. Block side post measurements are significantly different from ipsilateral pre-block (p = 0.0032) and contralateral post block control side (p = 0.0003).*
Figure 4. Radical 7 data for PI and PVI averaged across patients with the blocked side in red and the control arm in blue. The regional block was performed at time 0. Error bars depict 1 standard deviation.
Figure 5. iPhone data for average amplitude, PV, RT comparing block (red) vs. control (blue). Error bars depict 1 standard deviation.
### Patient Demographics

<p>| | |</p>
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>8</td>
</tr>
<tr>
<td>Right</td>
<td>11</td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
</tr>
<tr>
<td>Female</td>
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<tr>
<td>Mean Age</td>
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</tr>
<tr>
<td>Median Age</td>
<td>55</td>
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<tr>
<td>Std Dev. of age</td>
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**Block Type:**

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<table>
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<tbody>
<tr>
<td>Axillary</td>
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<tr>
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<td>Total</td>
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**Table 1.** Summary of patient demographics

<table>
<thead>
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<th>Current Study</th>
<th>Bergek et al. 2015</th>
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<tbody>
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<td>SC, IC</td>
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<td><strong>Sensor</strong></td>
<td>LNCS DC-I</td>
<td>R2 25-a</td>
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<tr>
<td><strong>Rad 7 vers.</strong></td>
<td>7.3.3.1</td>
<td>7.8.0.1</td>
</tr>
<tr>
<td><strong>Sampling</strong></td>
<td>30/min</td>
<td>1/min</td>
</tr>
</tbody>
</table>

**Table 2.** Major differences between the current study and the study performed by Bergek et al. in 2015. Abbreviations: AX – Axillary, SC – supraclavicular, IC – infraclavicular, RC – retroclavicular.