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ORIGINAL RESEARCH

Low temperature increases capillary blood refill time following mechanical fingertip compression of healthy volunteers: prospective cohort study

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Abstract
Capillary refill time has been accepted as a method to manually assess a patient's peripheral blood perfusion. Recently, temperature has been reported to affect capillary refill time and therefore temperature may interfere with accurate bedside peripheral blood perfusion evaluation. We applied a new method of analysis that uses standard hospital pulse oximetry equipment and measured blood refill time in order to test whether lowered fingertip temperature alters peripheral blood perfusion. Thirty adult healthy volunteers of differing races (skin colors) and age (young: 18–49 years and old: ≥50 years) groups were recruited. We created a high fidelity mechanical device to compress and release the fingertip and measure changes in blood volume using infrared light (940 nm). Capillary refill times were measured at the fingertip at three different temperature settings: ROOM TEMPERATURE, COLD by 15 °C cold water, and REWARM by 38 °C warm water. The COLD group has decreased fingertip temperature (23.6 ± 3.6 °C) and increased blood refill time (4.67 s [95% CI 3.57–5.76], $p < 0.001$). This was significantly longer than ROOM TEMPERATURE (1.96 [1.60–2.33]) and REWARM (1.96 [1.73–2.19]). Blood refill time in older subjects tended to be longer than in younger subjects (2.28 [1.61–2.94] vs. 1.65 [1.36–1.95], $p = 0.077$). There was a negative correlation ($r = -0.471$, $p = 0.009$) between age and temperature. A generalized linear mixed-effects model revealed that lower temperature (OR 0.63 [95% CI 0.61–0.65], $p < 0.001$) rather than age (OR 1.00 [0.99–1.01], $p = 0.395$) was the independent factor most associated with increased blood refill time. Lowered fingertip temperatures significantly increase blood refill time which then returns to baseline when the fingertip is rewarmed. In our limited number of population, we did not find an association with age after the adjustment for the fingertip temperature.

Keywords Capillary refill time · Blood refill · Peripheral blood perfusion · Shock · Monitoring

1 Introduction

An accepted bedside method for the rapid detection of shock states can be performed by measuring the capillary refill time (CRT) or other measures of blood refill time at the fingertips of patients [1, 2]. However, it is unclear whether factors like temperature, age, or skin color cause alterations in these types of bedside measures.

By definition, CRT is the time required for a distal capillary bed (e.g., fingertip) to regain its color after having received enough compression to cause blanching of the fingertip [1, 3]. Measurement of CRT involves subjective visual inspection by an observer so it includes inter-observer variability [4]. The observer measures CRT using information of the color change of a reflection light on the fingertip. The optical technology of infrared spectroscopy has been used

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to noninvasively measure the concentration of hemoglobin and oxygen saturation [5]. And so it is used to monitor the blood refill time (BRT) at the fingertips [2, 6]. Optically measured BRT rather than visually assessed CRT allows for a high fidelity mechanical measurement of peripheral blood perfusion. Since the mechanisms how to measure and assess peripheral blood perfusion are different between BRT and CRT, we differentiate these two measures in this report.

It is possible that advanced age and low temperature affect peripheral blood perfusion and hence impact the clinical assessment [1, 2]. Schriger and Baraff [3] reported that healthy elderly subjects (n = 100, median CRT: 1.5 s) might have lower peripheral blood perfusion compared to younger subjects (n = 104, median CRT: 1.2 s). However, because it was an observation, confounders such as temperature, which might also impact the measurements need to be taken into account. Schriger et al. found a significant prolongation of CRT when the subject's hand was immersed in cold water (n = 20, CRT alteration: from 1.3 to 2.9 s). To the best of our knowledge, this was the first study that tested the effect of lowered fingertip temperature on CRT. Their result indicates that lowered fingertip temperature lowers peripheral blood perfusion; however their conclusion was qualitative and, due to a lack of fingertip temperature measurements, the effects of temperature on peripheral blood perfusion are not quantified. Anderson [7] conducted a study on healthy volunteers (n = 1000) and found that low body temperature is associated with low peripheral blood perfusion measures and reported that 1 °C decrease in patient temperature was associated with CRT increase by 5% [95% CI 1–10%]. However, because it was an observational study, the quantitative temporal association between lowered temperature and low peripheral blood perfusion remains unclear.

In order to test whether lowered fingertip temperature increases the time for a fingertip to recover its blood volume after it is released from compression and to define a quantitative temporal association between lowered temperature and BRT, we conducted a healthy volunteer study in which BRT was measured optically with a pulse oximeter. We measured BRT and fingertip temperature under three different conditions wherein the subject's hands were at room temperature, immersed in cold water and rewarmed by warm water. Our study hypothesis is that lowered fingertip temperature increases BRT.

2 Methods

2.1 Setting and design

This was a prospective cohort, healthy volunteer study with controlled experiments. The study was conducted at the University of Pennsylvania (Philadelphia, PA) and the data was analyzed at the Feinstein Institute for Medical Research (Manhasset, NY). The study was approved by the Institutional Review board of University of Pennsylvania (protocol no. 823336) and informed patient consent was obtained from the subjects.

All procedures were performed in a climate controlled environment at an ambient temperature of 20–22 °C. BRT was measured for each volunteer in a seated position with relaxed hands. At the same time, the surface temperature of the same fingertip was measured by a thermocouple thermometer.

We measured BRT under three different conditions: hands at room temperature (ROOM TEMPERATURE), hands immersed in cold water (COLD, 15 ± 2 °C), and hands immersed in warm water (REWARM, 38 ± 2 °C). A thermocouple sensor was attached to the fingertip as an adjunction of the BRT sensor. The fingertip temperature was recorded along with each BRT measurement (Fig. 1).

2.2 Study population

A total of 30 adult (23–61 years) healthy volunteers were recruited for this study from the greater Philadelphia area (Table 1). To obtain data on the effect of infrared wavelength used during standard hospital pulse oximetry (940 nm) on each skin tone, we recruited a diverse population of study volunteers: diverse ethnic and racial backgrounds and/or young (18–49 years) and old (≥ 50 years). The health of a subject was assessed prior to enrollment to determine eligibility.

2.3 Measurements of BRT by the study device

Our primary outcome measure was BRT and its association with altered fingertip temperature. We defined BRT as the time required for a fingertip to recover its blood volume after it is released from compression. An investigational device was used in this study as a noninvasive peripheral hemodynamic monitor to measure the finger's peripheral blood volume recovery time (Fig. 1). The device consists of two components: a measuring device and a fingertip compression device. A pulse oximeter (OLV-3100, Nihon Kohden Corporation, Tokyo, Japan) was used as the measuring device to capture pulse oximetry waveforms. The OLV-3100 is on the market in Japan as an approved medical device and conforms to the safety standard of IEC 60601-1. Its sensor passes light of two wavelengths through the fingertip (red: 660 nm, infrared: 940 nm) and the device measures the light intensity to generate a waveform. We used one wavelength (infrared light: 940 nm) to trace the change in hemoglobin concentration that reflects the recovery of blood flow to the fingertip (Fig. 2). The sensor was attached to the fingertip of subject's index finger.

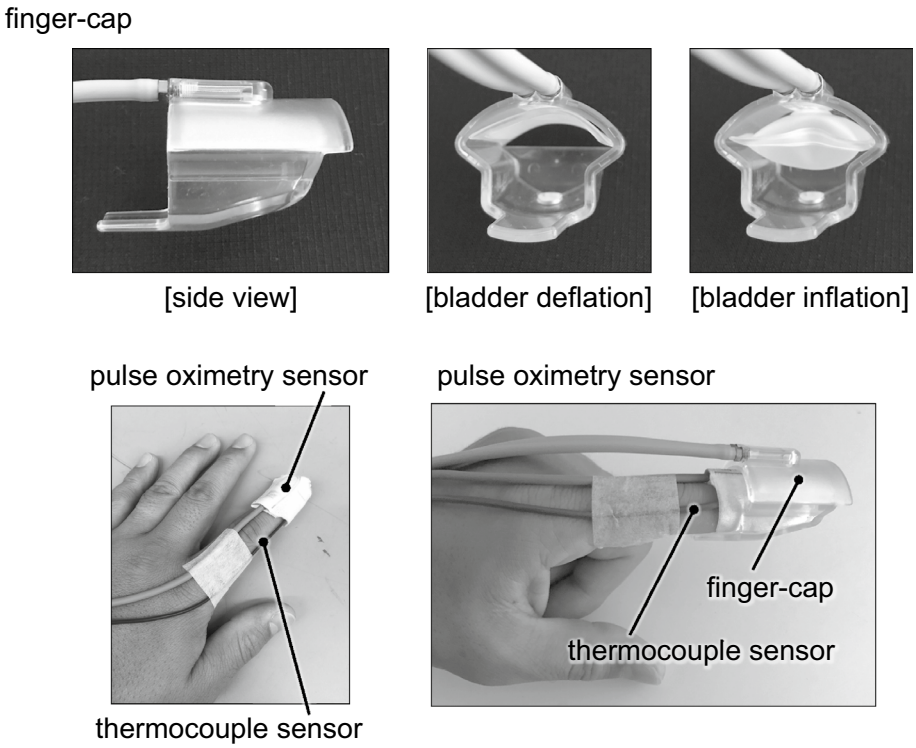

Fig. 1 Finger-cap and sensors attached to the fingertip. The fingertip compression device is composed of an air pump and a finger-cap with a polyurethane soft bladder adjunct to the pulse oximetry sensor. The air pump supplies air to the bladder when measuring BRT. The device controls the pressure of the inflated bladder at approximately 400 mmHg and provides firm, but safe compression to the fingertip. The duration of the bladder inflation is 5 s for each measurement. The thermocouple sensor was attached on the side of the fingertip in order to avoid interference in either the transmission light from the pulse oximetry sensor or the fingernail compression with the polyurethane bladder

Table 1 Demography of study subjects

	Races			Total
	Asian	White	Black or African American	
Young (< 50 years)	5	5	5	15
Old (≥ 50 years)	5	5	5	15
Total	10	10	10	30

The number of subjects is shown in each box

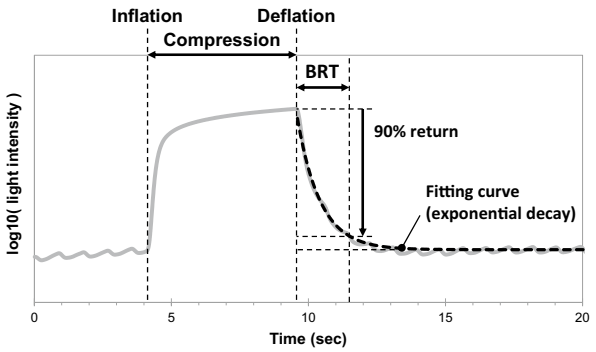

Fig. 2 Light intensity recorded by the measuring device. The light intensity transmitted through the fingertip increases during compression as blood, which is the major absorber of the light, is squeezed out of the fingertip. The compression phase is followed by the release phase during which the light intensity returns to the original level

The fingertip compression device is composed of an air pump and a finger-cap with a polyurethane soft bladder adjunct to the pulse oximetry sensor. This investigational device was qualified as non-significant risk device by the IRB. The device was provided from Nihon Kohden Corporation. Continuous leakage currents (section 19 of IEC 60601-1) and dielectric strength (section 20 of IEC 60601-1) were evaluated and it cleared the tests by Nihon Kohden. The air pump supplies air to the bladder when measuring BRT. The device controls the pressure of the inflated bladder at approximately 400 mmHg and provides firm, but safe compression to the fingertip. The duration of the bladder inflation is 5 s for each measurement. The device deflates the bladder pressure 5 s after the inflation. The thermocouple sensor was attached on the side of the fingertip in order to avoid interference in either the transmission light from the pulse oximetry sensor or the fingernail compression with the polyurethane bladder (Fig. 1).

Our device is not yet commercially available on the market. Therefore, a clinical evaluation of the accuracy of BRT compared to measurements of the clinical gold standard, such as CRT visual inspection with a chronometer, has not been performed and the validation data is not available at this point.

Light intensity was recorded by the measuring device and the data was analyzed thereafter. The light intensity transmitted through the fingertip increases during

compression as blood, which is the major absorber of the light, is squeezed out of the fingertip. The compression phase is followed by the release phase during which the light intensity returns to the original level. The curve fitting the recovery phase of the intensity waveform (intensity returning to its original levels) is modeled as an exponential decay using the least squares method. The time for 90% return of the fitting curve was reported as BRT. An example of the waveform during and after the compression is shown in Fig. 2.

The BRT measurement was repeated 10 times at each test condition making the total number of measurements per subject 30.

2.4 Experimental protocol

BRT was first measured at room temperature. The hand was then immersed into a cold water bath maintained at a temperature of 15 ± 2 °C for 5 min and then into a temperature controlled cold box maintained at the same temperature (15 ± 2 °C) for 3 min. BRT was measured inside the box. A commercial thermoelectric cooler/warmer (goFridge, Mini Fridge Portable Electric Cooler) with a hole and a rubber holder to hold the subject's arm was used. The box helped with maintaining the skin temperature during the measurements and it was also used to avoid interference from the ambient light. Finally, the hand was rewarmed up to normal body temperature using a warm water bath and another temperature controlled box, both of which were maintained at 38 ± 2 °C. Measurements were acquired after the fingertip temperature exceeded 30 °C.

The measurements were acquired 10 times in succession at ROOM conditions, then 10 times again at COLD conditions and finally 10 times at REWARM conditions.

2.5 Statistical analysis

The results are reported as mean ± standard deviation (SD), mean [95% confidence interval (CI)], maximum, minimum, and/or median (inter-quartile) values, appropriately. The averages of 10 measurements of BRT and fingertip temperature were assigned as the BRT and temperature values for each subject under the test condition. BRT and fingertip temperature in the three conditions (ROOM TEMPERATURE, COLD, and REWARM) were compared by repeated-measures analysis of variance (ANOVA). Post-hoc comparison was performed using the Bonferroni test. BRT in the two age groups (OLD, ≥ 50 years vs. YOUNG, 18–49 years) was compared using Student's t-test and in the different ethnic groups (ASIAN, WHITE, and AFRICAN AMERICAN) were compared using one-way ANOVA. Pearson's correlation coefficient was used to determine the correlation between fingertip temperature and age. Multivariate analysis was performed to determine the associations between BRT and other variables (age, race, gender, fingertip temperature). A generalized linear mixed-effects model was used to seed the association between BRT and the variables with adjustment. Since there was no reference of difference in BRT between different age, race, gender, or fingertip temperature groups and there was no known reference of variance of BRT, we did not perform a power calculation of statistics in this study. A p-value < 0.05 ($p < 0.05$) was considered statistically significant. All statistical analyses were performed using IBM SPSS software for Mac, version 22.0 (IBM Corp., Armonk, NY).

3 Results

3.1 Temperatures at the fingertips were affected by that of their ambient environment

The differences in fingertip temperature under the three conditions are shown in Table 2. Fingertip temperature was different depending on the initial fingertip temperature and biological response to the test procedure of each subject. In the ROOM TEMPERATURE group, the minimum temperature of the fingertip was 23.9 °C. The mean fingertip temperature of the ROOM TEMPERATURE group was 32.1 ± 3.0 °C and was significantly different than the COLD (23.6 ± 3.5 °C) and the REWARM (36.8 ± 1.4 °C) groups.

3.2 BRT depends on the fingertip temperature

The mean BRT of the ROOM TEMPERATURE group was 1.96 [95% CI 1.60–2.33] s (Fig. 3). It increased

Table 2 Fingertip skin temperatures in the test groups

	Temperature control test		
	ROOM TEMP (n = 30)	COLD (n = 30)	REWARM (n = 30)
Temperature			
Mean ± SD (°C)	32.1 ± 3.0	23.6 ± 3.6	36.8 ± 1.4
95% CI of mean (°C)	31.0–33.2	22.3–25.0	36.2–37.3
Median (°C)	33.0	23.6	37.1
Maximum (°C)	35.2	30.0	38.9
Minimum (°C)	23.9	18.5	32.6
Percentile (°C)			
25	30.6	20.6	36.3
50	33.0	23.6	37.1
75	34.3	27.1	37.6

CI confidence interval

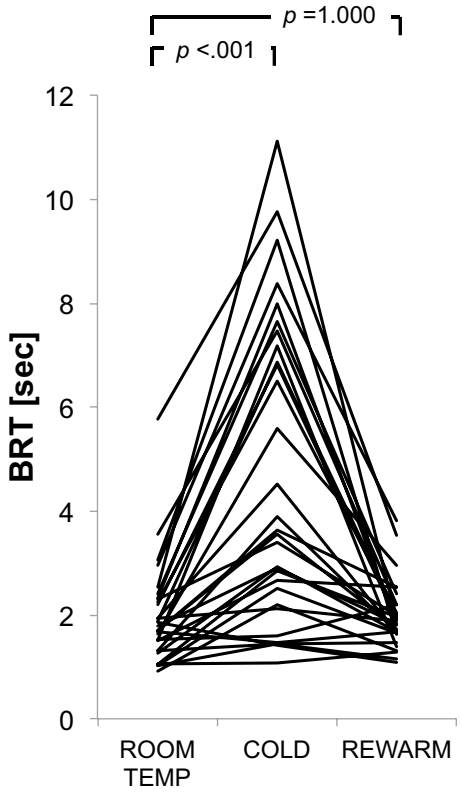

Fig. 3 BRT compared between the three different temperature settings. The mean BRT of the ROOM TEMPERATURE group was 1.96 ± 0.97 s. It increased significantly in the COLD (4.67 ± 2.93 s, $p < 0.01$) group. The increased BRT returned to ROOM TEMPERATURE levels after the hand was rewarmed (REWARM group: 1.96 ± 0.62 s, $p = 1.00$). *BRT* blood refill time

significantly in the COLD (4.67 [95% CI 3.57–5.76] s, $p < 0.001$) group. The increased BRT returned to ROOM TEMPERATURE levels after the hand was rewarmed (REWARM group: 1.96 [95% CI 1.73–2.19] s, $p = 0.986$).

3.3 Correlation between BRT and subject's characteristics

BRT in older subjects (age ≥ 50) tended to be longer than younger subjects (age < 50) (2.28 [95% CI 1.61–2.94] s vs. 1.65 [95% CI 1.36–1.95] s, $p = 0.077$). There were no significant differences in BRT among the different racial groups (ASIAN, 1.85 [95% CI 1.22–2.49] s vs. WHITE, 2.07 [95% CI 1.67–2.48] s vs. AFRICAN AMERICAN, 1.97 [95% CI 1.00–2.95] s, $p = 0.887$) (Figs. 4, 5). In the ROOM TEMPERATURE group, there was moderate but statistically significant negative correlation between age and the fingertip temperature ($r = -0.471$, $p = 0.009$, Fig. 6).

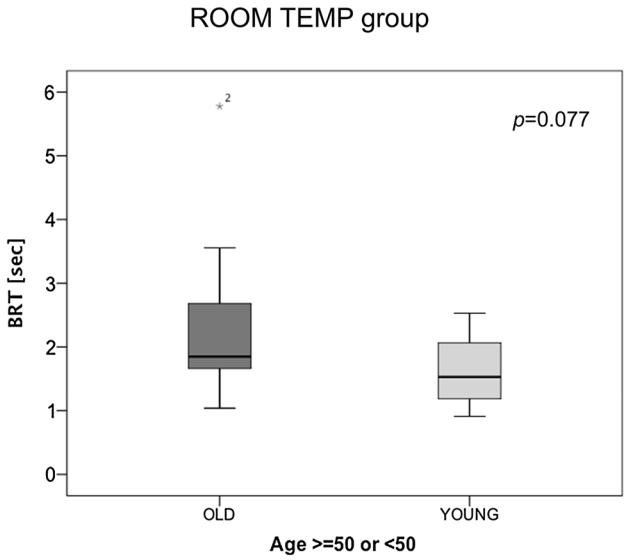

Fig. 4 BRT at room temperature compared between the two different age groups. BRT in older subjects (age ≥ 50) tended to be longer than in younger subjects (age < 50) (2.28 ± 1.20 vs. 1.65 ± 0.53 s, $p = 0.077$). *BRT* blood refill time

3.4 BRT is negatively associated with the temperature at the fingertip

Figure 7 shows a scatter plot of BRT with fingertip temperature. There was a negative correlation between BRT and fingertip temperature. We used a generalized linear mixed-effects model to find the association between increased BRT

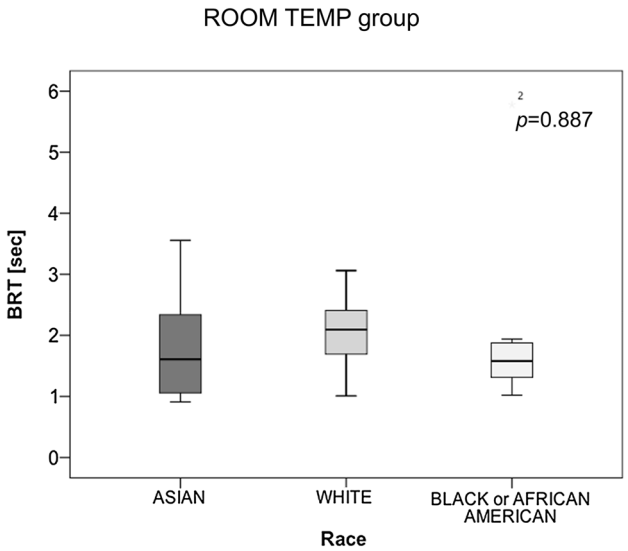

Fig. 5 BRT at room temperature compared between the three different race groups. There were no significant differences in BRT among the different racial groups (ASIAN, 1.85 ± 0.89 s vs. WHITE, 2.07 ± 0.57 s vs. AFRICAN AMERICAN, 1.97 ± 1.37 s, $p = 0.887$). *BRT* blood refill time

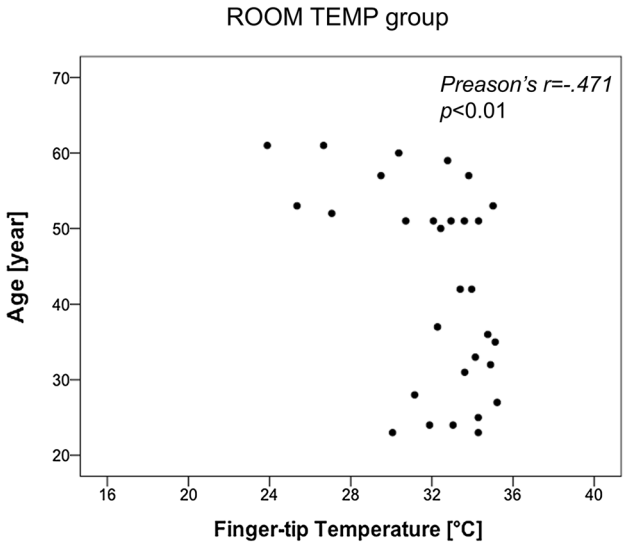

Fig. 6 Correlation between subject's fingertip temperature and age. In the ROOM TEMPERATURE group, there was moderate but statistically significant negative correlation between age and the fingertip temperature ($r = -0.471$, $p < 0.01$)

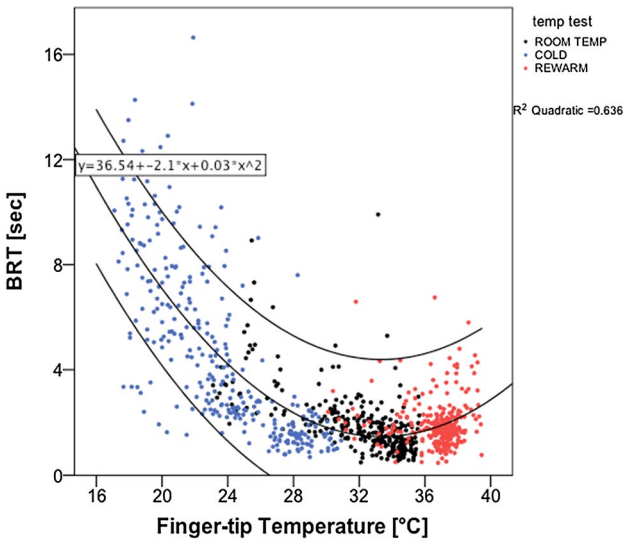

Fig. 7 A scatter plot of BRT with fingertip temperature. There was a negative correlation between BRT and fingertip temperature. *BRT* blood refill time

and external factors (Table 3). Lowered fingertip temperature was significantly associated with increased BRT (odds ratio 0.63 [95% CI 0.61–0.65], $p < 0.001$); however, there was no statistically significant association between BRT and age (1.00 [0.99–1.01], $p = 0.395$), gender (1.04 [0.84–1.30], $p = 0.720$), or race (Asian vs. Black and African American, 1.14 [0.88–1.49], $p = 0.322$; White vs. Black and African American, 1.11 [0.85–1.44], $p = 0.453$). The order in which the measurements were taken had no effect on BRT.

Table 3 Regression analysis of increased BRT

	Odds ratio and 95% CI	*p*-value
Test group		
Room temperature	0.115 [0.083–0.158]	< 0.001
Cold	0.034 [0.019–0.061]	< 0.001
Rewarm	Reference	
Temperature (°C)	0.629 [0.605–0.654]	< 0.001
Female	1.041 [0.835–1.297]	0.720
Age (year)	0.996 [0.987–1.005]	0.395
Race		
Asian	1.143 [0.877–1.489]	0.322
White	1.106 [0.850–1.438]	0.453
Black & African American	Reference	
Measures		
1st	0.749 [0.464–1.209]	0.237
2nd	0.751 [0.465–1.214]	0.242
3rd	0.757 [0.469–1.223]	0.256
4th	0.727 [0.450–1.174]	0.192
5th	0.780 [0.483–1.260]	0.309
6th	0.810 [0.502–1.308]	0.389
7th	0.802 [0.496–1.295]	0.366
8th	0.933 [0.578–1.507]	0.776
9th	0.903 [0.559–1.458]	0.676
10th	Reference	

CI confidence interval

3.5 Alterations in fingertip temperatures change BRT readings

BRT of the COLD and REWARM groups were compared to those of the ROOM TEMPERATURE group (Figs. 8, 9). Figure 8 shows the percentage of BRT readings that were above the defined normal range as a result of altered fingertip temperature. The mean BRT ± 2SD at ROOM TEMPERATURE is considered the normal range for a given individual. This bar graph depicts the percentage (± 95% CI) of BRT readings that were measured outside of the normal range for a series of fingertip temperatures. It should be noted that as fingertip temperature decreases, the chance of an elevated BRT reading increases. When the fingertip temperature was below 24 °C, the percentage of abnormal BRT readings became as high as 90%.

Figure 9 shows the percent difference between individual BRT readings and the baseline BRT values. Baseline BRT was defined as the subject's mean BRT at ROOM

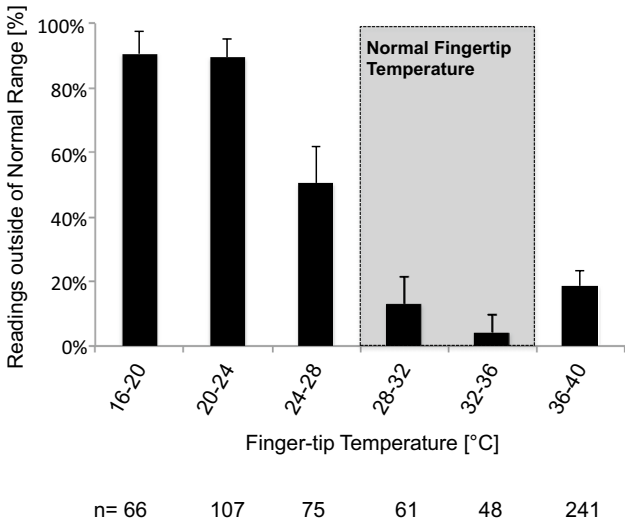

Fig. 8 Change of BRT readings by alterations in fingertip temperatures. The figure shows the percentage of BRT readings that were above the defined normal range as a result of altered fingertip temperature. The mean BRT ± 2SD at ROOM TEMPERATURE is considered the normal range for a given individual. This bar graph depicts the percentage (± 95% CI) of BRT readings that were measured outside of the normal range for a series of fingertip temperatures

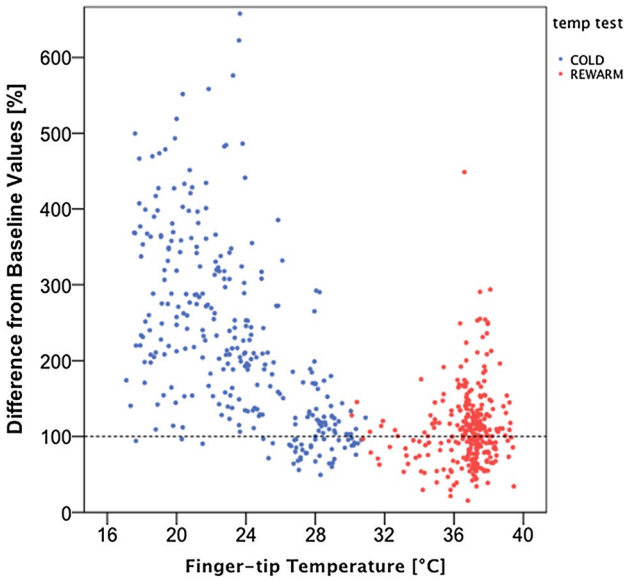

Fig. 9 Change of BRT readings by alterations in fingertip temperatures. The figure shows the percent difference between individual BRT readings and the baseline BRT values. Baseline BRT was defined as the subject's mean BRT at ROOM TEMPERATURE. The percent difference of BRT readings increased as fingertip temperature decreased

TEMPERATURE. The percent difference of BRT readings increased as fingertip temperature decreased.

4 Discussion

This study was conducted to determine if lowered fingertip temperature would cause a prolongation in the blood refilling time in the fingertip after release from compression. Our data obtained by objective optical measurements from healthy volunteers, demonstrate a significant observation whereby lower fingertip temperature is associated with prolonged BRT in healthy humans.

It is plausible that low temperature affects peripheral blood perfusion and hence impacts the clinical assessment of peripheral blood perfusion monitorings [1]. We urge healthcare providers to be cautious in the interpretation of peripheral blood perfusion measures under some conditions, such as at low ambient temperature in the emergency fields outside hospitals. The concept has been accepted since Schriger and Baraff [3] found a significant prolongation of CRT when the subject's hand was immersed in cold water. However, in our study, the experimental group with rewarmed fingertip temperature was not intended to mimic febrile patients in clinical settings. There are many pathological differences in the capillary beds of febrile patients compared to those in patients who passively receive heat on their peripheral body. BRT returned to the baseline levels when the fingertips were rewarmed. Prolonged BRT by cooling became undetectable when the temperature was normalized. We believe that the results of our study make a strong case about the causality of lowered temperature on altered BRT.

We observed, interestingly, a greater variability between subjects fingertip temperatures than was expected. There was a subject whose fingertip temperature was 35.2 °C but also there was other subject with a fingertip temperature of 23.9 °C. These temperatures were both measured at room temperature. The experimental conditions and our procedures were consistent throughout our study population. Therefore, a huge gap of the baseline fingertip temperature between subject to subject can be attributed to each individual, who has their own response pattern to the ambient temperature. As can be seen in Fig. 6, there was negative correlation between age and the fingertip temperature. This infers that the response might be different by the age groups. We also observed fast or slow response patterns of fingertip temperature alteration when the subjects hand was immersed in cool water. The variability of human response to the altered temperature condition affects the fingertip surface temperature of each individual.

More recently, Lima et al. [8] showed that the skin-temperature gradient was well correlated with abnormal peripheral blood perfusion in critically ill patients. Critically ill patient may have a low peripheral blood perfusion due to the body's auto regulation. There are two scenarios,

in which health-care providers may encounter a patient who has a low finger-tip temperature. One is lowered finger-tip temperature by an ambient condition, such as that used in our experiment. Another scenario is a low finger-tip temperature seen at a room temperature. Critically ill patients who are in low peripheral blood perfusion may have less amount of heat transfer and it contributes their lower finger-tip temperature. Health-care providers encounter a fingertip that is pale and feels cold to touch when they measure CRT in either scenario.

Interestingly, van Genderen et al. [9] reported that CRT to predict postoperative complications showed the best predictive performance (the highest AUC number of ROC analysis) among three different measures of peripheral blood perfusion, including optically measured peripheral perfusion index (the Massimo SET Radical pulse oximeter) and the skin-temperature gradient between the index finger and the forearm. It can be inferred that CRT measurements may involve a subjective bias of examiner who measures CRT. We used optically measured BRT to test our hypothesis in order to avoid the subjective bias of a researcher and so we believe that the results of our study make a strong case about the causality of temperature on altered peripheral blood perfusion.

Age is considered to be one of the factors that may affect CRT in healthy volunteers [1, 3]. Schriger and Baraff [3] recruited over 300 healthy volunteers and measured CRT from diverse age groups. They reported that elderly subjects had increased CRT compared to younger subjects. The upper limit of the normal range in elderly subjects was 4.5 s compared with the 2.4 s in adult subjects. However, because the fingertip temperature was not measured, it is possible that low fingertip temperatures confounded CRT measurements in elderly subjects. We found a negative correlation between fingertip temperature and age in our study subjects, with the older subjects showing a trend towards increased BRT. In our study, we did not find an association between age and BRT after adjusting for temperature and other external factors. Our result suggests that the reported correlation between age and BRT can be confounded by the temperature at the fingertips and, that if the temperature at the fingertip is not measured, the interpretation of BRT evaluation can be misleading.

At room temperature, the surface temperature at the fingertips was 32.1 ± 3.0 °C in our study subjects (healthy volunteers). If the fingertip temperature is below this range and it is not measured, the BRT can confound and, as a result, any evaluation using it may be inaccurate. Health-care providers may make a decision based on this inaccurate evaluation of BRT. The percentage ($\pm$95% CI) of numbers that had the value over the normal range increases as the fingertip temperature decreases. When the fingertip temperature was below 24 °C, the percentage of BRT above the normal range was as high as 90%. In fact, we had a subject whose fingertip temperature was 23.9 °C at room temperature and the subject had a BRT of 3.1 s, which decreased to 1.6 s after the subject's hand was rewarmed. In the subjects who have lowered fingertip temperature, if the temperature is controlled properly, the value of BRT returns to the normal range. To the best of our knowledge, this is the first study to show a quantitative temporal association between lowered temperature and BRT.

CRT is a simple and non-invasive test and is thought to represent peripheral blood perfusion [2]. Therefore, a prolonged CRT serves as a sign of shock in critically ill patients. A number of observational studies in humans have emphasized its relevance in the initial triage [10] of patients sustaining severe and acute injuries [9, 11]. However, the usefulness of optically measured BRT is barely reported. The clinical usefulness of BRT in critical care was reported by Morimura et al. [6]. They were the first to use the pulse oximeter waveform to measure BRT in a critical care setting. They found good correlation between prolonged BRT and elevated blood lactate levels, suggesting that the value of BRT is correlated with the insufficiency of global tissue perfusion. Further studies may wish to evaluate the usefulness of BRT in clinical settings.

4.1 Limitations

A modified pulse oximeter was used to measure BRT in our study. The returning blood volume is traced with an infrared (940 nm) spectrum passing through the fingertip. Therefore, BRT by our method measures the blood recovery time optically, whereas a CRT measurement uses examiner's visual inspection of the skin color. Even though BRT has many similarities of methods with CRT, those two parameters may not measure the same pathological responses of the fingertip released from compression. We used the internal standard (normal values obtained at ROOM TEMPERATURE) for our analyses, therefore the trend and the difference we found in our study should be repeatable for other methods and our result should retain the generality. We currently lack a data of comparison between our BRT and CRT by visual inspection of health care providers. Our result warrants a clinical study to validate whether optical BRT measure represents CRT by visual inspection. Therefore, we are now conducting this study in a clinical setting.

In addition, another limitation of this study is generalizability of subject demographics in age. This study enrolled patients over 50 years but none of them were over 65 years. There are more advanced age groups in clinical settings. Therefore, a future clinical study may want to test BRT in more diverse population with advanced age groups.

5 Conclusions

Lowered fingertip temperatures significantly increased BRT. This is the first study to show a quantitative temporal association between lowered temperature and BRT. Temperature may be a major confounder of BRT and CRT in prior studies and at the bedside. If the fingertip temperature is unknown, we urge clinicians to be cautious in the interpretation of bedside measures of peripheral blood perfusion.

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Compliance with ethical standards

Conflict of interest JK and MJC have no known conflicts of interest associated with this study and there has been no significant financial support for this work that could have influenced its outcome. Kota S., HH, KH, NK, and SW are employees of Nihon Kohden Corporation and Nihon Kohden Innovation Center, INC. There are no products in market to declare. This does not alter the authors' adherence to all the journal's policies on sharing data and materials. Koichiro S., JWL, and LBB have a patent right of metabolic measurements in critically ill patients. Koichiro S. has a grant/research support from Nihon Kohden Corp.. JWL has a grant/research support from Zoll Medical Corp., Philips Healthcare, Nihon Kohden Corp., and the NIH, and owns intellectual property in resuscitation devices. LBB has a grant/research support from Philips Healthcare, the NIH, Nihon Kohden Corp., BeneChill Inc., Zoll Medical Corp, and Medtronic Foundation, patents in the areas of hypothermia induction and perfusion therapies, and inventor's equity within Helar Tech LLC.

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