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Research article

Pilot study on optimizing pressure for standardized capillary refill time measurement

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A R T I C L E I N F O

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A B S T R A C T

Purpose: Capillary Refill Time (CRT) measurement has gained increasing attention in the field of sepsis and septic shock. Recognizing pressure as a fundamental determinant in CRT measurement is crucial for establishing a standardized CRT measurement procedure. In this preliminary study, we elucidated the optimal pressing strength for CRT measurement by analyzing the CRTs measured under varying pressures.
Method: Seventeen healthy individuals were enlisted to undergo CRT tests on their fingertips at various pressure levels. The applied force was initiated at 0.5N and incrementally increased by 0.5N until it reached 10.5N. An integrated Photoplethysmography (PPG) device was employed to capture fluctuations in light intensity. The CRT was automatically derived from the PPG signals via a specialized algorithm. The study included correlation assessment and reliability evaluation. Box plot and Bland-Altman plot were used to visualize the impact of pressure levels on CRTs.
Results: A dataset of 1414 CRTs across 21 pressures showed significant differences (Kruskal-Wallis test, $p < 0.0001$), highlighting the impact of pressure on CRT. CRT values between 4.5N and 10.5N pressures varied less, with an Intraclass Correlation Coefficient (ICC) of 0.499 indicating moderate consistency. Notably, CRTs at 10N and 10.5N pressures revealed a high ICC of 0.790, suggesting strong agreement.
Conclusion: A pressure range of 4.5N–10.5N is recommended for stable CRT measurements, with 10.0N–10.5N providing optimal consistency and reliability.

1. Introduction

Sepsis is a predominant cause of death and critical illness globally [1,2]. The early identification of individuals with suspected infections that may progress to severe conditions is crucial. Additionally, timely and appropriate interventions are key in enhancing prognostic outcomes [3]. Research indicates that Capillary Refill Time (CRT) serves as a rapid, noninvasive, and reliable marker for identifying sepsis in patients. It offers a practical alternative to invasive blood lactate concentration measurements [4]. This attribute enables clinicians to make swift treatment decisions in emergency settings [4]. CRT is defined as the time taken for the skin's color to

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return after blanching [5]. Under conditions of adequate blood volume, blood vessels in the skin's proximal vascular bed remain naturally dilated, allowing significant blood flow. When substantial pressure is applied, blood is displaced towards the periphery, leading to skin pallor. Upon releasing the pressure, blood flow promptly resumes, reverting the skin to its normal perfused state. The duration of color restoration is referred to as CRT.

Septic shock, one of the most severe stages of sepsis, is characterized by exceptionally severe circulatory and cellular metabolic abnormalities, leading to a mortality rate exceeding 40 % [6]. Annually, approximately 19 million people globally are affected by septic shock [2,7]. It is identified as a microcirculatory disorder due to the crucial role of microcirculatory dysfunction in its progression [8]. Consequently, monitoring and addressing microcirculatory changes are vital for improving the prognosis of septic shock [9]. Peripheral skin and muscle blood flow, often compromised first and recovered last due to the body's compensatory mechanisms, sensitively and accurately reflect the most compromised state of the organism's microcirculation [10]. Thus, peripheral circulation is an intuitive indicator of microcirculatory status. CRT, as a visual marker of peripheral circulation, becomes significantly prolonged when peripheral circulation is disrupted, indicating the presence of a disorder.

Currently, CRT is primarily assessed through visual inspection by clinicians, a method renowned for its trainability, repeatability and easy of use, particularly advantageous in resource-limited regions [11]. However, this subjective approach faces challenges in consistency and reliability [12–15]. The lack of standardization in CRT measurement and interpretation limits its clinical effectiveness. Consequently, research has aimed to establish objective CRT measurement techniques. Notable advancements include digital CRT calculation software [16], the use of polarized light spectroscopy for erythrocyte concentration quantification [17], the automated pneumatic device for continuous CRT assessment [18], and the integration of fiber-optic sensors for precise plantar skin CRT measurement [19]. These developments significantly improve CRT measurement objectivity.

However, a critical aspect, contact pressure, remains underexplored and there is limited understanding of its influence on CRT. Kawaguchi et al. conducted a pivotal study to address this, testing four specific levels of applied force (1N, 3N, 5N, and 7N) [20]. Their results suggested that applying force between 3N and 7N for 2 s is optimal for CRT assessment. While this study's focus was on a narrow range of pressures, it marks a significant step towards standardizing CRT measurement methods concerning contact pressures.

In this pilot study, we investigated the impact of contact pressure on CRT to elucidate its underlying mechanisms. A universal testing machine (UTM) was employed to maintain consistent applied force at various levels, ranging from 0.5N to 10.5N in 0.5N increments. Seventeen healthy volunteers participated in CRT measurements. A comprehensive dataset of 1414 CRT measurements was compiled, facilitating analysis that included pairwise comparisons and reliability assessments.

2. Methods

2.1. Study protocol and measurements

The study was carried out with 17 healthy volunteers between May 2023 and August 2023 at the Department of Biomedical Engineering, Faculty of Environment and Life, Beijing University of Technology. Participants included adults aged 18 and older, free from significant organ dysfunction and peripheral vascular disease. Exclusion criteria encompassed individuals with diabetes mellitus, hypertension, systemic vasculitis, arterial occlusion in the upper limbs, as well as pregnant or breastfeeding women. Additionally, individuals with conditions that could impede accurate data collection, such as gray nails, nail polish, or thick nail beds, were also excluded. The demographic and health characteristics of the 17 participants are detailed in Table 1.

The measurements were conducted in a controlled environment, with ambient temperature consistently maintained at approximately 23 °C. Prior to testing, volunteers were seated and remained still for 15 min in the laboratory to ensure standard conditions. Fig. 1 presents a photograph illustrating the CRT measurement process on a participant's fingertip. During the assessment, Photoplethysmography (PPG) signals were continuously monitored from the left index fingertips of volunteers. The forearm was meticulously positioned for each participant to maintain a consistent alignment of the finger with the heart's position [21].

The experimental setup was designed to apply consistent pressure on the fingertip for 5 s. Starting at an initial pressure of 0.5N, the contact force was increased by 0.5N for each measurement, culminating at 10.5N. This process was replicated four times for every participant, yielding four distinct CRT signals across 21 pressure levels per individual. Concurrently, real-time PPG signals were collected alongside various physiological parameters, including finger temperature, body temperature, blood oxygen saturation, pulse rate, and blood pressure. These recorded physiological parameters are compiled in Table 1.

Table 1
Demographic characteristics and physiological parameters of the 17 volunteers.

sex	Number	Average Age	Average BMI
Male	10	26.60 ± 4.03	23.50 ± 2.12
Female	7	24.71 ± 1.25	19.83 ± 2.42

Temperature (°C)	Finger temperature (°C)	Blood oxygen (%)	Heart rate (bpm)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)
Physiological parameters were assessed prior to the 15-min meditation session					
36.6 ± 0.48	35.41 ± 1.47	97.18 ± 1.88	79.00 ± 11.83	111.82 ± 19.72	71.12 ± 8.89
Physiological parameters were measured post the 15-min meditation session					
36.79 ± 0.31	35.35 ± 1.32	97.65 ± 0.86	76.71 ± 11.06	110.00 ± 17.77	70.88 ± 9.18

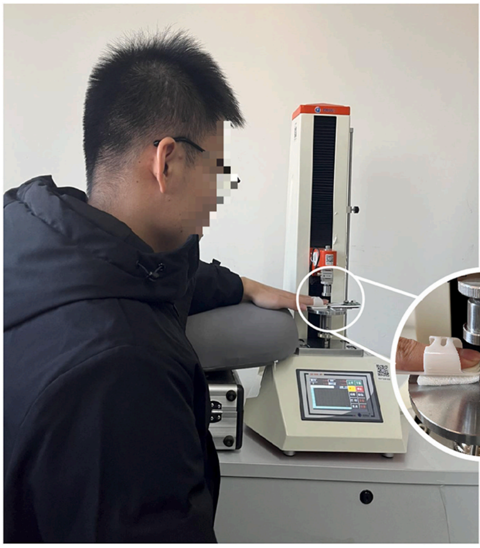

Fig. 1. Photograph of CRT measurement conducted on a participant.

Detailed intricacies of the CRT measurement system, covering the pressure control device, signal acquisition process, and auto-detection algorithm, are thoroughly detailed in Additional File 1 including 5 figures. Figure E1 showcases the universal testing machine, while its detailed configuration is highlighted in Figure E2. Figures E3 and E4 depict the typical patterns of light intensity changes and pressure signals recorded during CRT measurements, respectively. Additionally, Figure E5 illustrates the fitted signals used for automatic CRT extraction.

2.2. Statistical analysis method

Statistical analyses were performed using IBM SPSS Statistics 26 software. The methods employed included.

(1) **Data Normality Assessment:** CRT data normality was evaluated using the Kolmogorov-Smirnov test, with descriptive statistics presented as median values and interquartile ranges (25–75 %).
(2) **Comparison Between Groups:** Due to the non-normality of the data observed from Data Normality Assessment, the Kruskal-Wallis test was utilized to assessed correlations among CRTs across the 21 pressure levels.
(3) **Multiple Comparisons:** Pairwise comparisons using the Bonferroni correction quantitatively assessed differences in CRT among pressure groups. Non-significant differences indicated consistent CRT measurements under corresponding pressures. A two-sided p-value <0.05 denoted statistical significance.
(4) **Reliability Analysis:** Reliability, encompassing correlation and consistency of measurements, was evaluated using the Intraclass Correlation Coefficient (ICC).

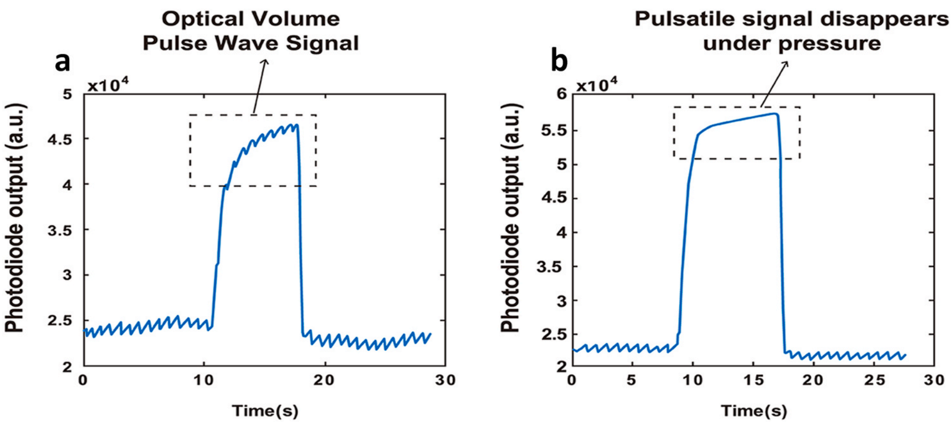

Fig. 2. Typical recorded light intensity. (a) Clear heartbeat signal observed at pressure of 1N and (b) absence of heartbeat signal at 2.5N applied pressure.

(5) **Analysis Visualization:** Bland-Altman plots and box plots graphically represented agreement and distribution of CRT measurements under different pressure conditions, respectively.

3. Results

Fig. 2 illustrates typical light intensity signals recorded under 1N (a) and 2.5N (b) applied forces from volunteer No. 2. At pressures ranging from 0.5N to 1N, the PPG signal maps consistently showed distinct beating signals during pressure application. Interestingly, in volunteers with a higher Body Mass Index (BMI) exceeding 23.5, noticeable beat signals persisted under a 1.5N pressure, and faint beat signals were observable at 2N pressure. However, beyond 2.5N pressure, pulsatile signals were absent in all participants.

After excluding 14 unsuitable signals, a total of 1414 CRT signals were successfully obtained and included in the analysis (see Fig. 3a). All CRT values remained below 4 s, with the majority ranging from 0.8 to 2 s, indicating observable variations among different volunteers.

4. Discussion

Given the considerable sample size, the Kolmogorov-Smirnov (K–S) test was initially utilized to evaluate the normality of CRT data. The test results indicated a significant deviation from normality ($p < 0.0001$), leading to the rejection of the null hypothesis that CRTs measured under different pressures follow a normal distribution.

Subsequently, the Kruskal-Wallis test revealed a significant association between pressure and CRT ($p < 0.0001$) at the 0.01 significance level. This demonstrates significant differences in CRT across various pressure levels ($p < 0.05$). Therefore, it can be inferred that pressure is a critical factor influencing CRT measurement outcomes.

Fig. 3b presents the median CRT values across different pressure levels, revealing an initial increase in CRT with rising pressure up to 4.5N, followed by stabilization at higher pressures. This pattern is consistent with the analytical results obtained using Bonferroni Correction, which indicate significant statistical differences in CRTs within the 0.5N–4N range (*$p < 0.05$). Conversely, CRT values between 4.5N and 10.5N did not show significant statistical differences. This variation is reflected in the occurrence of outliers in CRT measurements at lower pressures (0.5N–4N), as shown in the box plot (Fig. 3c). Furthermore, the box plot demonstrates a trend of decreased abnormal CRT values and increased measurement stability at higher pressure levels.

The analysis included calculating the ICC to evaluate intragroup correlation. For CRTs measured within the pressure range of 4.5N–10.5N, the ICC value was 0.499 (95 % CI, 0.409 to 0.603), indicating moderate consistency. Additionally, the ICC assessment was extended to intervals of 0.5N, 1N, and 2N. Notably, CRT measurements within the 10N–10.5N pressure range exhibited the highest ICC value at 0.790 (95 % CI, 0.669 to 0.859), reflecting a very strong consistency level within this specific interval.

In the recorded light intensity data (PPG signals), pulsatile signals were discernible under contact pressures ranging from 0.5N to 2.0N. Above this pressure range, the pulsatile signals uniformly disappeared in all volunteers upon application of higher pressure. This observation suggests that the proximal vascular bed of the finger, particularly its distributed arteries, remains incompletely

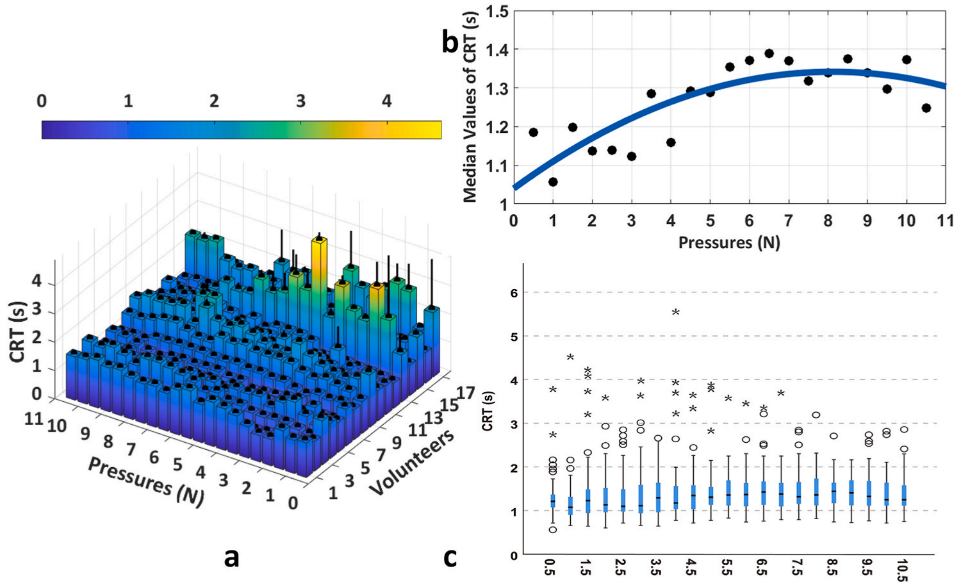

Fig. 3. Visualization of CRT data. (a) Three-dimensional bar graph of CRTs. CRTs were measured in 17 healthy volunteers under 21 different pressures spanning from 0.5N to 10.5N with incremental intervals of 0.5N. (b) Median Values of CRT plotted across 21 pressure levels. The curve is derived through second-order polynomial fitting using the equation $\boldsymbol{f(x) = -0.004578 * \hat{x}2 + 0.0743 * x + 1.04}$ with a sum of squared error (SSE) of 0.06389 and a root mean square error (RMSE) of 0.05958. (c) Box plot of CRTs measured across the 21-pressure spectrum.

compressed within a contact pressure range of 0–2.0N.

In our study, the maximum applied pressure was limited to 10.5N, as it typically results in complete compression of the tissue under examination. This conclusion is corroborated by the strain deformation data recorded simultaneously with the pressure and light intensity signals, showing a deformation range between 2.67 mm and 3.84 mm. Pressures exceeding 10.5N were not found to induce additional strain deformation; which suggests that the majority of participants experienced complete tissue compression at 10.5N. Consequently, the CRT measured at this pressure level predominantly reflects the extent of blood refilling.

Fig. 4a displays the deformation curve plotted against pressure levels, illustrating that tissue compression intensifies progressively with increasing pressure. This compression leads to the gradual displacement of blood from the proximal vascular bed into surrounding areas, resulting in higher CRT values and a reduced incidence of abnormal CRT values. This trend is further evidenced in the box plot of Fig. 3c, which shows a decrease in CRT anomalies and increased stabilization of CRT measurements as the applied pressure escalates.

From the ICC analysis, it has been determined that the measured CRT exhibits the highest stability within the pressure range of 10N–10.5N. This conclusion is further supported by the Bland-Altman plots depicting the CRTs measured at 10N and 10.5N pressures (Fig. 4b). These plots facilitate a visual representation of the data's reliability. Notably, the majority of CRT values lie within the 95 % consistency interval, equivalent to 1.96 standard deviations, indicating a high level of consistency in the measurements.

During the study, sensations experienced by the participants at different pressure levels were recorded through inquiries. Fifteen out of seventeen participants reported no pain throughout the pressurization process. However, a noticeable pressing sensation was reported by participants at pressures exceeding 9.0N. Notably, two volunteers experienced slight pain starting from 8N.

In recent years, the significance of CRT in septic shock management has gained increasing validation. Studies have shown that CRT, along with the Skin Mottling Score (SMS), are effective clinical indicators for early identification of high-risk septic shock patients with poor prognoses. These tools are crucial for the timely initiation of optimal treatments, influencing decisions on hospital admissions, and enhancing triage and early intensive care management [22]. Furthermore, a CRT exceeding 5 s post-resuscitation has emerged as a key differentiator, identifying patients with potentially worsening organ failure [23–25]. These findings suggest CRT's utility in guiding clinical phenotyping of septic shock and personalizing patient treatments. The ANDROMEDA-SHOCK study reinforced this, revealing that the CRT-targeted resuscitation group required less fluid and experienced lower organ dysfunction compared to the lactate-targeted group [26–28]. Bayesian Reanalysis also supports the efficacy of CRT-focused resuscitation strategies in reducing mortality and accelerating organ dysfunction resolution versus lactate-centered strategies [29]. The 2021 Surviving Sepsis Campaign Guidelines recommend incorporating capillary filling time as a complementary resuscitation guide in adults with septic shock, alongside other perfusion measures [3]. The increasing emphasis on CRT highlights its potential as an essential tool in assessing patients at risk of clinical deterioration [30].

Despite the promising application of CRT in such critical care settings, our study presents limitations that must be considered. The selection of healthy individuals without peripheral circulation issues constrains the direct applicability of our findings to clinical environments, where patients often present with various pre-existing conditions that could affect CRT readings. This selection criterion potentially limits the generalizability of our results to the broader population typically encountered in emergency settings, particularly in cases of septic shock where patients' conditions are more complex. With a modest sample size of 17 participants, chosen based on initial estimates of measurement variability and the minimum required to detect significant differences, our study was inherently exploratory. This size was deemed sufficient to achieve initial insights and lay the groundwork for future studies that can expand on these findings with a more diverse and clinically representative patient cohort. Future studies should aim to include a broader patient population to enhance the generalizability of these findings and validate the optimal pressure ranges for CRT measurement in a clinical environment.

5. Conclusions

This pilot study conducted a comprehensive analysis of contact pressure in CRT measurement. Utilizing a highly sensitive universal

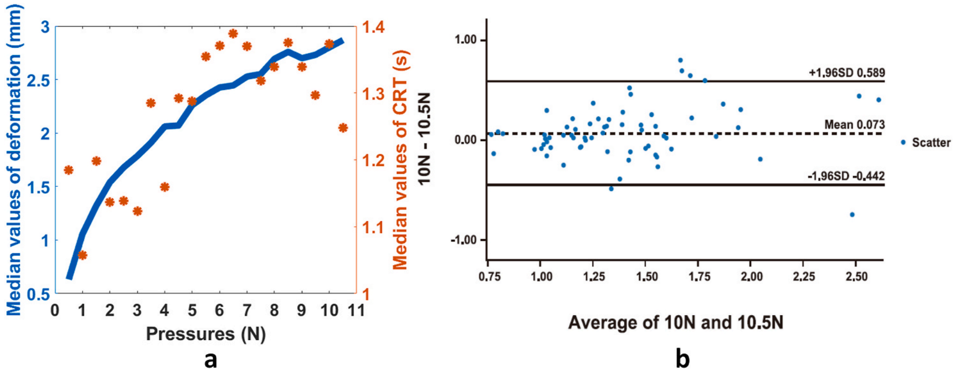

Fig. 4. Data visualizations. (a) Median values of deformation plotted against pressures. The median values of CRT are also scattered against pressure. (b) Bland-Altman plots of CRTs measured at 10N and 10.5N applied pressure.

testing machine, precise pressure ranging from 0.5N to 10.5N were systematically generated with high accuracy, maintaining a stringent tolerance of less than ±1 % relative errors at 0.5N increments. Methodological precision was maintained by a Proportional-Integral-Derivative control (PID) system, providing consistent 5-s pressure for each measurement. CRT values were captured with a PPG device and extracted via an autodetection algorithm.

From the 17 participants, a substantial dataset of 1414 valid CRT readings was compiled, laying a solid groundwork for statistical analysis and future research. The analysis revealed a non-normal distribution of CRT data and a significant correlation between CRT values and pressure levels. Notably, the study identified 4.5N–10.5N as the optimal pressure range for CRT assessment. In particular, pressures at 10N and 10.5N were found to provide the highest reliability in measurements, underscoring their critical role in achieving accurate and consistent CRT evaluations.

List of abbreviations

CRT	Capillary Refill Time
PPG	Photoplethysmography
ICC	Intraclass Correlation Coefficient
SMS	Skin Mottling Score
UTM	Universal Testing Machine
PID	Proportional-Integral-Derivative

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee Review Board of Beijing University of Technology (HS202312002) on November 28, 2023. This approval covers all aspects of the study, including the methodology, data collection, and analysis procedures. Informed consent was obtained from all participants included in the study. Detailed information about the study's objectives, procedures, potential risks, and benefits was provided to the participants. They were also informed of their right to withdraw from the study at any time without consequence. All consents were obtained in writing, and participants were assured of the confidentiality and anonymity of their responses.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Zi-Yu Ma: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **Shen Sun:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Shui-Cai Wu:** Methodology, Supervision. **Lan Lin:** Formal analysis, Investigation. **Yi-Xiong Chen:** Formal analysis, Investigation. **Dong Zhao:** Conceptualization, Methodology. **Stephen P. Morgan:** Conceptualization, Supervision, Writing – review & editing.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used [ChatGPT 4.0] in order to grammar checking and language polishing only. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of competing interest

None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35716.

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