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ORIGINAL ARTICLE

Development and Internal Validation of an AI-Enabled Cuff-less, Non-invasive Continuous Blood Pressure Monitor Across All Classes of Hypertension

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Abstract

Background Non-invasive, continuous blood pressure monitoring technologies require additional validation beyond standard cuff-based methods. This study evaluates a non-invasive, multiparametric wearable cuffless blood pressure (BP) diagnostic monitor across all hypertension classes with diverse subjects.

Methods A prospective, multicenter study assessed Nanowear's SimpleSense-BP performance, including induced and natural BP changes, significant BP variations (Systolic BP (SBP) $\geq \pm 15$ mm Hg and Diastolic BP (DBP) $\geq \pm 10$ mm Hg), and reference input value validity over 4 weeks.

Results 303 subjects (18–83 yrs; 50.16% Female) participated in algorithmic development and validation (Normal – 35%, Prehypertensive – 24%, Stage 1 – 24%, Stage 2 – 17%). 54 subjects were tested for induced change performance, 149 exhibited significant changes, and 91 validated reference value duration.

Conclusions The study clinically validated a continuous, AI-based BP diagnostic monitor using non-invasive wearable data. Further testing on diverse populations and external validation are recommended. The protocol was inspired by ISO 81060–2 and IEEE 1708:2019 standards.

Keywords Blood pressure · Artificial intelligence · Ambulatory · Hypertension · Diagnostic

Introduction

Hypertension, often dubbed the "silent killer," affects over 100 million Americans [1]. Effective management and early detection through home-based blood pressure (BP) monitoring are crucial due to the limitations of current devices in terms of ease of use and accuracy. Automated blood pressure monitors (ABPMs) are considered the gold standard for diagnosing hypertension due to their ability to avoid white coat hypertension (WCH) seen in clinical settings [2]. Despite their accuracy and ability to offer longitudinal data for personalizing treatment [3], ABPMs are underutilized, particularly among undiagnosed individuals, because they are not indicated for those without suspected hypertension. Challenges such as intra-individual variability in ABPM readings [4] arise from improper device use and patient awareness during measurements, which can affect results, especially in WCH-prone individuals.

Therefore, there is an unmet need for accessible, cost-effective devices that patients can easily use at home with

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automated quality control features to minimize manual operations and provide comprehensive, long-term BP data. Such data can enhance personalized treatment plans when combined with regular medical checkups.

The hypothesis behind non-invasive BP measurement devices is that a mathematical model can estimate BP from correlated physiological signals. However, studies like Microsoft's Aurora Project have shown negative results for devices using pulse wave analysis (PWA) and pulse arrival time (PAT) [5]. Nanowear's SimpleSense platform offers a promising alternative. This FDA-cleared wearable device uses innovative Nanosensor technology to estimate systolic and diastolic BP through artificial intelligence (AI) [6]. It incorporates demographic data, historical BP values, and physiological signals such as ECG and respiration rate. We validated the AI algorithm on various ethnicities and demographics across different hypertension stages (Normal, Prehypertension, Stage 1 and 2). Initially calibrated with traditional sphygmomanometer readings, SimpleSense-BP provides frequent readings with minimal manual intervention, although it does not meet ISO 81060–3 criteria for continuous monitoring.

We organized the manuscript as follows – We describe the device under evaluation in Section 2.1, followed by our study design, procedure for the simultaneous measurement of BP from our device, and a clinical gold standard sphygmomanometer in sections, and approach for data analysis in Sect. 2.2. We present the results in Sect. 3 and discuss limitations, insights, and outlook in in sections 4 and 5.

Methods

Device Description – SimpleSense-BP

The SimpleSense-BP Software Application is a software module within the SimpleSense Platform that accesses the physiological parameters like ECG, heart sounds, and thoracic impedance captured by the FDA-cleared SimpleSense Platform [7] (K212160) for processing into the vital sign outputs of the product. These outputs are returned to the SimpleSense Mobile Application or SimpleSense Web Application user interface (UI) for display and review by medical professionals. No manual operations are required by medical professionals for the device to function. Figure 1 presents the SimpleSense platform, including the hardware product, mobile app, and web interface.

SimpleSense-BP includes the following four software modules – (1) An input type, format, and data validation module to assess if the inputs supplied to SimpleSense-BP meet a pre-specified requirement by design. (2) A signal quality assessment is performed on the input data from the SimpleSense device. Only signals with adequate quality for further computation are used. (3) A feature extraction module that extracts a predefined set of features from the SimpleSense data and merges the data with the user's demographic information. The device-derived parameters are inclusive, but not limited to, Time between R peak (ECG) and S1 (Heart sounds), time between R peak (ECG) and S2 (Heart sounds), ECG morphological analysis (ECG), S1 and S2 root mean square amplitudes, ratio of S1 and S2 root mean square amplitudes (Heart sounds), R-R intervals (ECG), respiratory rate (thoracic impedance), posture and activity. The demographics data includes – age, gender, height, and weight. Finally, (4) a model for systolic and diastolic blood pressure that takes as input the set of features extracted by the feature extraction module along with the demographics data and returns an estimate of the systolic and diastolic blood pressure associated with that segment of SimpleSense device data which have been shown to have known associations to blood pressure [6].

Study Design

Subject Population

A prospective, multicenter, nonrandomized, observational study (NCT05473702) was conducted in Pennsylvania, New York, and New Jersey in the USA by Nanowear Inc. R&D and ClinCept LLC, Columbus, Georgia, USA in Georgia.

Subjects from the general population in the three geographic regions were screened and enrolled to meet the inclusion and exclusion criteria, as presented in Table 1. The study was conducted with three phases of enrollment with the same enrollment criteria. For the first arm, at least 85 subjects were required from Pennsylvania and Georgia for training and validation and New York and New Jersey for testing.

For the second arm, to ensure models operate accurately over a broad range of blood pressures, both within the specified range of the original model chosen by baseline reference value and outside the range of the baseline model, Nanowear enrolled an additional cohort of subjects. The enrollment was done until at least 10 subjects had a change in BP, meeting the criteria of at least 15 mmHg systolic or 10 mmHg diastolic for each of the 4 models used by the device to capture real-world examples and occurrences of patients who undergo such changes. The enrollment aimed to capture both induced and physiological changes in BP, ensuring a comprehensive evaluation of the device's performance.

For the third arm, to ensure the device maintains its accuracy for the labeled period of calibration, Nanowear enrolled another cohort of subjects, and performance evaluation was performed with measurements at baseline, at the end, and at an intermediate time point(s). Subjects were enrolled following IEEE 1708 specifications of at least 85 subjects, and

Fig. 1 SimpleSense Platform

Table 1 Subject Population enrollment criteria and BP clinical stratification boundaries

Inclusion Criteria:
- Age: 18 to 80 years
- Healthy or diagnosed with hypertension
- Normal sinus rhythm and no known valvular diseases

Exclusion Criteria:
- Subjects unwilling or unable to wear SimpleSense or reference device
- Subjects who are pregnant
- Subjects with implantable cardiac device (i.e., pacemaker or internal cardioverter defibrillator)
- Pediatric subjects (less than 18 years of age)
- Elderly (more than 80 years of age)
- Subjects with arrhythmias

Blood pressure classification	SBP (mmHg)		DBP (mmHg)	Total Subjects
Normal	< 120	and	< 80	≥ 21
Prehypertension	120–139	or	80–89	≥ 21
Stage 1 hypertension	140–160	or	90–100	≥ 21
Stage 2 hypertension	≥ 160	or	≥ 100	≥ 21

Gender: At least 26 males and 26 females

at least 21 subjects in each clinical stratification of Normal, Prehypertension, Stage 1 hypertension, and stage 2 hypertension. 4 measurements after the initial calibration measurement shall be made for each enrolled subject, separated by 7 days to cover an evaluation period of 21 days. The final enrollment totals and subject characteristics for all arms are described in Sect. 3.1.

Blood Pressure Measurement Procedure

Two independent nurse practitioner observers performed all measurements using the SimpleSense device and each subject's gold standard sphygmomanometer. Endpoints for BP classification were determined according to the 2014 eighth JNC report [8]. Baseline blood pressure measured at the start of the test was considered for classification. Three measurements were made with subjects seated in a chair with elbows resting on the armrest, back upright against the backrest, and feet flat on the floor. The average of the three measurements was used to establish the clinical stratification of the subjects. The participants were required to wear the SimpleSense device, while the two trained observers used a sphygmomanometer and an Omron blood pressure cuff GUDID 10073796266353 to measure their blood pressure sequentially with no more than 90 s between measurement initiations to limit the effect of natural time-dependent BP variability and no less than 60 s to allow recovery of the brachial artery in the arm. The data collected simultaneously and in sync by SimpleSense was utilized to train models to estimate blood pressure using SimpleSense data and demographics information. Figure 2 provides an illustration of the study procedure for development and validation.

Nanowear presented the details of the procedure in a previously published article [6], where we followed the most recent recommendations available at the time [9]. To summarize, study participants were asked to perform blood pressure-modifying activities to raise the SBP and DBP dynamic range based on suggested methods in the literature [10]. Subjects sat on a chair or stool with their legs up and held a warm heat pad wrapped in an insulating cloth for 10 min to lower their blood pressure. Subjects were then asked to walk briskly to raise their blood pressure (light exercise) for 10 min. Subjects were then given an ice pack to hold in their hand for about 10 min, called cold pressor stimulus, to increase their BP. After each activity, the observers recorded three consecutive blood pressure readings or 24 total sphygmomanometer readings and 12 Omron readings per patient over the 90-min recording period. The results and how the changes were distributed are shown in the supplementary materials. We now expand on this work with additional test populations and sub-group analysis. Further, we have updated the algorithm to use hypertension diagnosis specific models for each class of hypertension to potentially find diagnosis specific relationships between SimpleSense data and blood pressure.

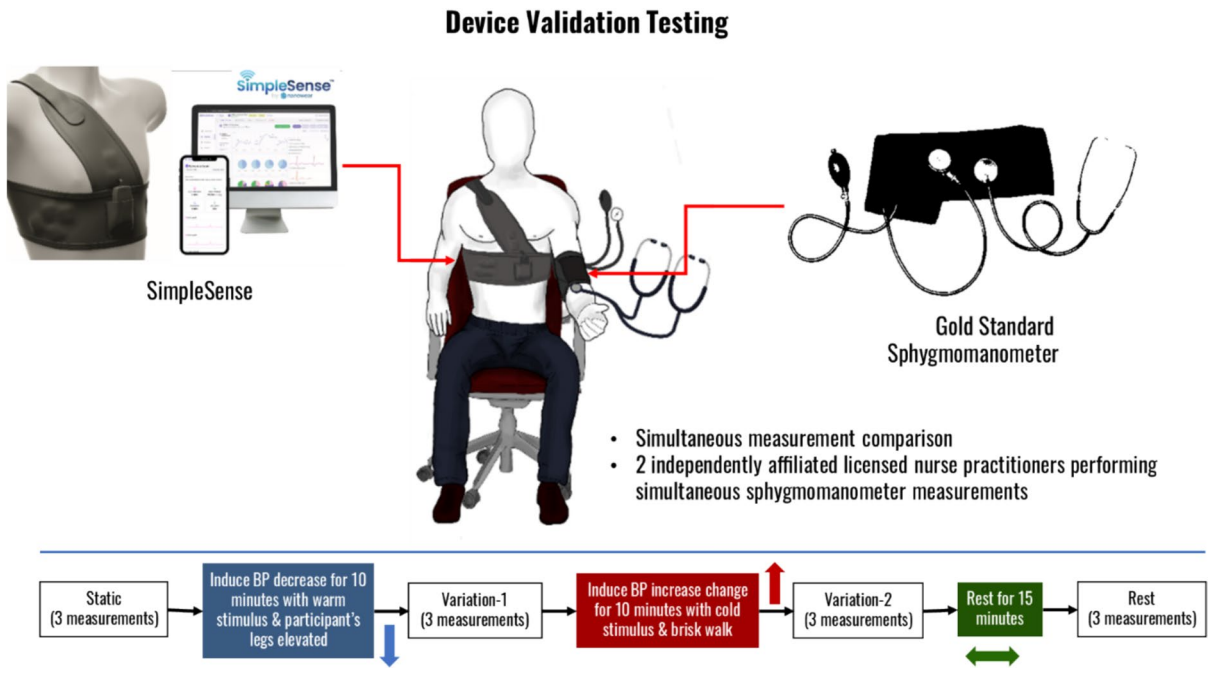

Fig. 2 Diagram of the overall study conducted for the development and validations of SimpleSense-BP

Data Preparation and Analysis

A 60-s-long segment of data from SimpleSense that corresponds with the observer-entered sphygmomanometer blood pressure was extracted for all the subjects. This SimpleSense data was combined with the sphygmomanometer readings of systolic and diastolic blood pressure from the observers to form the data sets for training and testing. Each segment was subjected to a data quality assessment, and segments of data of insufficient quality due to noise were removed from further consideration, a feature already existent from the SimpleSense Platform [7]. From the recorded data that has been deemed to be of acceptable quality, a dataset was prepared with the 60-s-long segments of SimpleSense device data and the associated target systolic and diastolic blood pressure values for training the SimpleSense-BP algorithm.

The Pennsylvania and Georgia datasets were used as training, and the data sets from New York and New Jersey were sequestered as independent test validation data of the AI-based algorithm.

Accuracy, as defined by the Institute of Electrical and Electronics Engineers (IEEE) 1708:2014 (including the 2019 amendment)[11] and the International Standards Organization (ISO) 81,060–2: 2018 standards[12], were used to evaluate the accuracy of estimated blood pressure. Following the recommendations to induce change by the IEEE 1708 standard, study participants performed activities that can modulate blood pressure for up to 90 min.

For the first and third arm, Mean Absolute Difference (MAD) (Equation S1), Mean Difference (MD) (Equation S2), and Standard deviation of differences (SD) (Equation S3) are used to analyze the performance of the models. The statistical aspect of the criteria is discussed in IEEE 1708-2019a and in ISO 81060–2. Additionally, the MAD value for the systolic and diastolic pressures were also computed using bootstrap with resampling. 1000 iterations were performed, taking samples equal to the available test set observations with replacement to arrive at the bootstrap mean MAD and the 95% confidence interval.

where p_i is the test device measurement, y_i is the average of the adjacent two reference measurements taken before and after device measurement as defined in ISO 81060–2:2018, and n is the data size.

To report the accuracy of the device, mean absolute difference (MAD), mean difference (MD), and standard deviation of difference (SD) were used. The MAD, MD, and SD are reported with data binned in different patient-specific parameters to evaluate the effect of potential confounders. Bootstrap resampling was conducted to calculate the MAD values for lower 95% and upper 95% confidence intervals of the MAD for the Systolic and Diastolic BP model. A pre-specified limit for MAD of no greater than 6 mm Hg [11], and MD $\leq \pm 5$ mmHg and SD ≤ 8 mmHg [12] was considered acceptable based on established validation practices for blood pressure measurement devices in the field.

For the second arm, three measurements for each condition were averaged and not averaged for error performance calculation. Both results are presented. We performed two sub-analyses – Sub analyses 1 and 2 as described in Sects. 2.3.1 and 2.3.2. Overall performance as primary analysis and performance in each clinical stratification as secondary analysis were computed for both sub-analyses.

In the supplementary materials, the systolic and diastolic values are graphically plotted as:

- Bland–Altman Scatter plots of the measurement differences between the test device and reference measurement vs. the average of them, along with the limits of agreement.
- Scatter plots of the test device measurements vs. the reference device measurements with slope and intercept of the fit line and the confidence intervals of the slope and intercept values.

Assessment of Device Performance in Tracking BP Recovery After an Induced Change

This sub-analysis aims to assess the device's performance once the stimulus for inducing BP increase is removed and there is a real-world potential for BP to return to baseline value—this analysis measures the device's accuracy when there is a significant decrease in blood pressure. Specifically, this sub-analysis reflects performance evaluation at the change point (an increase in BP of 15 mmHg systolic or 10 mmHg diastolic) and following change, which is error performance of recalibrated estimates on Variation 2 and rest. Measurements included in the analysis are depicted in Figure S5a. In another analysis, across the entire test population, all significant changes of SBP $\geq \pm 15$ mm Hg and DBP $\geq \pm 10$ mm Hg regardless of whether stimulus induced were evaluated with the device recalibrated prior to observed change using sphygmomanometer and performance evaluated on the measurements after the change was observed as depicted in Figure S5b.

Overall Assessment of Device Performance Inclusive of Ability to Track Induced Change and Recovery of BP

Overall performance was evaluated on Static, Variation 1 (BP lowering using warm stimulus and leg raising), Variation 2 (BP increase using brisk walk and cold pressor stimulus), recalibrated estimates on Variation 2, and rest after recalibration. Only those subjects who exhibited an SBP increase of ≥ 15 mm Hg or DBP increase ≥ 10 mmHg due to the application of cold pressor and brisk walk stimulus were included in this performance evaluation. Measurements included in the analysis are depicted in Figure S6a. In another analysis, across the entire test population, all

significant changes of SBP ≥ ± 15 mm Hg and DBP ≥ ± 10 mm Hg regardless of whether stimulus induced, nominal changes below the significant change threshold and overall performance across all measurements are compared. Measurements included in the analysis are depicted in Figure S6b.

Blood Pressure Algorithm Validation for the Duration of Validity of an Initial Calibration

To ensure the device maintains its accuracy for the labeled period of calibration, Nanowear enrolled an additional cohort of subjects, and performance evaluation was performed with measurements at baseline, at the end, and at an intermediate time point(s). Subjects were enrolled following IEEE 1708 specifications of at least 85 subjects and at least 21 subjects in each clinical stratification of Normal, Prehypertension, Stage 1 hypertension, and stage 2 hypertension.

4 measurements after the initial calibration measurement were taken for each enrolled subject, separated by 7 days to cover an evaluation period of 21 days.

Results

Subject Characteristics

Overall BP Estimation Algorithm Development and Validation Cohort There was no overlap of subjects between the training and test data sets, i.e., none of the measurements from subjects in the training data set were included in the test data set and vice versa. The training set includes 185 subjects from Pennsylvania (over 20 locations such as State College, Bellefonte, Jersey Shore, Center Hall), Atlanta, and Alpharetta, Georgia (up to 5 locations). The test validation included 118 subjects in New York and New Jersey (over 20 locations such as Central Park South, Manhattan; Jamaica, Queens; Valhalla, New York, Suffern, New York; Hoboken, New Jersey; Borough Park, Brooklyn; Canarsie, Brooklyn; Brooklyn Heights, Brooklyn and Park Hill, Staten Island). A total of 303 subjects were enrolled with demographics, as shown in Table 2, with Ethnicity and demographics reflecting the US census (White 58.9%; Hispanic – 19.1%; African American 13.6%; Asian 6.3%). Figures S1 through S4, and Table S1 present the extent of induced changes observed based on sphygmomanometer measurements. Table S2 presents the test population distribution of blood pressures.

BP algorithm performance evaluation, when there was a significant change in the underlying measured BP A subgroup of the test population for the overall algorithm development and additional new subjects were recruited from the test geographic location to evaluate the performance of the BP algorithm for conditions where there was a change of at least 15 mm Hg systolic or 10 mmHg diastolic. Only subjects who manifested this type of change were included in this evaluation. In addition to 118 test subjects, 54 were specifically enrolled for induced change performance, as shown in Table 2, while 149 among the total test population exhibited significant changes naturally or through induced means. Table S3 provides details on types of changes observed and number of subjects exhibiting each type of change.

Table 2 Demographics and subgroup information

		Overall Development and Validation		Calibration Period Evaluation	Change test evaluation
	Subgroup	Number of Subjects in Training (N)	Number of Subjects in Test (N)	Number of Subjects (N)	Number of Subjects (N)
Gender	Male	84 (45%)	67 (57%)	52 (57%)	27 (50%)
	Female	101 (55%)	51 (43%)	39 (43%)	27 (50%)
Race	Asian	14 (8%)	31 (26%)	16 (18%)	8 (15%)
	Black	59 (32%)	32 (27%)	18 (20%)	6 (11%)
	Hispanic	12 (6%)	22 (19%)	11 (12%)	5 (9%)
	White	100 (54%)	33 (28%)	46 (51%)	35 (65%)
Clinical Stratification	Normal	63 (34%)	42 (36%)	24 (26%)	11 (20%)
	Prehypertensive	43 (23%)	30 (25%)	23 (25%)	19 (35%)
	Stage 1 Hypertension	49 (26%)	25 (21%)	23 (25%)	14 (26%)
	Stage 2 Hypertension	30 (16%)	21 (18%)	21 (23%)	10 (19%)
Age	18—30 years	46 (25%)	11 (9%)	10 (11%)	5 (9%)
	31 – 40 years	38 (21%)	25 (21%)	14 (15%)	6 (11%)
	41 – 50 years	42 (21%)	28 (21%)	16 (15%)	12 (11%)
	51 – 60 years	24 (13%)	23 (19%)	24 (26%)	17 (31%)
	61 – 70 years	17 (9%)	14 (12%)	13 (14%)	5 (9%)
	71—83 years	18 (10%)	17 (14%)	14 (15%)	9 (17%)

BP algorithm performance evaluation and evaluation of the calibration duration A subgroup of the test population for the overall algorithm development and additional new subjects were recruited from the test geographic location to perform recordings once a week for 4 weeks so that the validity of the calibration value over an intended calibration period of 21 days or 4 weeks could be evaluated. A total of 91 subjects were enrolled, as shown in Table 2.

Performance Evaluation

Overall Performance

In this evaluation, we present the results of error performance for all variations included as overall performance and performance under each condition. Table 3 presents the performance statistics.

The systolic bootstrap confidence intervals were [5.16 mmHg, 5.68 mmHg], and diastolic bootstrap confidence intervals were [4.45 mmHg, 4.94 mmHg]. Tables S4 and S5 present errors for systolic blood pressure and diastolic blood pressure, respectively, for each clinical category and consequent model selected for estimating blood pressure for each of the conditions used to induce blood pressure variation.

As described in Sect. 2.2, we present the performance data analysis in the form of a scatter plot with actual against estimated values (Fig. 3a and 3c, for SBP and DBP, respectively) and the Bland Altman plots with the limits of agreement and bias (Fig. 3b and 3d, for SBP and DBP, respectively). All results show that the performance was maintained within acceptable limits (MAD < 6 mm Hg, MD < ± 5 mm Hg and SD < 8 mm Hg) and with the limits of agreement from the Bland Altman plots were well within the acceptability limit of ± 15 mm Hg.

Patient-Specific Confounders

When used as inputs, patient-specific information could confound the BP estimation models. For example:- the models may estimate higher BP for older subjects, as would generally be true but will result in significant errors for older subjects with normal BP. Tables S6 and S7 present the confounder analysis for SBP and DBP, respectively.

Assessment at Significant BP Changes Induced by Maneuvers in the Protocol

Centered on a change in the underlying BP, analysis of performance provides insight into the ability of BP estimation algorithms to estimate blood pressure with the ability to track actual physiological change and not trivial time-dependent or sequence of events dependent changes (such as coincidental changes associated with how a protocol has a prescribed sequence of activities that the subjects are required to perform). Tables S8 through S11 present the number of subjects who had blood pressures that crossed clinical stratification boundaries based on the clinical stratification before the increase in BP was observed and clinical stratification after change was observed. The tables present the cohorts based on the clinical stratifications for the subjects when they were enrolled, i.e., based on the static measurements. This illustrates the impact of the choice of an initial reference value or diagnosis as insignificant when compared to requisite calibration values of PWTT, PWA or PDA-based models.

Results for assessment of BP accuracy around a time-point of induced BP change As described in Sect. 2.3.1, Table S12 , and Figure S7 provide the performance results as the performance metrics and the Bland Altman plots as part a. Part b results are presented in Table S13 and Figure S8. All results show that the performance was maintained within acceptable limits (MAD < 6 mm Hg, MD < ± 5 mm Hg and SD < 8 mm Hg) and with the limits of agreement from the Bland Altman plots were well within the acceptability limit of ± 15 mm Hg.

Results for assessment of BP accuracy overall including points of significant induced BP changes. As described

Table 3 Error Performance Results overall and for each induced change condition

BP type	Condition	MAD	MD	SD
Systolic	Overall	5.43	−0.07	6.71
	Static	4.55	−0.15	5.72
	BP decrease (Warm Stimulus and Leg raise)	5.54	−1.34	6.6
	BP Increase (Cold Stimulus and Brisk Walk)	5.56	1.6	6.75
	Rest	6.23	−0.15	7.55
Diastolic	Overall	4.68	−0.58	5.89
	Static	4.05	−0.72	5.2
	BP decrease (Warm Stimulus and Leg raise)	4.82	−1.1	5.95
	BP Increase (Cold Stimulus and Brisk Walk)	5.18	0.13	6.48
	Rest	4.78	−0.52	5.98

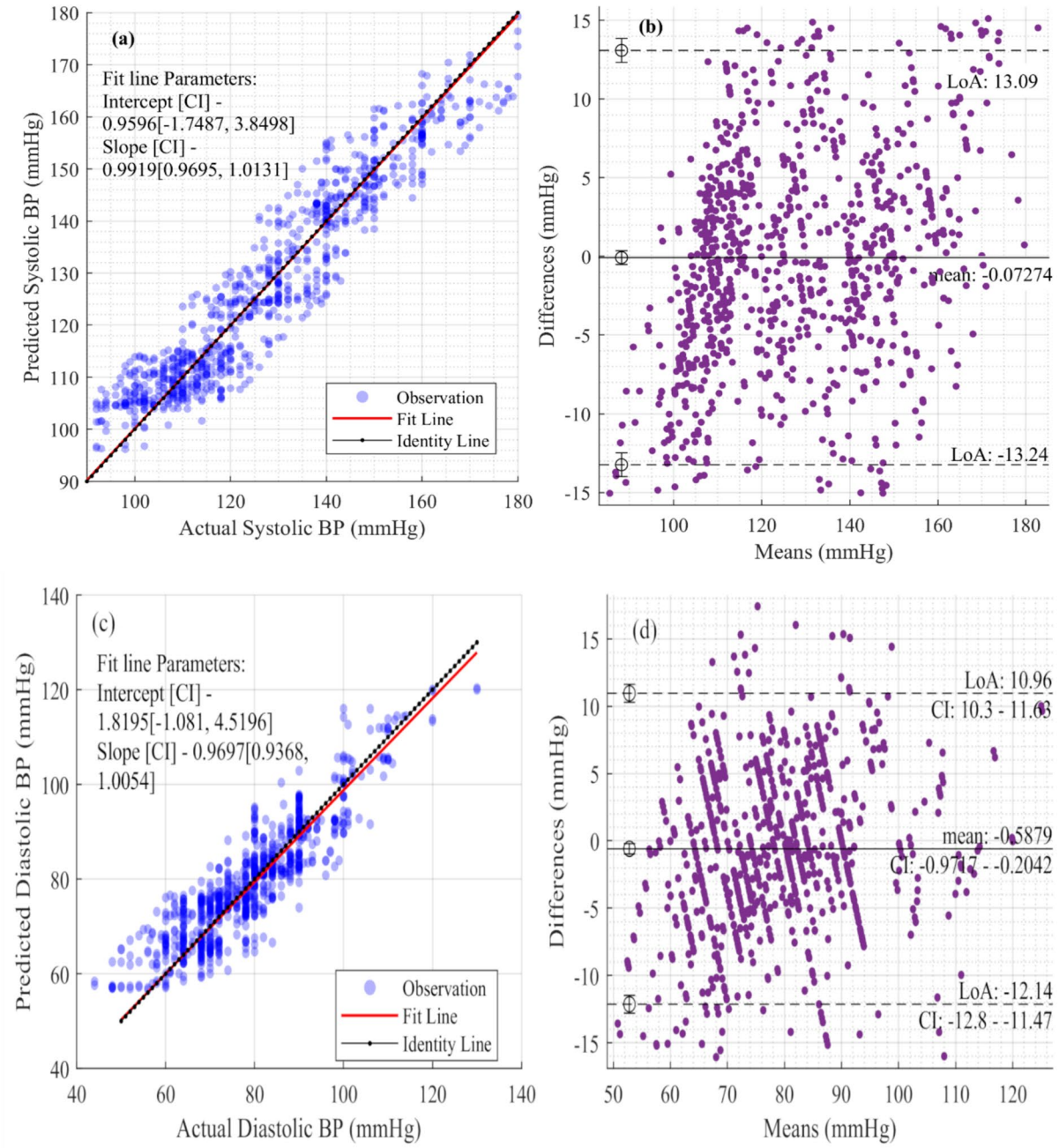

Fig. 3 (**a**) Predicted vs. actual SBP with a fit line and fit line parameters. (**b**) Bland Altman Plots between actual and estimated SBP. (**c**) Predicted vs. actual DBP with a fit line and fit line parameters. (**d**) Bland Altman Plots between actual and estimated DBP

in Sect. 2.3.2, Table S14, and Figure S9 in the supplementary materials provide the performance results as the performance metrics and the Bland Altman plots as part a. Part b results are presented in Table S15 and Figures S10. Table S16 and Figure S11 provide results of the analysis on points of nominal or no change for comparison. All results show that the performance was maintained within acceptable limits (MAD < 6 mm Hg, MD < ± 5 mm Hg and SD < 8 mm Hg) and with the limits of agreement from the Bland Altman plots were well within the acceptability limit of ± 15 mm Hg.

Assessment Duration of Validity of the Reference BP Values

As described in Sect. 2.3.3, Table S17 presents the statistical error performance metrics for validation of the duration over which a reference value may be used while maintaining the same level of performance (MD < ± 5 mm of Hg and SD < 8 mm of Hg).

Discussion

The study presents a unique protocol that validates an AI-enabled, cuff-less, non-invasive continuous blood pressure (BP) diagnostic monitor, known as SimpleSense-BP, developed by Nanowear Inc. The research design is comprehensive, prospective, and multicenter, encompassing 303 subjects from diverse hypertensive categories and varied ethnic and demographic backgrounds. SimpleSense-BP utilizes a multiparametric approach integrating various physiological parameters to estimate BP, demonstrating its rigor through a validation process that revealed BP measurementmean difference were less than 5 mm Hg compared to traditional cuff-based sphygmomanometer over a 30-day follow-up period. The mean difference for systolic BP (SBP) was −0.07 mm Hg and for diastolic BP (DBP) was −0.58 mm Hg, with standard deviations of 6.71 mm Hg and 5.89 mm Hg, respectively. Additionally, the device effectively tracked significant BP changes induced by various stimuli (SBP ≥ ± 15 mmHg; DBP ≥ ± 10 mmHg, 232 occurrences were observed, and 130 occurrences of crossover in hypertension classification) while maintaining acceptable error performance of less than 5mm Hg under international standards for blood pressure devices, ISO 81060–2.

The results presented in Sect. 3.2.3 show that the Bland–Altman plots indicate potential systemic bias, with overestimation at lower BP values and underestimation at higher values, necessitating further refinement of the algorithm. A plausible explanation for this condition is that BP is estimated using 1 min of data from central physiological parameters such as ECG, heart sound, and impedance, so comparing these measurements to gold standard devices, which are more spot measurements, reveals a gradual underfitting like the difference between SimpleSense-BP and sphygmomanometer measurements. Furthermore, trans-thoracic impedance is used primarily for respiration detection, with its potential role in stroke volume estimation acknowledged but not fully utilized in this study.

Continuous blood pressure monitoring and ability to ascertain diagnostic changes across all classes of hypertension, could provide significant benefits to clinicians managing hypertensive patients, such as assessing the duration of time a patient has BP above a clinically relevant threshold and the time of day when the patient has high BP. Clinicians can decide whether to prescribe rapid-acting or extended-release as well as individualized timing for each patient taking medications. In the US, intermittent or spot-checking, patient-initiated BP monitoring is currently available through devices that rely on PWTT, PWA, or PDA. The need for such pervasive and continuous BP monitors has inspired several innovative medical device designs in the recent past. Notably, BioBeat [13], LiveMetric [14], and Caretaker Medical LLC [15] have received FDA clearances to market the devices in the USA at the time of writing. Aktiia watch has received a CE mark. The Caretaker device and Aktiia Watch use Pulse Decomposition Analysis (PDA), and BioBeat uses Pulse Wave Transit Time (PWTT) with the pulse waveforms measured using optical sensors. The LiveMetric device uses applanation tonometry measured with a pressure sensor array and Pulse Wave Analysis (PWA). The Caretaker device utilizes a cuff and provides continuous blood pressure whereas LiveMetrics, BioBeat and Aktiia are watch-based devices for spot-checks or intermittent readings that could be near-continuous (for example:- BP readings every 30 s). These devices use physiological mathematical models that rely on subject-specific parameters to approximate the association between pulse waveform features and blood pressure. Notably, these physiological models have not been clinically validated on cohorts of subjects within each clinical stratification as described within the IEE 1708:2019a standard[11] (normal, prehypertensive, Stage 1, or Stage 2) and were primarily validated on a healthy or normotensive patient population. Further, these devices were not validated on a broad representation of ethnicities, ages, heights, weights, and other patient demographics representative of the US population.

These subject-specific parameters introduce reliance on a controlled calibration measurement, which needs appropriate placement by a medical professional and/or calibration against an arm cuff-based blood pressure monitor reference value to determine the parameters for each subject and each use.

It is yet unknown how accurate these models would be for significant variations in blood pressure within each clinical stratification and if the initial diagnoses change from one hypertensive stratification to another. More rigorous evaluation methods are needed, and different approaches are needed if these limitations cannot be overcome[16]. Alternative approaches are an area of substantial ongoing research effort. The motivation being that a yet undiscovered, arbitrarily complex relationship beyond the current PWT, PDA physiological models likely exists and could provide a more accurate association between non-invasive signals and BP [17–19]. We present this article as a contributive effort for the rigorous evaluation of such devices and using a novel device and method to achieve accurate and continuous BP monitoring.

Study Limitations

Some aspects were not part of the assessment that should be considered for future evaluations. Firstly, the study protocol did not involve an overnight blood pressure measurement for comparison. Although change tracking was evaluated for the duration of the study for subjects with significant changes in

BP within a 75-min duration, the study did not account for a specific cohort of subjects undergoing a change in therapeutic strategy, i.e., new medications of changes in dosage, during their participation in the study. However, the enrollment criteria used for the study did not exclude patients taking hypertensive management medication and did not have special controls or protocol deviations for such subjects; therefore, the enrolled population was representative of real-world normal controls and hypertensive patients. Further, evaluating the algorithm's performance during all uninduced naturally occurring BP changes suggests the ability to track real-world systemic blood pressure beyond controlled protocol-induced BP change tracking.

Limitations further include unknown accuracy in those with valvular disease, lung disease (impacting both heart sounds and ECG signal), those with bundle branch blocks, those with LVH and interconduction delay etc.

During the development of this validation study and at the time of writing, repeatable and controlled methods of inducing significant changes in blood pressure (at least 15 mmHg of SBP or 10 mmHg of DBP) for participants remained challenging, especially when careful consideration is required for the safety of subjects involved in the more severe hypertension classes because the protocol should only include activities that this population could tolerate. A standardized protocol, with specific emphasis on enrollment requirements—more volume, granularity, patient diversity, and extreme categories of hypertension, is a critical next step—new methods to safely and repeatably induce changes in BP for study subjects will allow better standardization of device evaluation [20]. Non-invasive sphygmomanometers using oscillometric measurement methods such as the standard BP cuffs are deemed safe and efficacious if they meet the performance acceptability criteria as per the international standards ISO 81060–2. With new methods and approaches for BP measurement emerging such as the method described herein, there is need for more expansive testing and validation. Efforts by international standards organizations such as ISO and IEEE are underway to develop improved validation protocols. In a parallel effort, the potential of AI and ML within this specific application may be realized with continuous advancements in non-invasive sensor materials technologies, hardware, and AI/ML methods and architectures. This article can contribute to such efforts.

Conclusions

This study developed and validated a continuous, non-invasive, cuffless, and wearable AI BP monitor on subjects across all stages of hypertension, ethnicities, and multiple geographies, including its ability to track any significant changes in BP (SBP $\geq \pm 15$ mm Hg and DBP $\geq \pm 10$ mm Hg) whether induced or natural. Such a device could potentially complement existing BP monitoring methods, offering additional data for clinical decision-making. A continuous improvement process for such devices with testing on diverse populations is warranted, along with external validation.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12265-024-10589-5.

Author Contributions Author contributions are listed in the same order as authorship. FL, AD, and JB were involved in writing (review & editing), John Boehmer was involved in conceptualization, device design, and interpretation of data. MR was involved in framing methodology, validation, and writing (original draft), PS was involved in data curation, validation, visualization, and writing (original draft). SK was involved in writing (original draft).VV was involved in project administration, conceptualization, supervision, funding acquisition, and writing (review & editing). VV was involved in conceptualization, supervision, funding acquisition, and resources. MF was involved in writing (review and editing). All authors reviewed and approved the manuscript.

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Data Availability The datasets generated during and/or analyzed during the current study are not publicly available due to the presence of sensitive Personally Identifiable Information (PII) for the participating subjects, but are available from the corresponding author on reasonable request.

Declarations

An independent Institutional Review Board (IRB), Advarra Inc. (Columbia, MD, USA), approved the protocol (IRB protocol #14–90-0093). This study was conducted in accordance with the of Helsinki and in compliance with relevant FDA regulations. All subjects provided written informed consent prior to participation and completed the study. Conflicts of interest pertinent to the study are provided in the following section titled disclosures.

Disclosures

- A. Deshmukh, F. Lopez-Jimenez, J. Bisognano, and M. Fudim report no relevant conflicts of interest.
- S. Kapa, J. Boehmer, are advisors for Nanowear, Inc with potential equity benefit but no direct cash compensation.
- M. Ramasamy, P. Kumar, V. Varadan, V. Varadan are employees of Nanowear, Inc and receive both equity and cash compensation benefits.
- M. Fudim is an editor in this journal.

References

1. Centers for Disease Control and Prevention: Hypertension Cascade: Hypertension Prevalence, Treatment and Control Estimates Among U.S. Adults Aged 18 Years and Older Applying the Criteria from the American College of Cardiology and American Heart Association's 2017 Hypertension Guideline—NHANES 2017–2020. Available at: https://millionhearts.hhs.gov/data-reports/hypertension-prevalence.html. Accessed 3 Aug 2023.
2. Cohen JB, Lotito MJ, Trivedi UK, Denker MG, Cohen DL, Townsend RR. Cardiovascular Events and Mortality in White Coat Hypertension. Ann Intern Med. 2019;170:853–62. https://doi.org/10.7326/M19-0223.
3. Sola J, Cortes M, Perruchoud D, De Marco B, Lobo MD, Pellaton C, et al. Guidance for the Interpretation of Continual Cuffless Blood Pressure Data for the Diagnosis and Management of Hypertension. Frontiers in Medical Technology. 2022;4. https://doi.org/10.3389/fmedt.2022.899143.
4. Bo Y, Kwok K-O, Chung VC-H, Yu C-P, Tsoi KK-F, Wong SY-S, et al. Short-term reproducibility of ambulatory blood pressure measurements: a systematic review and meta-analysis of 35 observational studies. Journal of Hypertension. 2020;38:2095–109. https://doi.org/10.1097/hjh.0000000000002522.
5. Mukkamala R, Shroff SG, Landry C, Kyriakoulis KG, Avolio AP, Stergiou GS. The Microsoft Research Aurora Project: Important Findings on Cuffless Blood Pressure Measurement. Hypertension. 2023;80:534–40. https://doi.org/10.1161/HYPERTENSIONAHA.122.20410.
6. Kumar PS, Rai P, Ramasamy M, Varadan VK, Varadan VK. Multiparametric cloth-based wearable, SimpleSense, estimates blood pressure. Sci Rep. 2022;12:13059. https://doi.org/10.1038/s41598-022-17223-x.
7. FDA 510(k) Summary - SimpleSense Platform. https://www.accessdata.fda.gov/cdrh_docs/pdf21/K212160.pdf. Accessed 7/31/2023.
8. Bangalore S, Gong Y, Cooper-DeHoff RM, Pepine CJ, Messerli FH. 2014 Eighth Joint National Committee Panel Recommendation for Blood Pressure Targets Revisited: Results From the INVEST Study. J Am Coll Cardiol. 2014;64:784–93. https://doi.org/10.1016/j.jacc.2014.05.044.
9. Mukkamala R, Yavarimanesh M, Natarajan K, Hahn J-O, Kyriakoulis KG, Avolio AP, et al. Evaluation of the Accuracy of Cuffless Blood Pressure Measurement Devices: Challenges and Proposals. Hypertension. 2021;78:1161–7. https://doi.org/10.1161/HYPERTENSIONAHA.121.17747.
10. Verberk, W.J. (2019). Design of clinical trials to validate cuffless blood pressure monitors. In: Solà, J., Delgado-Gonzalo, R. (eds) The handbook of cuffless blood pressure monitoring. Springer, Cham. https://doi.org/10.1007/978-3-030-24701-0_12.
11. IEEE Standard for Wearable, Cuffless Blood Pressure Measuring Devices - Amendment 1. IEEE Std 1708a-2019 (Amendment to IEEE Std 1708–2014). 2019:1–35. https://doi.org/10.1109/IEEESTD.2019.8859685.
12. Standards I. ISO 81060–2:2018/Amd 1:2020 Non-invasive sphygmomanometers Part 2: Clinical investigation of intermittent automated measurement type. 2020. Available at: https://www.iso.org/standard/73339.html. Accessed 07/23/2023.
13. FDA 510(k) Summary Biobeat Platform-2 and BB-613WP Patch. https://www.accessdata.fda.gov/cdrh_docs/pdf22/K222010.pdf. Accessed 07/28/2023.
14. FDA 510(k) Summary LiveOne LM1P https://www.accessdata.fda.gov/cdrh_docs/pdf20/K201302.pdf. Accessed 07/28/2023.
15. FDA 510(k) Summary for CareTaker Continuous Non-Invasive Blood Pressure Monitor, CareTaker Wireless Vital Signs Monitor, CareTaker Physiological Monitor. https://www.accessdata.fda.gov/cdrh_docs/pdf16/K163255.pdf . Accessed 07/28/2023.
16. Mukkamala R, Hahn JO, Inan OT, Mestha LK, Kim CS, Toreyin H, et al. Toward Ubiquitous Blood Pressure Monitoring via Pulse Transit Time: Theory and Practice. IEEE Trans Biomed Eng. 2015;62:1879–901. https://doi.org/10.1109/tbme.2015.2441951.
17. Visco V, Izzo C, Mancusi C, Rispoli A, Tedeschi M, Virtuoso N, et al. Artificial Intelligence in Hypertension Management: An Ace up Your Sleeve. J Cardiovascul Develop Disease. 2023;10:74.
18. Thambiraj G, Gandhi U, Mangalanathan U. Chapter 4 - Data-driven models for cuffless blood pressure estimation using ECG and PPG signals. In: Sridhar R, Gangadharan GR, Sheng M, Shankaran R, editors. Edge-of-Things in Personalized Healthcare Support Systems: Academic Press; 2022;77–113.
19. Maqsood S, Xu S, Tran S, Garg S, Springer M, Karunanithi M, et al. A survey: From shallow to deep machine learning approaches for blood pressure estimation using biosensors. Expert Syst Appl. 2022;197:116788. https://doi.org/10.1016/j.eswa.2022.116788.
20. Mukkamala R, Stergiou GS, Avolio AP. Cuffless Blood Pressure Measurement. Annu Rev Biomed Eng. 2022;24:203–30. https://doi.org/10.1146/annurev-bioeng-110220-014644.