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Diurnal cardio-respiratory changes in ambulatory individuals deciphered using a multi-parameter wearable device

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Abstract

Background: Recent technological developments enable big data-driven insights on diurnal changes. This study aimed to describe the trajectory of multiple and advanced parameters using a medical-grade wearable remote patient monitor.

Methods: Parameters were monitored for 24 h in 256 ambulatory participants who kept living their normal life. Parameters included heart rate, blood pressure, stroke volume, cardiac index, systemic vascular resistance, blood oxygen saturation, and respiratory rate. Diurnal variations were evaluated, and analyses were stratified based on sex, age, and body mass index.

Results: All parameters showed diurnal changes ($p < 0.001$). Females demonstrated higher heart rate and cardiac index with lower systemic vascular resistance. Obese participants had a higher blood pressure, and lower stroke volume and cardiac index. Systemic vascular resistance was higher among the elderly. Diurnal changes corresponded with awake–sleep hours and differed between sex, age, and body mass index groups.

Conclusion: Wearable monitoring platforms could decipher hemodynamic changes in subgroups of individuals, and might help with efforts to provide personalized medicine, pre-symptomatic diagnosis and prevention, and drug development.

Keywords

patient-generated health data, noninvasive monitoring, ambulatory blood pressure monitoring, photoplethysmography, diurnal changes

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Introduction

Patient-generated health data (PGHD) is an emerging field in which health-related data are gathered from a patient using different tools such as wearable sensors, mobile apps, and home monitoring devices.[1] In the cardiovascular field, patient monitoring has been in use for decades; 24-h ambulatory monitoring of blood pressure (BP) and electrocardiography are usually used offline, but still provide precious information to the physician, allowing better diagnosis of hypertension and arrhythmias.[2] Furthermore, ambulatory

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data monitoring of cardiac implantable electronic devices such as pacemakers and implantable cardioverter defibrillators enables the interrogation of suspected arrhythmias.[3] Recently, implantable miniaturized pressure sensors in the pulmonary artery transmit the pulmonary artery pressure on-demand and help guide medical treatment in patients with heart failure.[4]

Advanced, minimally or noninvasive, wearable, and convenient PGHD devices are now emerging and can be used to collect various physiological parameters and vital signs.[1,3,5] A few devices have been developed and cleared by the US Food and Drug Administration (FDA), usually to monitor a single or a few parameters. These sensors can monitor parameters such as heart rate (HR), heart rate variability, respiratory rate (RR), blood oxygen saturation (SpO_2), thoracic fluid content, and BP.[5] By using these wearable devices, novel insights with clinical implications are now readily available, potentially allowing to shed more light on physiological behaviors and changes during daily activity. This, in turn, could help improve health and medical care by tailoring it to the specific needs of an individual. However, more advanced parameters such as stroke volume (SV) and cardiac output (CO) were not readily available until recently.

Monitoring of advanced physiological parameters such as CO or systemic vascular resistance (SVR) provides better insights into the hemodynamics of cardiovascular conditions. Yet, so far, their measurement required cumbersome or invasive equipment, restricting our knowledge to complex hospitalized patients. Recent developments in the field of noninvasive sensors introduced wearable monitors that turned accurate and continuous ambulatory monitoring of advanced physiological parameters into a reality (see Table S1 for several examples, including links that provide the full capabilities of each).[6,7]

This study aimed to describe the diurnal variations in multiple advanced cardiovascular parameters across sex, age, and body mass index (BMI) in a large cohort of ambulatory individuals using a wearable photoplethysmography (PPG)-based device.

Materials and methods

Ethical considerations

This multi-center prospective, observational study conformed with the principles outlined in the Declaration of Helsinki, and includes deidentified physiological data from individuals participating in several studies, each approved by a relevant Institutional Review Board (IRB) (the Meuhedet Health Services, Tel Aviv, Israel, Approval Number 2021-11-15; Commissie voor Medische Ethiek ZNA, EC, Approval Number 5238, NCT03883113; the Tel Aviv University, Tel Aviv, Israel, Approval Number 0002522-1; and the Sheba Medical Center, Approval Number 7500-20-SMC, NCT04826250). Participants signed informed consent during enrollment as defined by the local IRB. The researchers had no personally identifiable information of the individuals included in the analysis.

Study participants

The data included in this study were recorded and pooled from groups of healthy volunteers living their everyday life, participating in trials that integrated continuous hemodynamic monitoring, with no other intervention during the period in which it was collected. Inclusion criteria were males and females, aged 18 years and above, without acute or chronic medical conditions. Participants were recruited from the above-mentioned participating medical centers. Exclusion criteria included age under 18 years, arrhythmias, pregnancy, lack of judgment or mental illness, and employees of the recruiting centers.

Study design

The wearable PPG-based monitor was applied following a concise personal medical history questionnaire, a baseline anthropometric data acquisition, and device calibration against an FDA-cleared cuff-based BP monitor. Physiological measurements were then collected automatically every 5 min for 24 h while the participants were free to continue with their normal daily activities. The data were transmitted to a dedicated data cloud repository for analysis.

The PPG-based monitoring device

PPG is commonly applied for pulse oximetry, transmitting light that is absorbed by a detector on the other side of relatively thin body parts such as fingers, ear lobes, etc. While passing through the tissue, the light wavelengths show a unique absorbance pattern according to the presence of oxy or deoxyhemoglobin. The currently used sensor is based on reflective PPG, in which part of the transmitted light is reflected from the tissue and detected by a photodiode detector positioned near the light source transmitter (BB-613WP, Biobeat Technologies Ltd., Petah Tikva, Israel). The high resolution of the PPG wave combined with advanced algorithms allows the sensor to capture changes and track vital signs derived from the pulse contours. Calibration of the BP measurements was described elsewhere.[6] The devices' advanced hemodynamic readings were previously compared to invasive and noninvasive gold standard methods in unstable, long-term clinical scenarios and animal models of shock and were found to be accurate, precise, and reliable.[6,8] The hemodynamic reading is wirelessly uploaded to a data cloud repository, enabling online and future analysis. The device is FDA-cleared for noninvasive cuffless BP (both systolic and diastolic at an

effective range of 60–250 and 40–150 mmHg, respectively), HR (40–240 beats per minute), SpO_2 (70%–100%), RR (4–40 breathes per minute), SV (20–115 ml/beat), CO (1.5–13 L/min), and body temperature (32–42° C), all from a single sensor. It also provides cardiac index (CI), pulse pressure (PP), mean arterial pressure (MAP), and SVR, all Conformité Européene (CE) mark certified. More information on the various validation studies of the different physiological parameters performed with the device could be found in the link provided in Table S1.

Statistical analysis

Daytime was defined between 7 am and 00:00 am, and nighttime between 00:00 am, and 7 am. Paired-sample *t*-test was used to compare between day and nighttime. Since there is an ongoing discussion on the differences in physiological parameters between sexes, different BMI, and age, and since BP could influence other hemodynamic parameters, the whole population was stratified based on sex at birth, age, BMI, and hypertension. Independent-sample *t*-test was used for between-strata and group-matching comparisons. As a result, not all participants entered the final comparisons. Between groups/strata comparisons of categorical data were tested using the chi-square test. Levene's test was used to assess the equality of variance before the independent-sample *t*-test. Within-group comparison (day vs. night) was done with dependent samples *t*-test. Significance was defined when the *p*-value was below 0.05 (two-tailed). Data in tables appear as mean ± standard deviation and in the figures as mean ± 95% confidence interval.

All descriptive statistical analyses were performed by using IBM SPSS version 25.

Readings regarded as "spurious readings" (basic definitions of either bad signals or signals defined as out of the sensor's measurement range) were automatically removed by the monitoring platform's algorithm and not included in the analysis. Thus, all collected measurements were regarded as technically valid. The next step was to aggregate the 5-min data (using all data points) into hourly measurement aggregates using Python's data analysis library.[9]

Results

In total, 256 participants (19–80 years old; males = 103) were included in the analysis. Demographic data and measured parameters during 24 h, daytime, and nighttime, are presented in Table 1. When looking at the 24-h changes, we found significant diurnal changes in all parameters ($p < 0.001$). Except for RR and SVR, all parameters demonstrated a similar trend, reaching the lowest levels around 5 am, and gradually increasing toward the daily peak at around 10 am (Figure 1). Greater day–night changes were observed in HR and CI, with a reduction of 12 beats per minute (15.2 ± 7.6%) and 0.6 L/min/m^2 (19.1 ± 10.0%) during the nighttime, respectively. SVR measurements revealed an opposite trend with lower and stable levels during the day and gradually increasing during the night to a peak at 5 am (an increase of up to 212 dynes/sec/cm^{-5}, 15.7 ± 9.9%). RR gradually declined from a peak at midnight to nadir at 10 am and then gradually rose again.

Table S1 shows matched stratification based on sex (men 101, women 144). The average age of men was 43.2 ± 15.3 (43.3 ± 15.4 pre-matching), BMI was 25.8 ± 4.0 (27.4 ± 12.6 pre-matching), and 53% had hypertension (HTN) (same as pre-matching). The average age of women was 44.0 ± 13.2 (43.6 ± 13.4 pre-matching), BMI was 25.4 ± 4.9 (25.2 ± 4.8 pre-matching), and 53% had HTN (50% pre-matching). Following the matching, we found that women had higher HR and CI during all periods ($p < 0.05$), and SVR was higher among men in all periods ($p < 0.05$) (Figure 2). Nighttime-associated elevation in SVR was significantly ($p = 0.014$) higher in women (an increase of up to 248.5 ± 166.6 dynes/sec/cm^{-5}, 17.9 ± 11.1%) than in men (182.3 ± 113.4 dynes/sec/cm^{-5}, 14.5 ± 8.9%).

Table S2 shows matched stratification based on age (<50 or ≥50 years old). The average age of the young group ($n = 134$) was 36.7 ± 7.6 (35.6 ± 8.1 pre-matching), BMI was 25.7 ± 3.9 (25.1 ± 6.6 pre-matching), 40% were males (41% pre-matching), and 60% had HTN (53% pre-matching). The average age of the older group ($n = 78$) was 60.3 ± 8.9 (60.2 ± 8.7 pre-matching), BMI was 26.6 ± 4.1 (28.3 ± 12.1 pre-matching), 31% were males (39% pre-matching), and 60% had HTN (61% pre-matching). Following the matching, we found that the younger group had a higher HR and CI in all periods ($p < 0.05$), while the older group had a higher systolic BP and PP in all periods ($p < 0.05$). SVR was higher in the younger group during the daytime and the 24 h ($p < 0.05$) (Figure 3).

Table S3 shows matched stratification based on BMI (BMI < 30 or BMI ≥30). The average age of people without obesity ($n = 154$) was 45.1 ± 13.0 (42.4 ± 14.0 pre-matching), BMI was 24.5 ± 2.9 (37.3 ± 17.9 pre-matching), 36% were males (40% pre-matching), and 66% had HTN (47% pre-matching). The average age of people with obesity ($n = 33$) was 47.0 ± 13.5 (49.8 ± 13.7 pre-matching), BMI was 36.5 ± 21.2 (37.3 ± 17.9 pre-matching), 36% were males (41% pre-matching), and 67% had HTN (72% pre-matching). Following the matching, we found that people without obesity had increased SV and CI in all periods when compared to people with obesity ($p < 0.05$) (Figure 4).

Nighttime-associated elevation in SVR showed a trend ($p = 0.53$) to be higher in people with obesity (248.5 ± 166.6 dynes/sec/cm^{-5}, 17.9 ± 11.1%) than in men (182.3 ± 113.4 dynes/sec/cm^{-5}, 14.5 ± 8.9%). In all the groups examined, a significant difference was found between day and night in all indices, except for RR (Tables S2–S4). Figures S1–S4 show the values with error bars of standard deviation for the various subgroups.

Table 1. General characteristics of all participants.

Characteristic	$n = 256$			
Age (years)	**43.7 ± 14.6**			
Sex (m/f)	**103/153**			
BMI (kg/m^2)	**26.2 ± 10.0**			
	Day	**Night**	**Day vs. Night *p*-value**	**24 h**
Respiratory rate (breath/min)	15.0 ± 2.2	15.0 ± 2.2	ns	15.0 ± 2.2
SpO_2 (%)	97.0 ± 1.9	96.4 ± 2.6	<0.001	96.8 ± 2.1
Heart rate (beats/min)	76.4 ± 13.8	64.3 ± 10.7	<0.001	72.9 ± 14.1
Systolic blood pressure (mmHg)	129.0 ± 16.4	122.2 ± 15.0	<0.001	127.1 ± 16.3
Diastolic blood pressure (mmHg)	80.1 ± 10.8	74.6 ± 10.4	<0.001	78.5 ± 11.0
Mean arterial pressure (mmHg)	96.4 ± 11.8	90.5 ± 11.0	<0.001	94.7 ± 11.9
Pulse pressure (mmHg)	48.9 ± 11.4	47.6 ± 10.8	<0.001	48.6 ± 11.3
Stroke volume (mL)	80.6 ± 11.5	76.6 ± 10.9	<0.001	79.5 ± 11.4
Cardiac index (L/min/m^2)	3.5 ± 0.9	2.8 ± 0.7	<0.001	3.3 ± 0.9
Systemic vascular resistance (dynes/sec/cm^{-5})	1313 ± 297	1525 ± 342	<0.001	1374 ± 324

For each physiological parameter, the daytime, nighttime, and 24-h averages are presented, as well as comparing the differences between day and night. BMI: body mass index; SpO_2: blood oxygen saturation; ns: not significant. Significance set at $p < 0.05$.

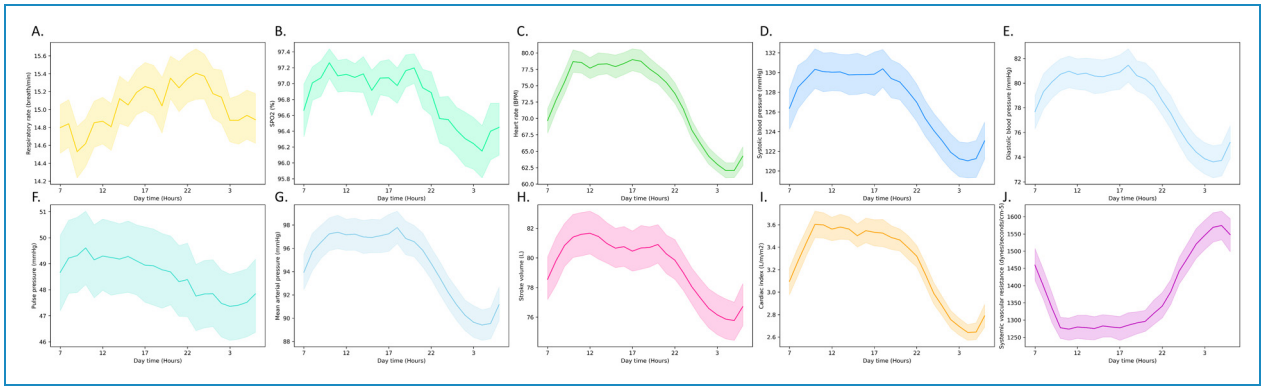

Figure 1. 24-h diurnal changes in measured parameters among all participants ($n = 256$). Data appear as a mean ± 95% confidence interval.

Discussion

Tracking physiological changes using a wearable, non-invasive, wireless platform allows a comprehensive analysis of 24-h trends of multiple and advanced cardio-pulmonary parameters at a high temporal resolution in ambulatory individuals living their everyday life. Moreover, it provides key insights and can help to understand better several advanced parameters such as BP, SV, CI, and SVR. Importantly, these devices do not interfere with everyday life, thus reducing a potential bias related to other frequently

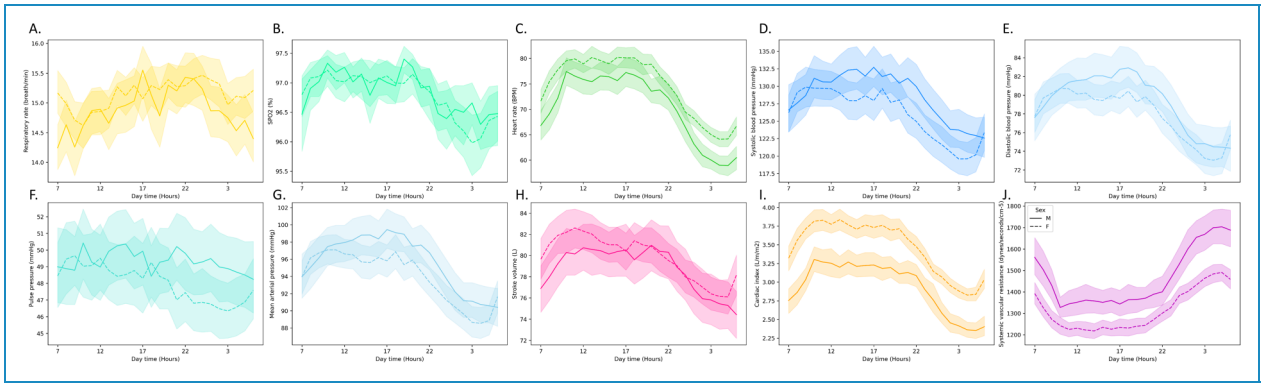

Figure 2. 24-h diurnal changes in measured parameters among matched male and female participants. M: males (full line, $n = 101$). F: females (dashed line, $n = 144$). Data appear as a mean ± 95% confidence interval.

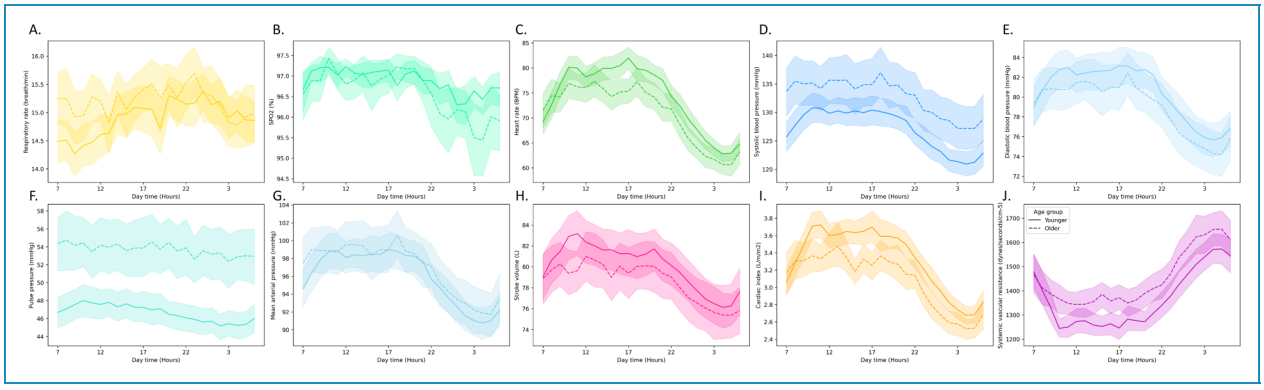

Figure 3. 24-h diurnal changes in measured parameters among matched participants, stratified by age. Older ≥ 50 years (full line, $n = 78$). Younger < 50 years (full line, $n = 134$). Data appear as a mean ± 95% confidence interval.

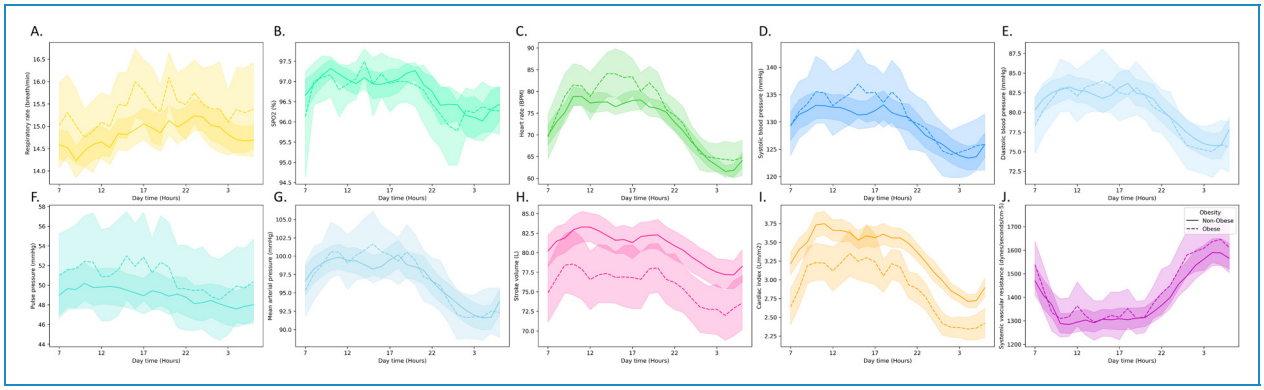

Figure 4. 24-h diurnal changes in measured parameters among matched participants, stratified by body mass index (BMI). Obese–BMI ≥ 30 kg/m^2 (dashed line, $n = 33$). Non-obese–BMI < 30 kg/m^2 (full line, $n = 154$). Data appear as a mean ± 95% confidence interval.

used devices, such as cuff-based ambulatory BP monitoring devices.[10,11]

The PPG-based device was shown to correlate with measurements obtained using both invasive and noninvasive BP monitoring devices, both in immobile and mobile conditions.[6,8,12] Specifically, and more related to this ambulatory setting, it showed a 24-h bias of −1.1 ± 1.5 and −1.1 ± 1.6 mmHg for diastolic BP and systolic BP, mean daytime bias was −1.9 ± 2.2 mmHg for diastolic BP and −1.9 ± 2.6 mmHg for systolic BP, while nighttime bias

was even smaller.[6] In previous studies, invasive or cumbersome technologies were used, limiting data acquisition to a much smaller group of participants, usually individuals with complex medical conditions during hospitalization.[13–18]

Several insights could be made when looking at the various monitored parameters. Similar to previous reports on diurnal changes, we found that most hemodynamic parameters, including BP, SV, and CI, were lower at night.[13,17] Contradictory to what is usually assumed, previous observational studies found conflicting data regarding changes of SVR during the night.[13,19] The current cohort demonstrated higher SVR values at night. As several theories have been suggested, the exact physiological mechanism is obscure. It has been found that physical activity, usually during the day, ensues an elevation in BP accompanied by a drop in SVR, mainly at the skeletal muscle level.[20] During the nighttime, the opposite mechanism may take control, leading to SVR elevation.

At the sympathetic nervous system level, epinephrine and norepinephrine concentrations are lower during nighttime, a fact that can explain the lower CI but not the higher SVR.[21] Also, there are conflicting data regarding the usage of alpha and beta-blockers and the change in the diurnal nature of BP, signaling that the mechanisms are more multifaceted.[22] The diurnal variations in the measured physiological parameters could be attributed to the lower metabolic demand at night, although the mechanism is complex. The depressed sympathetic tone may explain some phenomena, but as many cardiovascular functions are known to be regulated by the circadian clock, the hypothalamic control over it may have a crucial role.[22,23] Our findings may shed some light on various circadian clock effects.

The relatively large cohort in this study allowed us to test for differences in several subgroups. Physiological differences were noted between sex. Females exhibited elevated HR and CI with lower SVR than men. The reason is unknown and probably cannot be explained solely by hormonal differences, as both testosterone and estrogen are considered mainly as vasodilators, although reports are conflicting.[24,25] The mentioned diurnal hemodynamic changes may play a role in the different response men and women exhibit,[26] and could help in future efforts of better treatment adjustments in various medical conditions.

Among the obese, and not surprisingly, pre-matched data showed more cases of elevated BP (72% vs. 47% in the non-obese) and more significant changes in other vital signs compared with the non-obese group. However, when matching the groups with age and sex, only SV and CI differed between the groups.[27,28] These results allow us to specifically estimate the effect of obesity on the physiological changes beyond the associated effectors such as age, or sex.

Older age was associated with increased systolic BP, PP, and SVR, a finding that probably represents the higher incidence of hypertension with age, associated with vascular stiffness and disfunction.[29,30] The lower CI in older people correlates with the conclusions of previous imaging-based studies, yet this is the first demonstration of continuous changes in CI along the circadian cycle across different age groups.[31]

The monitoring devices used in this study could have a tremendous impact on patients with various medical conditions, and especially cardiovascular diseases. Having said that, when looking at the literature, we found only limited information regarding the normal values of advanced hemodynamic parameters among healthy population during their everyday living. Thus, we see this study as providing us with the basic physiological information and understanding on the diurnal changes among healthy individuals, serving as a starting point for future studies of patients that may suffer from changes in these parameters from normal values.

Moreover, such medical-grade wearable monitors have the potential to shed light on disease progression, as well as on the safety and efficacy of medical treatment, helping with future efforts to provide tailored and personalized medical care, as well as pre-symptomatic detection, diagnosis, and prevention, considering sex, age, BMI, and other demographic components. Also, they could be adopted for the de-centralization of clinical studies. Future studies should include a larger cohort of individuals with various medical conditions and preferably be used for longer periods.

In this study, we describe 24-h continuous noninvasive monitoring of advanced hemodynamic parameters and their different trends in various subgroups. Continuous noninvasive monitoring opens the door for the understanding of normal hemodynamic responses, augmenting diagnostic tools, and expanding follow-up options in the inpatient and outpatient settings. All of the participants recruited to this study were defined as healthy at recruitment. As such, none of them ever had a 24-h ambulatory BP monitoring study. The first time they ever had a continuous monitoring session was during this study. Indeed, the results of this monitoring study show that almost half of the participants had hypertension, correlating with data on the prevalence of hypertension in Western countries, including Israel.[6] Moreover, it emphasizes that most people are not aware of having hypertension.[6]

There were several reports of the use of wearable telemedicine platforms in patients with cardiac diseases. One of these studies was a meta-analysis evaluating the effectiveness of wearable sensors-assisted home-based cardiac rehabilitation in improving the cardio-respiratory fitness and health profile of patients with cardiovascular disease.[32] Within the scope of this analysis, authors looked at the effects on physical activity, quality of life, depression

levels, modification of cardiovascular risk factors/laboratory parameters, and adherence. Though no significant differences were noted, they have concluded that such technology tools can promote exercise-based interventions into a more home-based setting, with the potential to act as an adjunct or an alternative to center-based cardiovascular rehabilitation. As this is an ever-growing field, there are various ongoing efforts to further substantiate the role of wearable remote patient monitoring in providing clinical insights in this, as well as in other, patient populations, whether in prevention or in rehabilitation efforts.[33]

This study has some inherent limitations. Measurements were taken during everyday life. While we see this as an advantage of the system, this also influences the measurements. One could argue that the vitals were not taken in a controlled manner and a controlled environment; furthermore, no activity log was completed, not allowing us to stratify participants based on their level of daily activity. Despite this limitation, the data still represent a real-life setting, allowing us to better understand the diurnal changes. In this specific study, data on skin tone were not collected, which is another limitation of the study. We showed previously that this specific PPG-based device allows accurate measurement of BP in all skin type colors, based on the Fitzpatrick scale.[34] Future studies should include skin tone as another demographic feature. Lastly, we did not calculate or select a sample size for this observational study, as it involved variables that had not been previously collected in a similar setting. This would also need to be addressed in future studies utilizing similar monitoring devices.

Conclusions

In this study, we were able to show how diurnal changes corresponded with awake–sleep hours and differed between sex, age, and BMI groups. Similarly, and as a next step, the wearable monitoring platform we used could decipher hemodynamic changes in other subgroups, and might help with efforts to provide personalized medical care, pre-symptomatic diagnosis and prevention, and help with drug development efforts.

Contributorship: DN, AE, and YG designed research. DN, AE, MH, MF, and RM performed research. DN, NG, AE, and YG analyzed data. DN, AE, YK, EC, EH, NG, ABI, OA, RA, and YG provided discussion. DN, YK, NG, AE, and YG wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Ethical approval: The ethics committees of the Meuhedet Health Services, Tel Aviv, Israel; the Commissie voor Medische Ethiek ZNA, EC; the Tel Aviv University, Tel Aviv, Israel; and the Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel, approved this study (REC number 2021-11-15; 5238, NCT03883113; 0002522-1; and 7500-20-SMC, NCT04826250, respectively).

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