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# The presence of a circadian rhythm in pulse arrival time and its application for classifying blood pressure night-time dip

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***Abstract*— Circadian rhythms of blood pressure (BP) have key diagnostic significance in the assessment of hypertension. The night-time dip or rise in BP (10-20% decrease or increase compared to daytime BP), for example, has been shown to be a strong indicator for cardiovascular disease. However, current methods for assessing the circadian rhythms of BP can be disruptive to sleep, work, and daily activities. Pulse arrival time (PAT) has been suggested as a surrogate measure of BP. This work investigates the presence of a circadian rhythm in PAT and evaluates its application to classify nocturnal BP dip or rise. 769 patients who were discharged home from the ICU were selected from the MIMIC database. Our results show a clear and observable circadian rhythm of PAT that is strongly inversely correlated with BP ($r = -0.89$). The ratios between nocturnal and diurnal changes in PAT accurately classifies an individual as a nocturnal BP dipper (AUC = 0.72) or a riser (AUC = 0.71).**

***Clinical Relevance*—This work shows that you can accurately assess an individuals's circadian rhythm of BP using PAT.**

## I. INTRODUCTION

Monitoring circadian rhythms of blood pressure (BP) in an ambulatory setting has been shown to be a stronger indicator of hypertension (high BP) compared to spot measurements recorded in the clinic [1]. Ambulatory blood pressure monitoring (ABPM) is often performed over periods between 24 and 48 hours, with BP readings taken using a sphygmomanometer, an inflatable cuff placed around the arm. Typically, ABPM is programmed to take readings every 30 minutes during the day and every hour during the night [2]. However, ABPM has been reported to be very disruptive to sleep, work and daily activities [3]. Systolic blood pressure (SBP) in healthy individuals will typically dip by around 10% at night-time, this is known as the night-time dip [4]. There have been a large number of studies indicating that a nocturnal rise in SBP is associated with a greater risk of cardiovascular diseases [4].

Pulse arrival time (PAT) is defined as the time between the peak of the R-wave in the electrocardiogram (ECG) and a fiducial point in the photoplethysmogram (PPG), typically measured by a pulse oximeter on the fingertip. PAT has been proposed as a non-invasive surrogate measure of BP for a number of years [5]. However, to the authors' knowledge, this is the first work to identify a circadian pattern in PAT and evaluate its application to classify the night-time dip in SBP.

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## II. METHODS

### A. Dataset

Data for this study was extracted from the Medical Information Mart for Intensive Care III (MIMIC III) [6] database. MIMIC contains critical care information, recorded during routine care between 2001 and 2012, from the intensive care unit (ICU) at the Beth Israel Deaconess Medical Centre in Boston, Massachusetts, USA.

We selected a cohort of patients, whilst in the ICU, who were most likely to exhibit physiological profiles comparable to out-of-hospital individuals [7]. From the initial cohort of 10,282 patients for which waveform data was available, we considered only the last 24-hours during which a patient had simultaneous ECG and PPG waveforms. If the gap from the end of this day to the day of discharge from the ICU was more than two days, the patient was not included in the dataset as they were deemed sufficiently far from being discharged. Only patients that were discharged home, did not return to the hospital within 6-months and received full medical treatment (did not have a do-not-resuscitate/do-not-incubate code) were included in the cohort. Additionally, patients must have had at least 12 hours with valid measurements of PAT, SBP, heart rate (HR) and respiratory rate (RR), including at least one measurement during the night (midnight to 6am) and day (10am to 4pm). Measurements taken while the patient was under the effect of medications that were likely to significantly affect the vital signs being measured (such as vasopressors and $\beta$-blockers) were excluded as these would have had a significant impact on their circadian profiles. More details can be found in [7].

Patients were separated into gender and age groups to explore demographic related differences in circadian rhythms and BP dip status. The age groups used in this paper were a modified set of those specified by the United Nations 'Provisional guidelines on standard international age classifications' [8]. Patients were divided into individuals younger or older than a 65 years of age.

### B. Computing PAT

*1) Computing proximal fiducial point:* The R-peak of the ECG waveform (corresponding to left ventricular depolarisation) was used as the proximal point for PAT estimation. To suppress the impact of baseline wander, the ECG was filtered using an $8^{th}$-order Butterworth infinite impulse response (IIR) high-pass filter with a cut-off frequency of 0.5 Hz. The QRS complex of the ECG was detected by following the work of Pan and Tompkins [9]. The assessment of the quality of the ECG signal followed the work of Li et al [10].

*2) Computing distal fiducial point:* The PPG waveform was used as the distal waveform for PAT estimation. An 8$^{th}$-order Butterworth IIR band-pass filter was used with cut-off frequencies of 0.5 Hz and 10 Hz as recommended in [5]. To detect the peaks and onsets, and to assess the quality of the PPG signal, we followed the work of Villarroel [11]. The intersecting tangents method [5] was used to define the distal fiducial point in the PPG signal.

*3) Estimating beat-by-beat PAT:* PAT was estimated as the time delay between the ECG R-peaks and the distal PPG fiducial points. If there were none, or more than 1 PPG fiducial points located between two successive R-peaks, this indicated an error in the beat detection algorithm (for either the ECG or the PPG) and no PAT value was computed.

*4) PAT signal quality:* The signal quality index (SQI) for each PAT beat was calculated by a combination of outlier detection and the SQI metrics defined for the ECG and PPG signals. Outliers were detected by comparing each PAT value to the median of a 30-second running window with a step size of 25 seconds. The outlier SQI, $\text{SQI}_\text{o}$, was computed for every beat $k$ as:

$$\text{SQI}_\text{o}(k) = \begin{cases} 0 & \text{if } |\text{PAT}(k) - \text{med}_w| > t \times \text{MAD}_w \\ 1 & \text{otherwise} \end{cases} \tag{1}$$

where $\text{med}_w$ and $\text{MAD}_w$ are the median and the median absolute deviation for the window, $w$, respectively. $t$ is a threshold set as 1.96. For normally distributed data, this provided a 95% confidence interval. The SQI of each PAT beat, $k$, was subsequently calculated as:

$$\text{SQI}_\text{PAT}(k) = \text{SQI}_\text{o}(k) \times \min(\text{SQI}_\text{ECG}(k), \text{SQI}_\text{PPG}(k)) \tag{2}$$

where $\text{SQI}_\text{ECG}$ and $\text{SQI}_\text{PPG}$ are the SQI metrics for the ECG and PPG respectively. A Kalman filter was applied to adjust PAT values based on their signal quality. This reduced the impact of transient changes caused by noise and motion artefacts. We implemented a simple Kalman filter for a one dimensional signal, similar to Li et al [10]. PAT values with poor quality scores (defined as an SQI value $< 0.8$) were removed from the dataset.

Demographic (gender and age) related differences in the distributions of patient-wise SBP-PAT calibration gradients and correlation between PAT and SBP were investigated. This was performed using a two-sample unequal-variance t-test at the $p < 0.05$ level.

### C. Computing circadian rhythms

Circadian patterns in SBP, heart rate (HR) and respiratory rate (RR) can be observed in the last day prior to discharge from an ICU by averaging across a large cohort of patients [7]. The evaluation of the circadian rhythms of SBP, HR, RR and PAT was performed by averaging all measurements in each one-hour period of the day across the entire cohort. The mean hourly values were recorded left-aligned, (for example, the mean of the measurements between 1:00am and 1:59am was recorded as occurring at 1:00am).

Baseline values of PAT are not comparable person-to-person as they depend on properties such as patient height and arm length [5]. Therefore, in order to appropriately construct a circadian rhythm of PAT across a large cohort of patients, PAT deviations from mean, $\Delta$ PAT, were used.

### D. Blood pressure night-time dip classification

The dip ratio (DR) of a vital sign was computed as the percentage increase from mean daytime (10am to 4pm) to mean night-time (midnight to 6am). For example, the DR for SBP, $\text{DR}_\text{SBP}$, was computed as:

$$\text{DR}_\text{SBP} = \frac{\overline{\text{Night}} - \overline{\text{Day}}}{\overline{\text{Day}}} \times 100\% \tag{3}$$

Patients were classed as dippers if their $\text{DR}_\text{SBP}$ was less than -10 % and, conversely, risers if their $\text{DR}_\text{SBP}$ was more than 10 % [4].

We investigated the accuracy of using the DR of PAT ($\text{DR}_\text{PAT}$), HR ($\text{DR}_\text{HR}$), RR ($\text{DR}_\text{RR}$) and a combination of the 3 metrics using logistic regression to classify patients as dippers or risers.

The thresholds of 10% increase or decrease used for SBP night-time dip classification may not be equivalent for vital signs such as PAT. Therefore, the accuracy of using vital-sign DRs was assessed by a receiver operating characteristic (ROC) curve. Optimum vital signs for classifying night-time dip status was assessed by the area under the ROC curve (AUC). The optimum DR threshold for classifying night-time dip status was assessed using the ROC curve as the point that minimises the Euclidean distance to a true positive rate (TPR) of 1 and a false positive rate (FPR) of 0.

## III. RESULTS

Table I provides an overview of the demographics of the cohort selected from the MIMIC dataset. The length of stay (LOS) in the ICU is also provided.

TABLE I: Demographics of the cohort selected from MIMIC.

| # Patients | Age * | LOS * | % female |
|---|---|---|---|
| 769 | 57.4 (16.4) | 2.5 (2.4) | 42.9 |

* results are given as mean (standard deviation)

Patient-wise correlation between SBP and PAT had a mean and standard deviation of -0.27 and 0.32 respectively across the cohort. There were no significant differences found between males and females in the distributions of SBP-PAT calibration gradients as well as correlation between PAT and SBP. Significant differences ($p = 0.035$) were found in the correlation between PAT and SBP between patients older (mean $r = -0.31$) and younger than 65 (mean $r = -0.25$). Additionally, significant differences ($p = 0.01$) were found in the calibration gradients for patients older (mean gradient = $-544.9$ mmHg/s) and younger (mean gradient = $-350.6$ mmHg/s) than 65.

Figure 1 shows the circadian profiles of SBP, HR, RR and $\Delta$ PAT across all patients in the cohort. The correlation coefficient between the circadian rhythm of SBP and $\Delta$ PAT

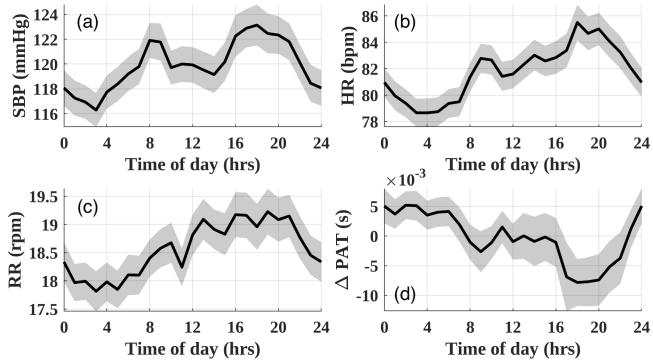


Fig. 1: Circadian rhythms of vital signs (a) SBP, (b) HR, (c) RR, (d) Δ PAT. Shaded regions show 95% confidence intervals.

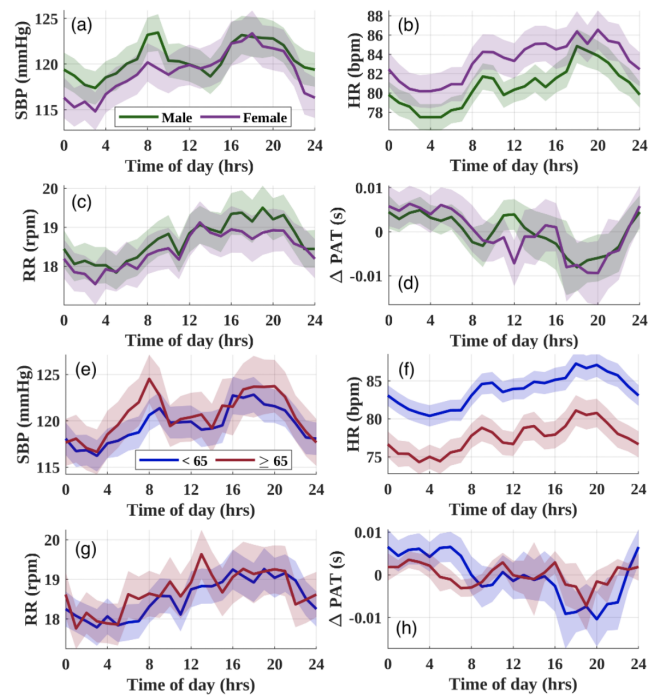


Fig. 2: Circadian rhythms split by (a-d) gender and (e-h) age groups. Shaded regions show 95% confidence intervals.

was -0.89. The correlation between SBP and HR was 0.81. The correlation between HR and Δ PAT was -0.79.

Figure 2 show the circadian rhythms of the vital signs split by gender and age groups respectively. The correlation between Δ PAT and SBP circadian rhythms was -0.84 for males, -0.81 for females, -0.86 for patients less than 65 years old and -0.78 for patients 65 or older. The correlation between Δ PAT and SBP circadian rhythms for males was -0.81 for patients less than 65 years old and -0.63 for patients older than 65. For females, the correlation between Δ PAT and SBP was -0.77 and -0.69 for the two respective subgroups.

Throughout the cohort, 113 patients were dippers and 51 were risers, based on their individual $DR_{SBP}$. Figure 3

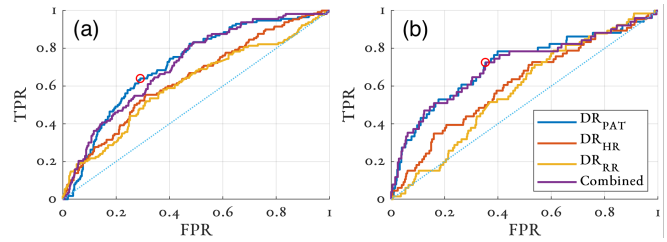


Fig. 3: ROC curves for SBP night-time (a) dip and (b) rise classification based on $DR_{PAT}$, $DR_{HR}$, $DR_{RR}$ and a combination of these metrics using logistic regression. For both dip and rise classification, $DR_{PAT}$ had the largest AUC. The optimum threshold for $DR_{PAT}$ is indicated by a red circle.

shows the results of SBP night-time dip and rise classification using the vital sign DRs. The AUC values for SBP dip classification using $DR_{PAT}$, $DR_{HR}$, $DR_{RR}$ and a combination of the metrics using logistic regression were: 0.72, 0.64, 0.61 and 0.70 respectively. The AUCs for SBP rise classification were: 0.71, 0.61, 0.58 and 0.70 respectively. The optimum threshold for BP dip and rise classification using only $DR_{PAT}$ was 1% and -0.24% respectively.

Table II provides the AUC for SBP dip and rise classification using only $DR_{PAT}$ when the cohort is split by gender and age groups.

TABLE II: AUC for BP dip and rise classification using $DR_{PAT}$ split by demographics.

| | | | | Age groups | |
|---|---|---|---|---|---|
| | All | Male | Female | $< 65$ | $\geq 65$ |
| SBP dip | 0.72 | 0.77 | 0.65 | 0.72 | 0.71 |
| SBP rise | 0.71 | 0.71 | 0.70 | 0.72 | 0.69 |

## IV. DISCUSSION

To the authors' knowledge, this is the first work that has looked into the presence of a circadian rhythm of PAT and its use in classifying the night time dip.

### A. Circadian rhythm of PAT

The distribution of patient-wise SBP-PAT correlation coefficients indicated a weak relationship between the two (mean $r = -0.27$). However, the circadian rhythm of Δ PAT had a strong negative correlation to the circadian rhythm of SBP ($r = -0.89$). It follows the salient features of the circadian rhythm of SBP, namely the night time dip and morning surge. Splitting the cohort by gender and age groups highlights the differences in circadian rhythm of the vital signs related to demographics (see fig. 2). In this cohort, males had a higher baseline SBP and lower baseline HR than females. There was an offset of around 5 beats per minute in the circadian rhythms for HR between the age groups. These results follow the work of Davidson et al [7] who similarly showed clear gender and age related differences in HR, SBP and RR circadian rhythms for patients in the ICU.

The circadian rhythms for patients older than 65 simultaneously had a larger peak-nadir excursion for SBP and a flatter rhythm for Δ PAT than patients younger than 65. This

implies a steeper SBP-PAT calibration curve, which is further supported by the significant difference in the distributions of patient-wise calibration gradients. The calibration curve relating changes in SBP to changes in PAT is thought to represent arterial properties such as arterial compliance - steeper gradients are thought to be associated with more elderly individuals with stiffer arteries [5]. Additionally, we found no significant difference between the correlation of SBP and PAT between males and females. This suggests that the relationship between PAT and SBP might not specific to a gender, indicating the need for individualised calibration curves.

PAT includes a component known as the pre-ejection period (PEP) which corresponds to the time delay between electrical depolarisation of the heart's left ventricle and ejection of blood through the aorta. PEP has been shown to be a large proportion of PAT (10-35%) and has been suggested to be a significant limitation to SBP estimation using PAT [5]. The strong correlations between the circadian rhythms of PAT and SBP in this work show that the effects of PEP can be reduced by averaging over long periods of time, suggesting that circadian rhythms of PAT may be unaffected by PEP. This could open the possibility to construct long-term circadian profiles of SBP using PAT.

### B. Blood pressure night-time dip classification

$DR_{RR}$ had poor accuracy to classify the night-time dip in BP, which is intuitive given the different mechanisms regulating the cardiovascular and respiratory system. $DR_{HR}$ improved classification, most likely driven by the baroreflex and the relationship between BP and HR. $DR_{PAT}$ provided the best indicator for classifying patients as dippers and risers. The combined metric using logistic regression showed no improvement in performance, suggesting that $DR_{HR}$ and $DR_{RR}$ offer no additional information to $DR_{PAT}$ for classifying night-time dipping status.

Table II shows the AUC scores for classifying dipper and risers using $DR_{PAT}$ across the whole cohort as well as demographic subgroups. For each subgroup there was a consistent proportion of dippers ($\approx$ 15 %) and risers ($\approx$ 7.5 %). There was a relatively consistent classification accuracy across all subgroups, suggesting that $DR_{PAT}$ could be a robust measure to classify the night-time dip in BP.

## V. LIMITATIONS

This study has several limitations worth discussing. Firstly, while the presence of a circadian rhythm of $\Delta$ PAT may be observable on a population level, its presence on an individual level still needs to be investigated. Additionally, there is little evidence as to how consistently the trends seen in $\Delta$ PAT will be observable in individuals outside of the hospital setting. Secondly, BP dippers or risers have been assessed based on an arbitrary threshold of 10% mean decrease or increase for one day of measurements. While this is currently the gold standard for night-time dip classification, it is very likely that noisy measurements in the cuff values lead to miss-labelling. Finally, although the sample size ($N = 769$) presented in this work is one of the largest available for assessing PAT circadian rhythm, it was still too small to allow for a comprehensive assessment related to age and gender subgroups.

## VI. CONCLUSIONS

This paper investigated the presence of a circadian rhythm of PAT for ICU patients and its relationship to SBP and the night-time dip. Our results show the presence of a clear, observable, demographically modified, circadian rhythm of PAT, that is strongly inversely proportional to SBP, for patients in the ICU. This suggests that it is possible to compute an individual's circadian rhythm in SBP using PAT alone. Additionally, we show that $DR_{PAT}$ is a strong predictor of SBP dipping status and therefore could be used as an indicator for cardiovascular disease. This work has important implications as it suggests that patterns of nocturnal changes in BP could be assessed using minimally invasive equipment (such as a wearable device) rather than an obtrusive ABPM, which has been shown to disrupt work, sleep and daily activities of individuals.

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