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# Hemodynamic changes in progressive cerebral infarction: An observational study based on blood pressure monitoring

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## Abstract

Progressive cerebral infarction (PCI) is a common complication in patients with ischemic stroke that leads to poor prognosis. Blood pressure (BP) can indicate post-stroke hemodynamic changes which play a key role in the development of PCI. The authors aim to investigate the association between BP-derived hemodynamic parameters and PCI. Clinical data and BP recordings were collected from 80 patients with cerebral infarction, including 40 patients with PCI and 40 patients with non-progressive cerebral infarction (NPCI). Hemodynamic parameters were calculated from the BP recordings of the first 7 days after admission, including systolic and diastolic BP, mean arterial pressure, and pulse pressure (PP), with the mean values of each group calculated and compared between daytime and nighttime, and between different days. Hemodynamic parameters and circadian BP rhythm patterns were compared between PCI and NPCI groups using *t*-test or non-parametric equivalent for continuous variables, Chi-squared test or Fisher's exact test for categorical variables, Cox proportional hazards regression analysis and binary logistic regression analysis for potential risk factors. In PCI and NPCI groups, significant decrease of daytime systolic BP appeared on the second and sixth days, respectively. Systolic BP and fibrinogen at admission, daytime systolic BP of the first day, nighttime systolic BP of the third day, PP, and the ratio of abnormal BP circadian rhythms were all higher in the PCI group. PCI and NPCI groups were significantly different in BP circadian rhythm pattern. PCI is associated with higher systolic BP, PP and more abnormal circadian rhythms of BP.

KEYWORDS
blood pressure (BP), hemodynamic parameters, progressive cerebral infarction (PCI), stroke

## 1 | INTRODUCTION

Stroke is the second commonest cause of death globally and a leading cause of disability, with poor prognosis and high recurrence rates.[1,2] Over 80% strokes are ischemic, where cerebral infarction (CI) happens due to the lack of blood supply. Progressive CI (PCI) is an important clinical complication in the early stage of ischemic stroke, accounting for 20%–40% of CI.[3,4] In patients with PCI, neurological symptoms worsen in a stepwise manner within 7 days after onset, leading to high risks of disability and mortality.[3–5] The early detection of PCI plays a key role in providing efficient intervention to improve rehabilitation and minimize the risks of PCI-induced severe clinical events.[6] However,

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at present, the diagnosis of PCI mainly depends on the standardized neurological scale, which can only be derived after the deterioration of neurological function and the aggravation of clinical symptoms. Considering the increasing incidence of ischemic stroke, there is a high clinical need for early detection of PCI.[3,6]

Many physiological, clinical, and neuroimaging features have been studied as potential risk factors of PCI,[7] for example, diabetes, homocysteine, National Institutes of Health Stroke Scale (NIHSS) score on admission, fibrinogen and intracranial artery stenosis.[4] The excess thrombin generation and fibrin turnover with a high D-dimer level were observed in patients with PCI compared with stable and improving patients.[3] However, existing early indicators of PCI are inconclusive. In addition, the biomarkers derived from lab tests are not always available in clinical practice. Currently, there is a lack of well recognized and clinically available test for reliable early detection of PCI.

Blood pressure (BP), as one of the commonest physiological parameters in clinical practice, can reflect PCI-related hemodynamic changes.[8] PCI is associated with hemodynamic changes in the collateral circulation, decrease in brain tissue perfusion, and edema, which may influence the regulation of BP and its variability.[9] On the other hand, hypertension is a main risk factor for ischemic stroke.[10] The post-stroke BP increase is associated with a higher risk of neurological deterioration in patients with ischemic stroke.[11] High values of systolic blood pressure (SBP), SBP variability, mean arterial pressure (MAP), and pulse pressure (PP) are associated with poor functional outcome, early neurological deterioration, recurrence of stroke, and high mortality.[10,12] Zhao and coworkers performed a dynamic analysis of BP in PCI patients, where BP was measured every 8 ± 1 h from 16 h to 5 days after admission, with SBP, diastolic blood pressure (DBP), and MAP recorded.[5] They found that high SBP, abnormal circadian rhythm of BP (extreme-dipper), and a medical history of hypertension for over 5 years, were associated with PCI. The existing studies indicated that the hemodynamic parameters derived from BP may enable the early detection of PCI. However, there is a lack of comprehensive investigation on the association between BP-derived hemodynamic parameters and the occurrence of PCI.

To fill this research gap, we comprehensively analyzed the relationship between PCI and the changes in BP-derived hemodynamic parameter based on post-admission BP measurements in 7 days among ischemic stroke patients. The underlying scientific hypothesis is that the BP-derived hemodynamic parameters could be significantly different between ischemic stroke patients with PCI and those with non-progressive cerebral infarction (NPCI).

## 2 | METHODS

### 2.1 | General information

This study was approved by the Ethics Committee of Zhoushan Hospital. The requirement for informed consent was waived because of the retrospective nature of this study. A total of 80 patients with ischemic stroke who were hospitalized in Zhoushan Hospital from October 2019 to May 2022 were included in the study, including 40 patients with PCI and 40 patients with NPCI. The inclusion criteria were as follows: (1) patients admitted to the Acute Stroke Unit within 24 h of CI onset; (2) age ≥18 years with no previous stroke history; (3) PCI was defined as the neurological deficits that did not show any improvement and continued to progress within 1 week under regular treatment, with the NIHSS score increased by at least 2 points.[13,14] The exclusion criteria were as follows: (1) patients with severe impairment of consciousness, transient ischemic attack, hemorrhagic stroke, subarachnoid hemorrhage, intracranial infection, intracranial hemorrhage, intracranial tumor, trauma, or neurodegenerative disease; (2) severe cardiac, hepatic, and renal insufficiency; (3) comorbid hematologic disease, malignancy, autoimmune disease; (4) more than two consecutive BP recordings missing (i.e., with any interval more than 4 h between recordings). There was no statistically significant difference between the two groups in terms of sex and age ($p > .05$ for both).

### 2.2 | Medical history, NIHSS, and blood test

For all included patients, clinical information was collected: history of hypertension, diabetes mellitus, and atrial fibrillation, NIHSS at admission and 7 days after admission, and time to clinical event of neurologic deterioration after admission. The blood test results included total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatinine, urea nitrogen, fibrinogen, vitamin B12, and folic acid.

### 2.3 | Data collection of blood pressure

The monitoring equipment was applied after the patient was admitted in the Acute Stroke Unit. Noninvasive BP monitoring was performed using an automated sphygmomanometer in the non-hemiplegic arm with the patient lying supine for at least 3 min (Figure 1A). The first BP, that is, the baseline SBP and DBP, was retrieved from the first recording after admission. Patient's BP was measured every 2 h along with other physiological parameters during the acute phase of cerebral infarction (Figure 1B). All patients completed the entire BP measurement process in the Acute Stroke Unit.

In this study, the BP metrics from the original BP recordings were retrospectively collected for data analysis. The BP recordings of the 80 included patients (PCI and NPCI, 40 for each) in the first seven consecutive days after admission were retrieved. In total, 9152 BP recordings were included for analysis. Each BP recording included four BP metrics: SBP, DBP, MAP, and PP (Figure 1C).

The hemodynamic parameters were calculated from the BP metrics for daytime (i.e., diurnal: 6:00 to 22:00) and nighttime (i.e., nocturnal: 22:00 to 6:00 next day), respectively (Figure 1B). The hemodynamic parameters include: the diurnal mean SBP (DMSBP, i.e., the mean of SBP values measured after 6:00 and before 22:00),

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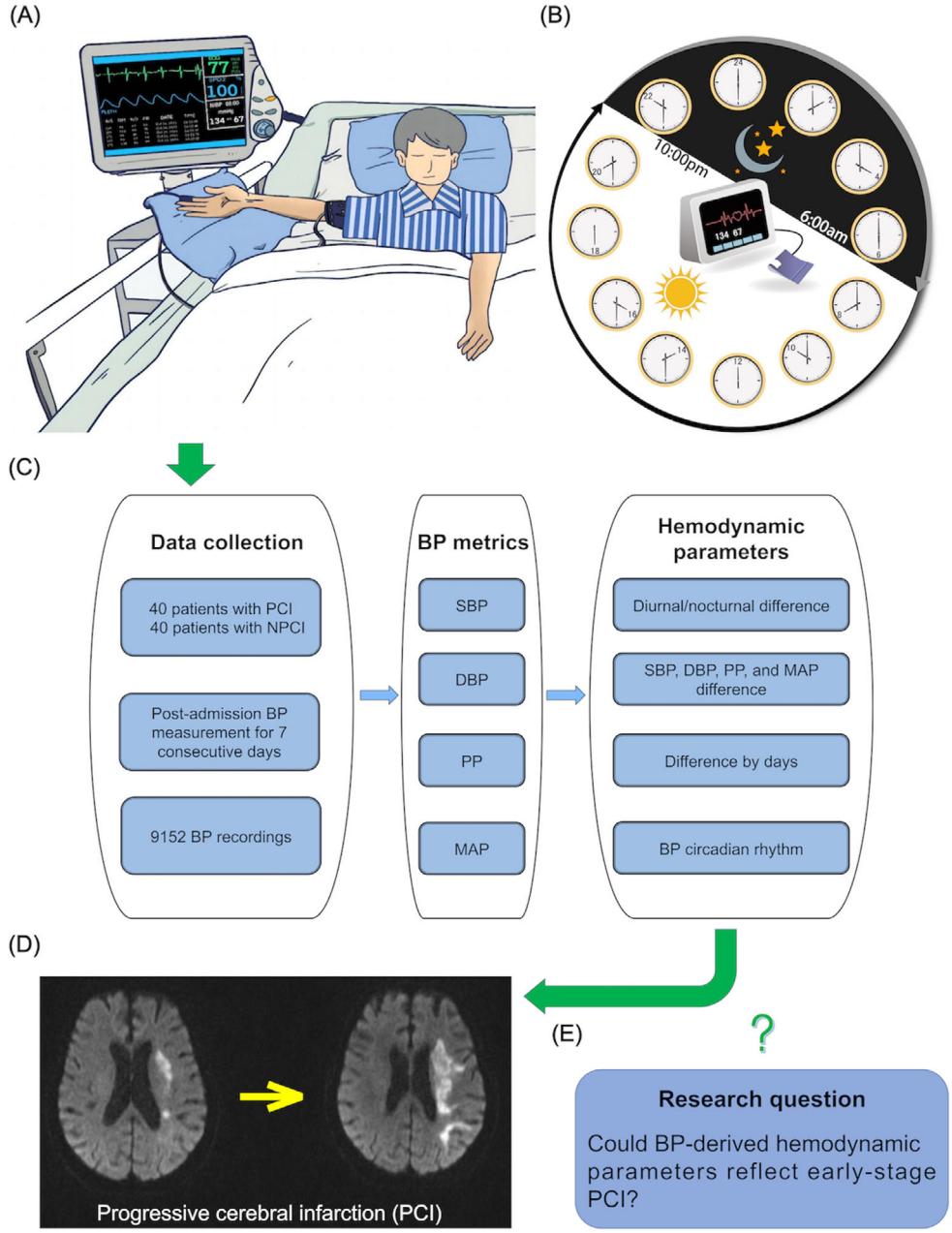


**FIGURE 1** Flowchart and research question of the study. (A) Physiological measurement and data collection. (B) Automatic blood pressure measurement based on a 2-h interval. (C) Data analysis and calculation of hemodynamic parameters. (D) Clinical imaging of PCI. Similar level of cranial diffusion-weighted magnetic resonance images were recorded before and after progression in a patient with cerebral infarction. (E) Research question. BP, blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; NPCI, non-progressive cerebral infarction; PCI, progressive cerebral infarction; PP, pulse pressure; SBP, systolic blood pressure.

nocturnal mean SBP (NMSBP), 24-h mean SBP (24-hMSBP), diurnal mean DBP (DMDBP), nocturnal mean DBP (NMDBP), 24-h mean DBP (24-hMDBP), 24-h mean PP, 24-h mean MAP (24-h averaging is the mainstream processing method for PP and MAP), and nocturnal BP decrease rate (NBPDR). The related formulas were listed as follows: PP = SBP-DBP, MAP = DBP + 1/3 *(SBP—DBP), NBPDR = (DSBP-NSBP)/ DSBP. Regarding the circadian rhythm of BP, dipper, extreme-dipper, non-dipper and reverse-dipper patterns were defined as 10% ≤ NBPDR < 20%, NBPDR ≥ 20%, 0 ≤ NBPDR < 10%, and NBPDR < 0, respectively. Among these rhythms, extreme-dipper, non-dipper, and reverse-dipper were deemed as abnormal BP rhythms.[15]

## 2.4 | Statistical analysis

Statistical analysis was performed using SPSS software (version: 26.0; IBM Corp, USA). The quantitative data with normal distribution were

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**TABLE 1** Data characteristics of the two groups of patients.

| Variables | Study group ($n = 40$) | Control group ($n = 40$) | t/$\chi$2/Z value | $p$ value |
|---|---|---|---|---|
| Sex male [case (%)] | 24 (60) | 22 (55) | 0.205 | .651 |
| Age [M (P25, P75)] | 71.50 (66.27, 77) | 71.28 (67.25, 80.50) | −0.563 | .573 |
| Hypertension [cases (%)] | 35 (87.5) | 27 (67.5) | 4.588 | .032 |
| Diabetes mellitus [cases (%)] | 16 (40) | 15 (37.5) | 0.053 | .818 |
| Atrial fibrillation [cases (%)] | 15 (37.5) | 18 (45) | 0.464 | .496 |
| Admission NIHSS [M (P25, P75)] | 6.5(3, 10.75) | 6.0 (2.25, 11) | −1.010 | .992 |
| 7-day NIHSS [M (P25, P75)] | 10 (6.25, 14.75) | 3.5 (2, 10) | −3.948 | .000 |
| Baseline SBP (mm Hg) | 166.2 ± 28.6 | 155.4 ± 22.5 | −1.876 | .064 |
| Baseline DBP (mm Hg) | 82.5 ± 15.6 | 82.7 ± 17.9 | 0.053 | .958 |
| Triglycerides [M (P25, P75), mmol/L] | 1.15 (0.88, 1.48) | 1.07 (0.81, 1.50) | −1.227 | .220 |
| Total cholesterol [M (P25, P75), mmol/L] | 4 (3.24, 5.63) | 4.39 (3.46, 4.85) | −0.346 | .729 |
| Low-density lipoprotein cholesterol [M (P25, P75), mmol/L] | 2.4 (1.91, 3.82) | 2.73 (2.19, 3.34) | −0.866 | .386 |
| High-density lipoprotein cholesterol (mmol/L) | 1.14 ± 0.34 | 1.13 ± 0.26 | 0.407 | .685 |
| Creatinine [M (P25, P75), umol/L)] | 72.75 (63.45, 92.20) | 71.7 (60.65, 80.05) | −0.702 | .482 |
| Urea nitrogen [M (P25, P75), mmol/L)] | 4.64 (3.79, 6.38) | 5.05 (3.58, 6.93) | −0.303 | .762 |
| Fibrinogen (g/L) | 4.84 ± 1.49 | 3.91 ± 1.06 | −3.379 | .001 |
| Folic acid [M (P25, P75), nmol/L] | 11.94 (9.23, 24.78) | 15.85 (9.42, 22.55) | −0.183 | .855 |
| Vitamin B12 [M (P25, P75), pmol/L] | 286.50 (184, 408.75) | 352 (182, 599.75) | −1.265 | .206 |

expressed as mean ± standard deviation, and the quantitative data of skew distribution were expressed by M (P25, P75) where M, P25, and P75 are the median, 25% and 75% quartiles, respectively. For normally distributed quantitative data, independent samples *t*-test was used for comparison between PCI and NPCI groups, and paired samples *t*-test was used for intra-group comparison of the values in different days, or corresponding BP parameters. For quantitative data with skewed distribution, the Mann–Whitney *U*-test was used for comparison between groups, and the Wilcoxon signed-rank test was used for comparison within groups. Count data were compared using the Chi-squared test or Fisher's exact test.

The multicollinearity was evaluated using the tolerant test, where the variance inflation factor value smaller than 5 was considered as no collinearity with other variables.[16] In this case, Pearson correlation analysis was performed to double check if any linear relationship existed between two variables, defined as absolute value of correlation coefficient higher than 0.3.[17] When collinearity was observed, principal components analysis was performed where the principal components were reserved in order until the proportion of variance explained was above 0.9. The selected principal components were used to substitute the variables with multicollinearity. Time-to-event analysis based on the first PCI event was performed using Cox proportional hazards regression for all covariates. Binary logistic regression analysis was used to analyze the independent risk factors of PCI. For both Cox and logistic regression analyses, the variates with $p < .1$ in univariate analysis were selected for multivariate analysis.[18] Significant difference was defined as $p < .05$.

## 3 | RESULTS

### 3.1 | Characteristics of two groups at baseline

There was no significant difference between the two groups in other factors except NIHSS on the 7th day after admission, hypertension and fibrinogen (Table 1).

### 3.2 | SBP and DBP: Comparison between PCI and NPCI groups

#### 3.2.1 | Difference between PCI and NPCI groups in SBP and DBP

As shown in Figure 2, the PCI group has higher SBP and lower DBP than the NPCI group, whereas the majority of these differences are not statistically significant. The DMSBP on the first day and NMSBP on the third day were significantly higher in the PCI group ($p < .05$ for both). There was no significant difference in DBP parameters.

#### 3.2.2 | Differences between diurnal, nocturnal, and 24 h values in PCI and NPCI groups

Regarding SBP, significant differences between DMSBP, NMSBP, and 24-hMSBP (pairwise) appear on the first and third days after admission in the NPCI group, and only on the first day in the PCI group ($p < .05$ for

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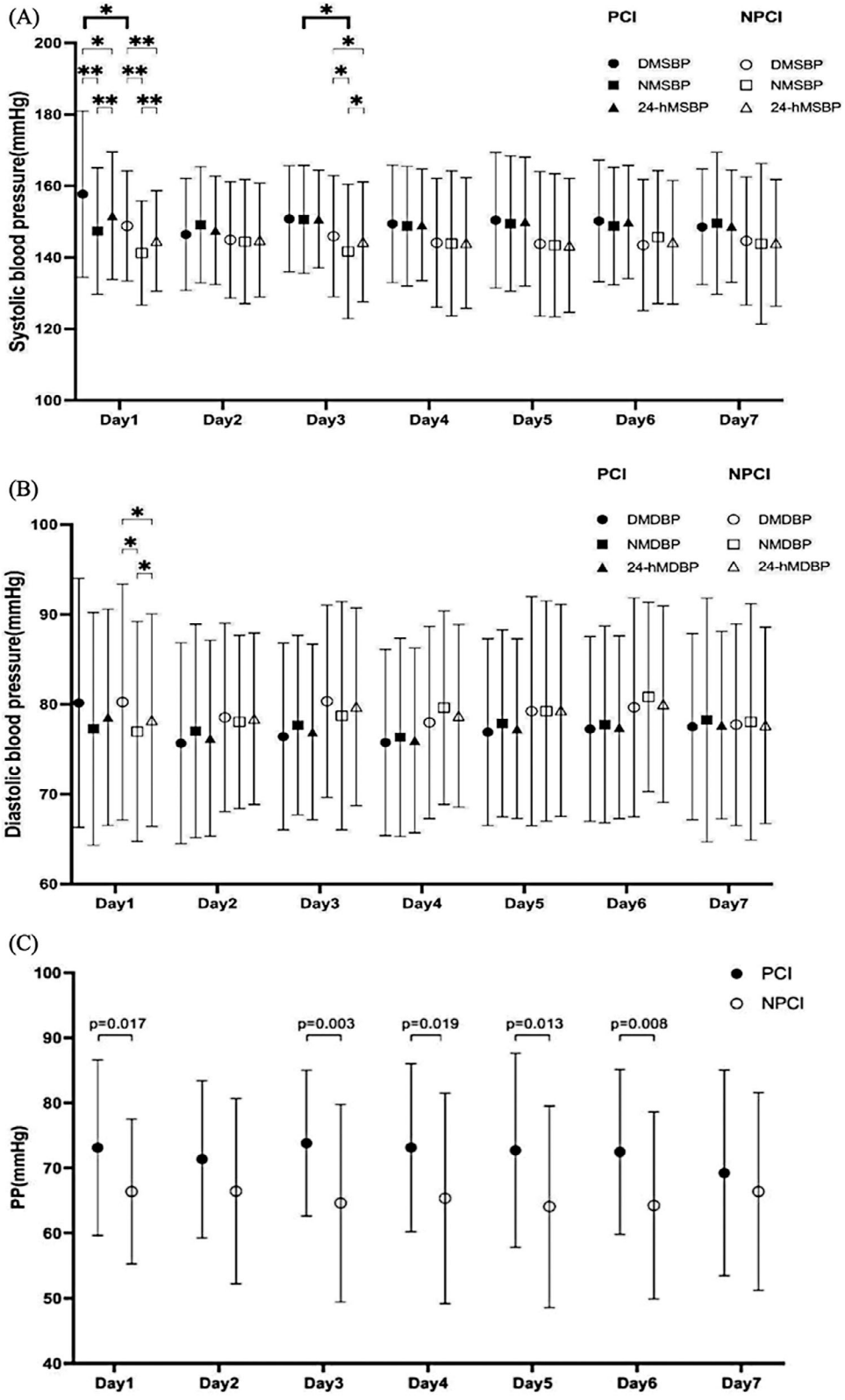


**FIGURE 2** Intra- and inter-group comparisons of BP-derived hemodynamic parameters in each day in PCI and NPCI patients. (A) systolic blood pressure. (B) diastolic blood pressure. (C) pulse pressure. DMSBP, diurnal mean systolic blood pressure; NMSBP, nocturnal mean systolic blood pressure; 24-hMSBP, 24-hour mean systolic blood pressure. DMDBP, diurnal mean diastolic blood pressure; NMDBP, nocturnal mean diastolic blood pressure; 24-hMDBP, 24-hour mean diastolic blood pressure. PP, pulse pressure. The thin arms show significant difference among diurnal, nocturnal, and 24 h results. The thick arms show significant differences between PCI and NPCI groups. * and ** denote $p < .05$ and $p < .001$.

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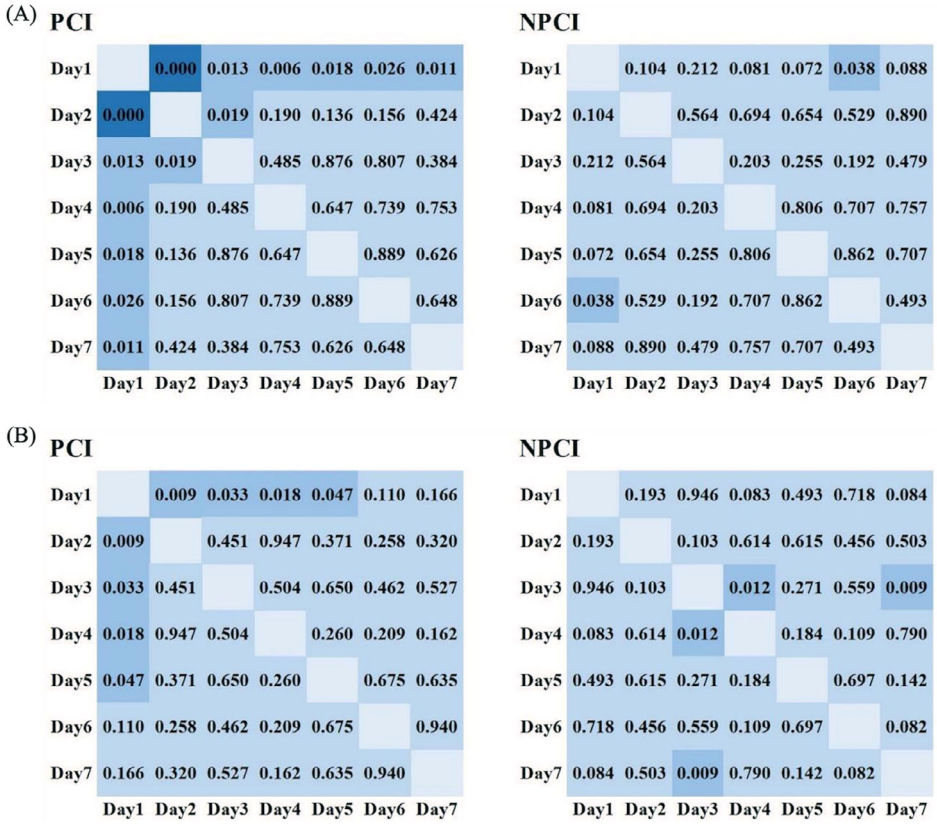


**FIGURE 3** Intra-group comparison of blood pressure values of different days. (A) DMSBP. (B) DMDBP. The *p* values of paired *t*-test were shown in the rectangles.

all, Figure 2A). Regarding DBP, we only observed significant differences between DMDBP, NMDBP, and 24-hMDBP in the NPCI group on the first day of admission (Figure 2B).

### 3.2.3 | Comparison between values of difference days in PCI and NPCI groups

In the PCI group, there was a sharp decrease of DMSBP on the second day after admission, followed by a milder but significant increase on the third day (Figure 3A). By contrast, the DMSBP of patients in the NPCI group decreased gradually over time. The only significant decrease appeared on the sixth day. There were no significant difference between different days in NMSBP, in both NPCI and PCI groups. Regarding 24-hMSBP, there was no significant differences between any 2 days in the NPCI group. In the PCI group, the only significant difference in 24-hMSBP was between the second and the first days where there was a sharp decrease ($p = .012$).

The DMDBP of patients in the PCI group was significantly higher on the first day of admission than on the following 4 days (Figure 3B). In the NPCI group, DMDBP of the third day was significantly higher than those on the 4th and 7th days. Regarding NMDBP, there was no significant difference between different days in the PCI group. In the NPCI group, the NMDBP of the second day was significant lower than that of the sixth day ($p = .013$). As for 24-hMDBP, the value of the second day was significantly lower in the PCI group than that of the first day ($p = .012$). In the NPCI group, the 24-hMSBP on the seventh day was significantly lower than that on the third and sixth days. The intra-group comparison results of DMDBP showed minor differences between PCI and NPCI groups.

## 3.3 | PP: Significant differences between PCI and NPCI

The 24-h mean PP in the PCI group were always higher than those of NPCI group. There were significant differences between PCI and NPCI groups on the 1st, 3rd, 4th, 5th, and 6th days (Figure 2C).

## 3.4 | MAP: No significant difference

There was no significant difference in 24-h MAP between PCI and NPCI group.

## 3.5 | Blood pressure circadian rhythm

As shown in Figure 4(A), in the PCI group, the NBPDR of the first day was significantly different from those of the 2nd, 3rd, and 5th days.

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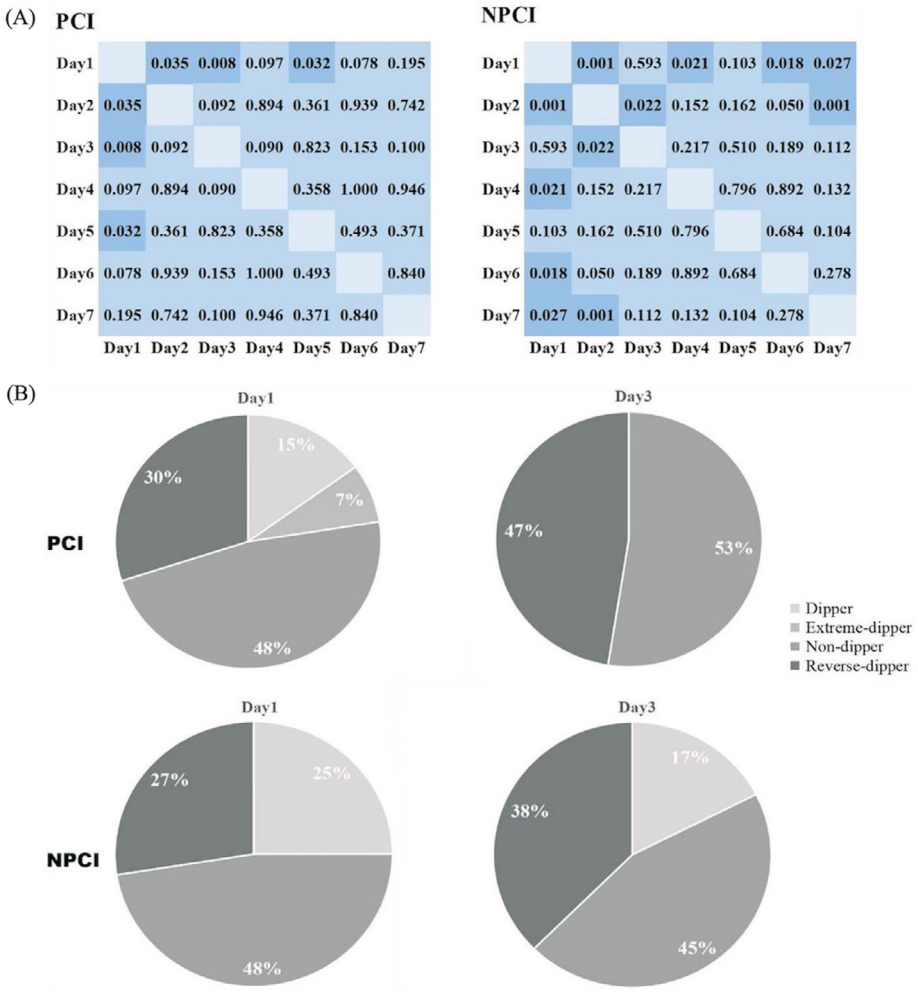


**FIGURE 4** NBPDR in PCI and NPCI groups. (A) Comparison of NBPDR within 7 days after admission in PCI and NPCI patients. (B) The percentage of circadian pattern of BP on the first and third days of admission in PCI and NPCI groups.

There was no significant difference among 2nd to 7th days. In comparison, in the NPCI group, there were significant differences between the 1st day and the 2nd, 4th, 6th, as well as 7th days; between the 2nd day and the 3rd as well as 7th days. In general, the variation of circadian BP rhythm was less obvious in the PCI group.

In Figure 4(B), on the first day of admission, there was no significant difference between the PCI group and the NPCI group ($p > .05$ in chi-square test). On the third day of admission, compared with NPCI patients, the percentage of dipper pattern was significantly lower and the percentage of abnormal BP rhythm (non-dipper, reverse-dipper) was significantly higher in the PCI group ($p < .001$).

## 3.6 | Potential risk factors of PCI

### 3.6.1 | Time-to-event analysis: Effect of baseline clinical parameters on PCI

Among the sixteen baseline variables (i.e., clinical parameters measured at admission), three (hypertension, fibrinogen, and baseline SBP) with $p$ value less than .1 in univariate Cox regression analysis were selected for multivariate analysis where collinearity was not observed. The multivariate analysis showed high fibrinogen and SBP at admission were associated with the development of PCI (Table 2).

### 3.6.2 | Logistic regression analysis: Potential risk factors of PCI

For continuous variables with $p$ <.1 in univariate analysis, multicollinearity was found among baseline SBP, 24-h DMSBP and 72-h NMSBP, and 5-day mean PP (correlation coefficients from 0.31 to 0.94, variance inflation factor > 5), where principal components analysis was performed. The first three principal components (proportion of variance explained: 90.69%) were selected and input with the hypertension history and fibrinogen into the multivariate logistic regression analysis based on backward stepwise approach. In the final multivariate regression model, the first principal component (Odds ratio 1.915, $p = .022$) and fibrinogen (Odds ratio 2.268, $p = .001$) were statistically significant (Table 3). Compared to other BP-derived hemodynamic

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**TABLE 2** Results of univariate and multivariate Cox regression analyses.

| Variables | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% CI | *p* value | Hazard ratio | 95% CI | *p* value |
| Sex | 1.141 | 0.606–2.148 | .682 | | | |
| Age | 1 | 0.975–1.025 | .971 | | | |
| Hypertension | 2.628 | 1.028–6.718 | .044 | 2.215 | 0.853–5.749 | .102 |
| Diabetes mellitus | 1.066 | 0.566–2.007 | .843 | | | |
| Atrial fibrillation | 0.807 | 0.425–1.531 | .512 | | | |
| Triglycerides | 1.204 | 0.818–1.771 | .346 | | | |
| Total cholesterol | 0.973 | 0.771–1.229 | .821 | | | |
| Low-density lipoprotein cholesterol | 0.906 | 0.678–1.211 | .507 | | | |
| High-density lipoprotein cholesterol | 0.989 | 0.322–3.036 | .984 | | | |
| Creatinine | 1.005 | 0.992–1.018 | .436 | | | |
| Urea nitrogen | 1.011 | 0.873–1.172 | .880 | | | |
| Fibrinogen | 1.350 | 1.118–1.630 | .002 | 1.340 | 1.112–1.615 | .002 |
| Folic acid | 1.007 | 0.980–1.034 | .637 | | | |
| Vitamin B12 | 0.999 | 0.998–1.001 | .296 | | | |
| Baseline SBP | 1.015 | 1.003–1.028 | .018 | 1.013 | 1.001–1.026 | .036 |
| Baseline DBP | 1.002 | 0.984–1.020 | .846 | | | |

**TABLE 3** Results of multivariate logistic regression analysis.

| Variables | B | wald | *p* value | Odds ratio | 95% CI |
|---|---|---|---|---|---|
| The first principal component | 0.650 | 5.261 | .022 | 1.915 | 1.099–3.336 |
| The second principal component | 0.461 | 2.622 | .105 | 1.585 | 0.908–2.769 |
| The third principal component | 0.546 | 3.819 | .051 | 1.727 | 0.998–2.986 |
| Fibrinogen | 0.819 | 10.261 | .001 | 2.268 | 1.374–3.742 |

parameters, PPs showed higher contributions in the first principal component (covariance approximating to or above 0.8), which indicated strong association between PP and PCI.

## 4 | DISCUSSION

### 4.1 | Summary of results

The prognosis of stroke depends on the progressive cerebral hemodynamic damage.[7,19] In this study, we reported the temporal features of BP-derived hemodynamic parameters in patients with PCI. We initially investigated the relationships between these hemodynamic parameters and PCI by comparing the results between PCI and NPCI groups. The pattern of temporal changes in BP-derived hemodynamic parameters was significantly different between PCI and NPCI groups. In the PCI group, both SBP and PP were significantly higher, accompanied by abnormal circadian BP rhythms. High baseline SBP, PP and fibrinogen were associated with PCI and might be potential risk factors of PCI.

### 4.2 | Consecutive BP recordings: Towards higher accuracy

To investigate the temporal fluctuations of BP-derived hemodynamic parameters, we used consecutive BP recordings with strict inclusion/exclusion criteria. In existing studies, the relationship between BP and PCI was investigated mainly based on the cross-sectional BP values rather than consecutive BP recordings.[9] The consecutive non-invasive BP recording not only enables the observation of temporal fluctuations of BP, but also reduces the effect of measurement errors and observer bias when compared to cross-sectionally recorded BP.[20,21] As far as we know, our study is among the first attempts towards BP-based PCI detection from a hemodynamic perspective.

### 4.3 | Role of SBP in PCI-related hemodynamic changes

In this study, we observed a post-admission decrease in BP which has different patterns in PCI and NPCI patients. In the PCI patients, SBP

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(including DMSBP and 24-hMSBP) dropped sharply on the 2nd day, with a milder increase on the 3rd day (Figures 2A and 3A). High SBP at admission was associated with PCI, and PCI patients have significantly higher 24-h DMSBP and 72-h NMSBP than NPCI patients. These parameters might be potential risk factors of PCI. Our findings are in accordance with existing clinical observations. On the one hand, in both PCI and NPCI patients, SBP fluctuates in a time-dependent manner in the first few days after an ischemic stroke.[22] An abrupt elevation in BP after an ischemic stroke was observed in the majority (approximately 80%) of the patients in a few hours or 1–2 days, and post-stroke BP elevations are generally transient and return to baseline level within a week among two-thirds of patients.[10,23] On the other hand, PCI patients seem to have larger SBP fluctuations, which may indicate the hemodynamic instability. Castillo and coworkers found that the fall in BP during the first day after admission is detrimental and associated with worsening neurological function for patients with acute ischemic stroke.[24] A sudden drop in SBP is considered the strongest predictor of poor prognosis of ischemic stroke and is associated with a final infarct volume of more than 60 mL.[24,25] Patients with a larger drop in BP in the first 24 h had a higher risk of recurrent ischemic stroke.[26] In addition, SBP is independently associated to the early mortality after acute ischemic stroke.[10] Arterial BP at admission independently predicts PCI, where high SBP at admission indicates poor prognosis.[3,27] In a study of ischemic stroke patients who received ambulatory BP monitoring within 72 h of admission, it was found that high daytime SBP was significantly associated with the recurrence of ischemic stroke.[2] High SBP was related to the deterioration of ischemic stroke, and high 24-h SBP could be used as a predictor of clinical deterioration caused by brain swelling.[28] Therefore, both post-stroke SBP and its fluctuations deserve more attention as potential indicators of PCI.

Our observation on SBP and PCI indicates a possible pathologic mechanism of PCI. Ischemic tissues are particularly vulnerable to the fluctuations of SBP.[29] When SBP decreases, cerebral vessels with impaired vasomotor response may not be able to dilate and increase cerebral blood flow, leading to ischemia and PCI.[10,15] The autoregulation of CI patients is impaired, which makes cerebral perfusion more dependent on SBP, where a low perfusion pressure might increase the infarct area.[27] We speculated that the DMSBP increase on the third day might indicate the compensatory mechanism of cerebral perfusion maintenance.[25] In addition, studies have shown that hypertension within a few hours after stroke can lead to the destruction of the blood-brain barrier, an increase in cerebral perfusion pressure, and finally the formation of edema.[28] Patients of CI with well-developed collateral circulation often have a lower post-stroke BP.[22,30] In the first few hours after onset, stroke deficits are unstable, prone to sudden worsening with clot propagation or collateral failure.[31] Collateral failure is a likely mechanism for most ischemic stroke-in-progression,[32] of which SBP may reflect the severity from a hemodynamic perspective. The underlying pathophysiology between SBP and PCI deserves more in-depth investigation.

### 4.4 | Pulse pressure

In this study, we observe that PP has strong explanatory power in the first principal component of BP-derived parameters, which indicates that PP might be associated with PCI during its development. Studies showed that 24-h PP is an independent risk factor for stroke and an independent predictor of long-term mortality.[21,33] Grabska and coworkers calculated the mean PP 7 days after stroke in 1677 patients and found that elevated PP in the acute phase of CI was an independent predictor of poor early prognosis.[34] PP plays an important role in predicting the recurrence of CI and is positively correlated with the deterioration (i.e., progression) of neurological dysfunction.[1,35]

High PP is recognized as a marker of large arterial stiffening and widespread atherosclerosis,[36] which affect the macro- and microcirculation, inducing remodeling of vessel walls.[34,37] For cerebral circulation, increased pulsatile stretching means damaged adaptive properties as a result of endothelial damage and stiffening, and low perfusion during diastole, both leading to the aggravation of CI.[5,38] Our observations highlight the significance of PP monitoring in early detection of PCI. Of note, the observations were based on a small cohort. Large-scale validation is essential and may derive quantitative PP thresholds/metrics to estimate the risk of PCI.

### 4.5 | Circadian BP rhythm

In this study, we found that the variation of circadian BP rhythm was reduced in the PCI group where pathological circadian rhythms were more frequent and lasted longer. In the PCI group, on the third day after admission, we observed a low percentage of normal dipper pattern with high percentages of abnormal BP circadian rhythm patterns (non-dipper and reverse-dipper). We speculated that the abnormality in BP circadian rhythm might be associated with metabolic imbalance caused by higher sympathetic activity in the PCI patients.[39] We also observed the instability in NBPDR over time, which might reflect the hemodynamic instability in the early stage of PCI.

The pathologically reduced or abolished dipper pattern after an acute ischemic stroke may lead to more target organ damage, which could deteriorate the neurological outcome.[40,41] The patients with dipper pattern after an ischemic stroke showed good prognosis, whilst the abnormal circadian rhythm patterns were associated to poor prognosis.[42] The abnormal circadian rhythm patterns of BP (non-dipper and reverse-dipper) are independent predictors of stroke in patients with hypertension,[43] and are associated with more severe baseline stroke and poorer short-term functional recovery.[42] In accordance with existing studies, our observations suggest that abnormal circadian rhythm of BP might be an early indicator of PCI. In the future, large-scale prospective studies may further clarify the trends of NBPDR in PCI patients.

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### 4.6 | Significance for clinical practice and research

The occurrence of PCI involves multifactorial pathology, including hemodynamic and metabolic factors.[9] The underlying pathophysiological mechanisms include expansion of thrombus, collateral circulation angiemphraxis, decrease in brain tissue perfusion, brain cell edema, and apoptosis.[14] Our results may provide new materials for the pathological research of PCI and hemodynamic factors. Our study also highlight the significance of BP monitoring and management in clinical practice since BP is recognized as a treatable risk factor for CI.[40]

We found that fibrinogen was associated with PCI and may be a potential risk factor for PCI, which is consistent with previous studies. High fibrinogen level was found associated with neurological deterioration and poor functional prognosis in early CI.[4,44] The measurement of fibrinogen is inexpensive and widely available. The fibrinogen measurement and continuous monitoring of BP dynamics at the early stage of ischemic stroke may provide more information of cerebral hemodynamics, enabling earlier detection of PCI.

### 4.7 | Limitations and future directions

There are some limitations in this study. First, it was a single-center study based on a small cohort. The possible inaccurate or incomplete case identification may lead to bias in patient selection. Although all patients received standardized treatment in the same stroke unit, we did not have complete data on whether some patients were taking antihypertensive medications during the study period and could not detect statistically significant BP differences due to antihypertensive treatment. Second, this was a retrospective study. It was not our aim to study the sequence of BP-related changes and PCI from a pathologic perspective, and our results do not demonstrate a direct causal relationship between BP changes and PCI outcomes. It is worthwhile to further explore long-term BP changes in PCI patients. In addition, our estimation of NBPDR was based on a relatively low number of BP recordings. Frequent BP measurement in daily activities is essential for accurate estimation of NBPDR and circadian rhythm of BP. In the future, more prospective multicenter studies can be used to validate our findings and elucidate the underlying mechanisms. Recent studies have reported that BP and hemodynamic changes are effective indicators in the diagnosis and treatment of large groups of brain disorders.[45,46] Therefore, with methodological adaptation (e.g., including other proposed metrics of cerebral circulation), the findings might be extended to the cohorts with other brain disorders, for example, hydrocephalus and cerebral atrophy, to enable the early detection of severe symptoms and improve the diagnosis and treatment.[47]

## 5 | CONCLUSIONS

We observed a decrease of BP in post-stroke patients, where the pattern was different in patients with PCI and NPCI. PCI patients showed higher daytime and nighttime SBP, higher PP, and more abnormal circadian rhythms of BP. PCI was associated with admission high SBP, PP and fibrinogen. These factors deserve further attention in the early detection of PCI.

### AUTHOR CONTRIBUTIONS

Conceptualization, Ling Li, Songbin He, Fangyu Dai, Haipeng Liu, and Gary Tse; Methodology, Fangyu Dai and Haipeng Liu; Software, Ling Li; Validation, Bin Wu, and Jiaoxuan Dong; Formal analysis, Ling Li, Bin Wu, Jiaoxuan Dong, and Jie Xu; Investigation, Ling Li, Bin Wu, Jiaoxuan Dong, and Jie Xu; Resources, Ling Li, Bin Wu, Jiaoxuan Dong, Songbin He, Jie Xu, and Fangyu Dai; Data curation, Jiaoxuan Dong and Bin Wu; Writing-original draft preparation, Ling Li, Haipeng Liu, and Gary Tse; Writing-review & editing, all authors; Visualization, Ling Li and Haipeng Liu; Supervision, Songbin He, Fangyu Dai, Haipeng Liu, and Gary Tse; Project administration, Fangyu Dai; Funding acquisition, Ling Li and Songbin He. All authors read and approved the final manuscript.

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### CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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