Normal Systolic Blood Pressure at Presentation With Acute Ischemic Stroke Predicts Cardioembolic Etiology

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Background—Early insight into the possible etiology of ischemic stroke allows for early initiation of mechanism-specific secondary stroke prevention. Initial systolic blood pressure during acute ischemic stroke may relate to stroke etiology. We sought to determine whether normotension at presentation with acute ischemic stroke predicts cardioembolic etiology.

Methods and Results—All patients presenting with acute ischemic stroke within 12 hours of symptom onset at a comprehensive stroke center from January 2015 to December 2017 were assessed. Normotension was defined as systolic blood pressure $\leq$130 mm Hg. The primary exposure was blood pressure on arrival at the hospital, and the primary outcome was cardioembolic etiology. Multivariable regression with stepwise selection was used to adjust for relevant covariates. We included 683 patients in our analysis, 303 (44%) of whom were diagnosed with cardioembolic etiology at 6 months. The probability of cardioembolic etiology was inversely associated with systolic blood pressure, and initial systolic blood pressure was significantly associated with cardioembolic etiology (odds ratio: 1.15; 95% CI, 1.05 to 1.26). Normotension was associated with 2.62-fold increased odds of cardioembolic etiology (95% CI, 1.46 to 4.72).

Conclusions—Normotension at presentation with acute ischemic stroke strongly predicts cardioembolic etiology. These patients may especially benefit from early and prolonged cardiac investigations. (Am J Cardiol. 2020;9:e014399. DOI: 10.1161/JAHA.119.014399.)

Key Words: blood pressure • etiology • ischemic stroke • prevention

Modern secondary stroke prevention is tailored to stroke etiology, for example, oral anticoagulation for atrial fibrillation and carotid intervention for high-grade stenosis. Early insights into possible etiology might alter both initial therapy and prioritization of subsequent investigations. Although most patients presenting with acute ischemic stroke experience a transient elevation in their blood pressure (BP), 1 to 5 some are normotensive or even hypotensive at presentation. Previous studies have suggested that lower BPs during acute stroke admission may be seen in patients with cardioembolic stroke, 3,4,6 to 9 in contrast to higher BPs in patients with small vessel disease. 3,6,7,9 However, no study has looked at the predictive power of the initial BP at the time of presentation within the early hours of symptom onset. This study aims to determine whether normotension during initial presentation with acute ischemic stroke predicts cardioembolic etiology.

Methods

This study was approved by the Ottawa Health Science Network Research Ethics Board. Informed consent from participants was deemed not required. The data collected for this study are available for access by qualified researchers trained in human subject confidentiality protocols who are collaborating with the Ottawa Stroke Program.

We retrospectively assessed consecutive patients presenting with acute ischemic stroke within 12 hours of symptom onset at the Ottawa Hospital, a comprehensive stroke center, from January 1, 2015, to December 31, 2017. Patients seen in the emergency department as part of an acute “code stroke” were followed from initial assessment through to discharge and subsequent follow-up in the outpatient setting, if applicable. Acute investigations include computed tomography and computed tomography angiography, except in patients with a...
known contraindication to contrast. Most patients received a transthoracic echocardiogram and at least 48 hours of Holter monitoring; some patients received additional testing, including extended rhythm monitoring, transesophageal echocardiogram, thrombophilia blood work, and cerebrospinal fluid analysis, at the discretion of the treating physician.

The diagnosis of stroke was confirmed with computed tomography or magnetic resonance imaging. Patients were excluded from primary analysis if they had a diagnosis other than ischemic stroke, including transient ischemic attack, or if the etiology of stroke was not specified in the patient record. The patient’s background characteristics were collected from electronic medical records.

The primary exposure was first recorded BP in the emergency department during acute presentation before any medical intervention, which was measured using automated devices. We independently analyzed systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) as continuous variables. Fractional polynomial modeling, as implemented in the R software package “mfp” (R Foundation for Statistical Computing),\textsuperscript{10,11} was used to determine whether initial BP and cardioembolic diagnosis shared a nonlinear relationship. SBP and DBP were also analyzed as dichotomous variables, with selected thresholds reflecting the probability distribution from fractional polynomial modeling or published guidelines.\textsuperscript{12} Our primary outcome was cardioembolic etiology at 6 months; etiology was determined by the treating stroke neurologist using TOAST criteria.\textsuperscript{13}

SBP, DBP, and MAP were further evaluated in separate multivariable logistic regression models. Stepwise selection was used to adjust for relevant covariates. Nonsignificant variables ($P > 0.05$) were eliminated in a backward stepwise fashion. Cardiac comorbidities were forced into each regression model a priori to account for potential confounding and were kept in each model, even if deemed nonsignificant. The remaining candidate covariates were derived with exploratory analysis.

### Table 1. Exploratory Univariate Analysis Stratified by Etiology of Stroke*

|                                | Cardioembolic (n=303) | Noncardioembolic\textsuperscript{†} (n=380) | Unadjusted OR (95% CI) |
|--------------------------------|------------------------|---------------------------------------------|------------------------|
| **Age, y, median (IQR)**       | 77 (69 to 85)          | 69 (58 to 79)                               | 1.05 (1.04 to 1.07)    |
| **Male sex**                   | 127 (41.9)             | 215 (56.6)                                  | 0.55 (0.41 to 0.75)    |
| **Cardiovascular risk factors**|                        |                                             |                        |
| Hypertension                   | 230 (75.9)             | 239 (62.9)                                  | 1.86 (1.33 to 2.60)    |
| Antihypertensive use           | 203 (67.0)             | 209 (55.0)                                  | 1.66 (1.21 to 2.27)    |
| Dyslipidemia                   | 148 (48.8)             | 180 (47.4)                                  | 1.07 (0.78 to 1.44)    |
| Current smoker                 | 23 (7.6)               | 59 (15.6)                                   | 0.45 (0.27 to 0.75)    |
| BMI,\textsuperscript{‡} median (IQR) | 26 (24 to 30)          | 27 (25 to 31)                               | 0.97 (0.94 to 0.99)    |
| **Cardiac comorbidities**      |                        |                                             |                        |
| Coronary artery disease        | 68 (22.4)              | 74 (19.5)                                   | 1.20 (0.83 to 1.73)    |
| Congestive heart failure       | 49 (16.2)              | 15 (3.9)                                    | 4.69 (2.58 to 8.55)    |
| Congenital heart disease       | 5 (1.7)                | 2 (0.5)                                     | 3.18 (0.61 to 16.51)   |
| Valvular heart disease         | 30 (9.9)               | 11 (2.9)                                    | 3.70 (1.82 to 7.51)    |
| Atrial fibrillation            | 189 (62.4)             | 20 (5.3)                                    | 29.84 (17.98 to 49.53) |
| Cardiomyopathy                 | 12 (4.0)               | 3 (0.8)                                     | 5.18 (1.45 to 18.53)   |
| **Clinical presentation**      |                        |                                             |                        |
| Baseline NIHSS score, median (IQR) | 11 (6 to 18)           | 7 (4 to 13)                                 | 1.07 (1.04 to 1.09)    |
| Time from LKW, h, median (IQR) | 1.66 (1.0 to 3.0)      | 2.15 (1.1 to 3.5)                           | 0.93 (0.87 to 0.99)    |
| SBP on presentation, mm Hg, median (IQR) | 150 (129 to 166)      | 158 (140 to 175)                            | 0.99 (0.98 to 0.99)    |
| DBP on presentation, mm Hg, median (IQR) | 83 (71 to 97)         | 85 (75 to 96)                               | 0.99 (0.98 to 1.01)    |
| MAP, mm Hg, median (IQR)       | 106 (94 to 118)        | 109 (99 to 121)                             | 0.99 (0.98 to 0.99)    |
| Heart rate, median (IQR)       | 81 (70 to 97)          | 79 (70 to 92)                               | 1.01 (1.00 to 1.02)    |

BMI indicates body mass index; DBP, diastolic blood pressure; IQR, interquartile range; LKW, last known well; MAP, mean arterial pressure; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SBP, systolic blood pressure.

*Results are n (%) unless indicated otherwise.

\textsuperscript{†}Noncardioembolic includes large vessel, small vessel, cryptogenic, and other causes.

\textsuperscript{‡}Missing 175 values.
univariate analysis and Fisher exact test, ANOVA, or Mann-Whitney U tests, as appropriate (P<0.10). Continuous variables that did not conform to the linearity assumption were recategorized into dichotomous or ordinal variables. Given concerns about potential selection bias, variables with missing data with a proportion ≥5% were included in our primary analysis, but missing data were not included during multivariable logistic regression. We performed all statistical analyses other than fitting the fractional polynomial model using SPSS v25.0 (IBM Corp) and SAS v9.4 (SAS Institute).

Results

Of 2058 patients assessed for possible acute stroke at the Ottawa Hospital, 695 patients had confirmed acute ischemic stroke with documented etiology, and 683 patients were included in our primary analysis. Twelve patients were excluded for lacking an early recorded BP. The median age of the primary analysis population was 74 years (interquartile range: 63 to 84) with an even distribution of men (50.1%) and women (49.9%). The median National Institutes of Health Stroke Scale score at initial presentation was 9 (interquartile range: 5 to 16), and the median time from when the patient was last known well was 2.0 hours (interquartile range: 1.0 to 3.3). In total, 303 (44.4%) patients were diagnosed with a cardioembolic etiology at 6 months. Noncardioembolic etiologies included large vessel disease (173, 25%), small vessel disease (78, 11%), cryptogenic stroke (97, 14%), and other etiologies (32, 5%; Table 1).

SBP, DBP, and MAP all shared an inverse linear relationship with cardioembolic diagnosis (Figure; for DBP and MAP, see Figures S1 and S2). For every 10-mm Hg decrease in SBP, there were 1.15 increased odds of cardioembolic etiology (95% CI, 1.05 to 1.26). The selection of dichotomous thresholds was based on previously published guidelines, and normotension was defined as SBP ≤130 mm Hg and DBP ≤80 mm Hg. These variables were entered into backward conditional regression models. When adjusted for the relevant covariates, SBP and MAP were significantly associated with cardioembolic etiology of stroke (Table 2). When represented in the same model as a dichotomous variable, SBP...
≤130 mm Hg (normotension) was associated with 2.62-fold increased odds of cardioembolic etiology (95% CI, 1.46 to 4.72). For SBP ≤130 mm Hg, sensitivity was 26.0% and specificity was 85.5%. In contrast, DBP ≤80 mm Hg was not significantly associated with cardioembolic diagnosis.

Discussion

In this study, patients who were normotensive at presentation with acute ischemic stroke were more likely to be found to have a cardioembolic etiology. Lower SBP at presentation was linearly associated with a greater probability of a cardioembolic etiology.

Our results are largely consistent with other studies investigating the relationship between BP in ischemic stroke and stroke etiology. Two studies have reported that admission SBP of patients with cardioembolic etiology was significantly lower than in patients with small vessel or large vessel etiologies, although patients presented beyond the early hours of acute symptom onset and lower SBP was not defined as normotensive.\(^5\)\(^7\) Marcheselli et al demonstrated that lower BP in the first 24 hours after stroke was significantly associated with cardioembolic etiology.\(^6\) A few studies have demonstrated higher SBPs in patients with lacunar strokes,\(^3\)\(^4\)\(^9\) whereas others have demonstrated conflicting results or no relationship between initial BP and stroke etiology.\(^2\)\(^8\) In relation to this literature, the BP measurements we captured were taken during the early hours of acute ischemic stroke onset. Moreover, our study reports the largest sample size to date, and we likely had the longest time to determine stroke etiology, which may have improved diagnostic accuracy. Finally, the current standard of care in Canada is to perform at least 2 weeks of continuous monitoring in patients with suspected cardioembolic stroke, and this may account for the high proportion of patients found to have a cardioembolic etiology.

The transient elevation in BP commonly seen during acute ischemic stroke has been associated with a number of potential mechanisms, including an autoregulatory response to improve cerebral perfusion to penumbral tissue,\(^1\)\(^14\) an acute stress response leading to increased levels of circulating catecholamines,\(^14\) or secretion of neurohormonal factors such as renin to angiotensin to aldosterone or brain natriuretic peptide.\(^6\) The spontaneous decrease in BP commonly observed over the hours to days following ischemic stroke\(^1\)\(^t\)\(^5\) argues against chronic untreated hypertension as a primary mechanism, although it may exacerbate this phenomenon.\(^5\) Cardiac hemodynamics, primarily cardiac output, may be affected in patients with a cardioembolic etiology and may prevent the transient BP elevation seen in other patients.\(^6\) Patients with cardioembolic stroke etiology were more likely to have been prescribed an antihypertensive medication (Table 1), which could partially counteract some of the proposed mechanisms. Our findings support the notion that BP during acute stroke is related to stroke etiology, which may account for the mixed pathophysiology in the literature.

Our findings also have implications for investigations of stroke etiology. Normotension or hypotension during acute ischemic stroke may eventually be seen as a reason to expedite echocardiography and prolonged cardiac monitoring, both of which have varying degrees of use in clinical practice.\(^15\)

Limitations of the current study include that it was retrospective and based on a single center, and results were

### Table 2. Multivariable Logistic Regression Models of Initial Blood Pressure for Prediction of Cardioembolic Diagnosis

| Model 1 (SBP)* | Model 2 (DBP)* | Model 3 (MAP)* |
|----------------|----------------|----------------|
| aOR 95% CI     | aOR 95% CI     | aOR 95% CI     |
| Clinical information |               |               |               |
| Age (per 1-y increase) | 1.04 1.02 to 1.07 | 1.04 1.02 to 1.06 | 1.04 1.02 to 1.06 |
| Female sex     | 1.77 1.09 to 2.88 | 1.82 1.12 to 2.94 | 1.91 1.16 to 3.13 |
| Baseline NIHSS score (per 1-point increase) | 1.04 1.01 to 1.08 | 1.05 1.02 to 1.09 | 1.05 1.01 to 1.08 |
| Tachycardia    | 2.04 1.16 to 3.62 | 2.14 1.21 to 3.77 | 1.96 1.10 to 3.49 |
| SBP (per 10-mm Hg decrease) | 1.15 1.05 to 1.26 | ... ... | ... ... |
| DBP (per 10-mm Hg decrease) | ... ... | 1.05 0.92 to 1.19 | ... ... |
| MAP (per 10-mm Hg decrease) | ... ... | ... ... | 1.15 1.01 to 1.32 |
| Cardiac comorbidities |               |               |               |
| Valvular heart disease | 2.82 0.98 to 8.12 | 2.93 1.03 to 8.38 | 2.70 0.93 to 7.84 |
| Known atrial fibrillation | 22.96 11.65 to 45.26 | 23.70 12.60 to 46.59 | 21.18 10.72 to 41.86 |

aOR indicates adjusted odds ratio; DBP, diastolic blood pressure; MAP, mean arterial pressure; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

*Additional adjustment for coronary heart disease and congestive heart failure.

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derived from a single initial BP measurement rather than a series of measurements. However, the use of a single reading renders our findings generalizable and pragmatic; ultimately, basing our analysis on the initial reading is more practical than compiling multiple measurements and may increase accuracy, given the eventual fall in BP commonly seen across cardioembolic strokes reported in our study may have been affected by our institution’s status as a comprehensive stroke center that accepts referrals for endovascular thrombectomy and receives patients with suspected large strokes by ambulance bypass from a large catchment area. In addition, stroke etiology was determined using patient records, and ancillary testing was performed at the discretion of the treating physician; these factors may have affected etiology reporting rates and contributed to the high proportion of cardioembolic etiology but should not have affected the accuracy of etiology determination and subsequent analysis. Further study, including prospective validation, is required to confirm our findings.

In conclusion, we demonstrated that patients who are normotensive at presentation with acute ischemic stroke are significantly more likely to have cardioembolic stroke etiology. This was established from the first BP measurement on arrival in the emergency department within a few hours of the time at which the patients was last known well. These patients may especially benefit from early and prolonged cardiac investigations.

Disclosures
None.

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SUPPLEMENTAL MATERIAL
Supplemental Figures:

Figure S1: Predicted Probability of Cardioembolic Diagnosis by Diastolic Pressure. Data calculated on 683 patients. Solid line indicates predicted probability. Shaded areas indicate 95% Confidence intervals.
Figure S2: Predicted Probability of Cardioembolic Diagnosis by Mean Arterial Pressure. Data calculated on 683 patients. Solid line indicates predicted probability. Shaded areas indicate 95% Confidence intervals.