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Clinical Study

Can Transient Drop in Blood Pressure in High-Risk Hypertensive Patients Cause Small Cerebral Infarcts?

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Background. Multiple, simultaneous, acute cerebral infarcts in different arterial territories are usually secondary to embolic occlusion of multiple cerebral arteries. We observed, however, that no cardiac or aortic source could be found in many of these patients. We therefore undertook this study to attempt to identify other factors that may be important in the causation of these infarcts. *Materials and Methods*. We performed a five-year retrospective review of all patients with multiple, near simultaneous, acute cerebral infarcts detected on diffusion-weighted MRI scans. *Results*. We identified 78 patients with acute infarcts, in different cerebral arterial territories. We found a cardiac embolic source in 15 (19 percent) patients. Forty-one patients (53%) had no obvious cause for their infarcts after detailed cardiovascular and hematological evaluation. In 16 of these patients (20% of all 78 patients), all with a history of chronic hypertension who had multiple, acute, small (<2 cms), deep subcortical or superficial cortical infarcts (and most, 93%, with extensive evidence of chronic small vessel disease on MRI FLAIR images), blood pressure was low or normal on initial presentation (mean arterial pressure, MAP: 85 ± 11.4 mm Hg). Analysis of the last prestroke blood pressure, within the previous 1 to 11 days available in 13 of 16 patients, revealed much higher BP (MAP: 113.6 ± 11.3 mm Hg), indicating a mean drop of 25.1 percent (range 11 to 44 percent). Two weeks after the stroke, blood pressure had risen again to greater than 160/100 mm Hg (MAP: 128.2 ± 14.3). *Conclusion*. Our study suggests that transient drop in blood pressure in high-risk hypertensive patients with severe, small vessel disease may sometimes result in small, cerebral infarcts. More research is needed to further clarify and confirm this possibility.

1. Introduction

Embolism originating from the heart or artery-to-artery emboli from more proximal to distal smaller branches is responsible for most cases of cerebral infarction [1–4]. Decreased perfusion secondary to hemodynamic failure is a much less common cause of infarcts (<10% of patients) [5], limited to infarcts in the vulnerable border zone between the territory vascularized by large cerebral arteries in patients with severe ipsilateral carotid or other large artery stenosis [6]. A recent hypothesis seeks to combine these mechanisms with the proposal that hypoperfusion can lead to impaired clearance of emboli from occluded arteries [7].

Multiple, acute cerebral infarctions in different arterial territories, which refer in this study to all ischemic damage detected on one diffusion weighted MRI scan (DWI), are of great interest because of their potential to provide useful information about stroke pathophysiology. Infarcts detected in this way may have occurred simultaneously or within a few days of each other. We observed that in our population of chronically hypertensive, elderly patients, no cardiac or aortic source of embolism could be found in some of these patients.

We therefore undertook an exhaustive retrospective analysis of all our stroke patients for a 5-year period, identifying patients with multiple, near simultaneous acute infarctions in different cerebral arterial territories. The aims of this analysis were to determine the possible causative factors responsible for these infarcts and the light that might be shed on the pathophysiology of cerebral infarctions in general.

2. Materials and Methods

2.1. Data Collection. Data was collected retrospectively on all patients who were admitted over a five-year period with a diagnosis of acute cerebral infarction. Our center stores all neuroimaging using a computerized picture archiving and communications system (PACS) facilitating retrieval and analysis of patient data. All patients admitted with a clinical diagnosis of acute stroke had a cranial CT and MRI within 72 hours.

2.2. MRI Scans. Patients were studied using a 1.5-T MR scanner (Philips Achieva) using the standard neurovascular coil. The following sequences were obtained: sagittal T1-weighted (TR/TE, 596/15), axial T1-weighted images (TR/TE, 677/15), axial fluid-attenuated inversion recovery (FLAIR: TR/TE/TI, 11000/140/2800), and axial fast spin-echo T2-weighted (TR/TE, 11000/140). Slice thickness was 5 mm with a skip of 1 mm. FOV was between 230 and 340 mm for all sequences. Echo-planar T2- and diffusion-weighted images were obtained with diffusion gradients in the x, y, and z planes by using 5 mm thick sections with skip of 1.0 mm (TR/TE, 3266/74; $b = 0$ and 1,000 s/mm^2). 3D time-of-flight images of the head and 2D time-of-flight images of the neck were obtained. ADC (apparent diffusion coefficient) maps were generated using the Philips Achieva software. Where the area of infarction was 1 cm or greater in width, operator-defined regions of interest (ROIs) were drawn over the core region of each infarction and the lowest ADC values were determined. All MRI scans of patients with a reported diagnosis of acute cerebral infarction were reviewed independently by both authors. Concordance between the findings of both reviewers was 98 percent.

2.3. Inclusion Criterion. Patients with multiple (two or more) acute cerebral infarcts were selected on the basis of (1) hyperintensity on DWI imaging and concomitant hypointensity on ADC mapping; (2) lesions had to be present in different cerebral vascular territories (both carotid circulations or both carotid and vertebrobasilar circulations).

2.4. Exclusion Criterion. (1) Multiple acute infarcts restricted to the territory of one large vessel, internal carotid artery (ICA), anterior cerebral artery (ACA) and middle cerebral artery (MCA), or to the vertebrobasilar circulation alone were excluded. (2) Congenital vascular variations such as fetal-type posterior cerebral artery with origin from the internal carotid artery or single, azygous, anterior cerebral artery were identified and if present, patients with infarcts in only one hemisphere or both ACA territories, respectively, were excluded.

The size and number of acute infarcts were recorded in every patient. Old infarcts and chronic small vessel disease were identified on MRI FLAIR/T2-weighted images. Arterial stenosis of more than 50 percent on MR angiography (MRA) was considered significant. Patients were considered to have a cardiac source of embolism according to the modified [8] TOAST criterion [9]. We defined small infarcts as being less than 2 cms in size [10].

2.5. Clinical and Laboratory Tests. All admitted patients had been evaluated by an experienced neurologist using a standardized stroke protocol. History, physical examination including blood pressure (BP) readings, antihypertensive medications, and risk factors had been recorded. BP recordings were done using a sphygmomanometer by staff nurses. In all patients the following investigations were carried out: full blood count, complete metabolic panel including urea, creatinine, lipid profile, glucose, serum electrolytes, liver enzymes, and troponin. Some patients also had tests for antiphospholipid antibodies, proteins C and S levels, antinuclear antibodies, rheumatoid factor, erythrocyte sedimentation rate, and C reactive protein. Twelve lead EKGs had been obtained in all patients and most patients had also been monitored by 3-lead electrocardiography for at least the first 48 hours after admission. Transthoracic (TTE) or transesophageal (TEE) echocardiography with microbubble test for patent foramen ovale was recorded in most (87%) patients within one week of stroke.

2.6. Statistical Analysis. Categorical variables across groups were compared using chi-square analysis. When the results indicated a significant difference at $P < 0.05$, all groups were compared, two at a time, to locate the difference more precisely. Continuous variables were compared using ANOVA, and particular differences were determined using Tukey's test.

3. Results

We identified 637 acute cerebral infarctions in the 58-month period studied. Of these, 121 patients (19 percent) had multiple infarctions. Forty-three patients had multiple infarcts restricted to a single carotid circulation or the vertebrobasilar territory alone and were not included for further analysis. The remaining 78 patients (12.2 percent of all acute infarcts), with infarcts in different large arterial territories (both carotids or both carotid and vertebrobasilar territories), were divided into four groups based on possible etiologic factors (Table 1). There was no record of a transient ischemic attack in the prior 3 months in any of these patients. All these patients received standard stroke care and as the initial evaluation was beyond the therapeutic window no patient received thrombolytic therapy.

Group 1 with 41 patients (52.6%) revealed no obvious cause for cerebral infarction on initial evaluation. There were 23 men and 18 women with an average age of 66.2 years with a range of 43 to 92 years. Infarcts were located in both carotid circulations in 41.5 percent, in both carotid circulations and vertebrobasilar circulation in 46.3 percent, and in carotid and vertebrobasilar circulations of one hemisphere in 12.1 percent. Infarcts were located only in deep subcortical regions in 22 of 41 patients (53.6 percent), only in superficial cortical areas in 3 patients (7.3 percent), and both deep and superficial

Table 1: Features of all 78 patients with multiple, acute cerebral infarcts in different arterial territories.

	No obvious cause on initial evaluation	Cardiac	Border zone infracts	Hematological	*P* value
	Group 1	Group 2	Group 3	Group 4	
Number of patients	41 (52.6%)	15 (19.2%)	18 (23.1%)	4 (5.1%)	
Average age (years)	66.2 ± 12	74.4 ± 9.8	62.6 ± 11.8	38 ± 12.7	<0.0001
Age range	43–92	53–86	47–85	26–55	
Male	23	6	10	2	NS
Female	18	9	8	2	NS
Diabetes	20 (48.7%)	4 (26.6%)	6 (33.3%)	1 (25%)	NS
Hypertension	38 (92.6%)	12 (80%)	16 (88.8%)	1 (25%)	NS
Cranial and cervical MR angiography (MRA) done	36 (87.8%)	13 (86.6%)	17 (94.4%)	3 (75%)	
Echocardiogram done:	35 (85.3%)	15 (100%)	15 (83.3%)	3 (75%)	
TTE	24	8	12	1	
TEE	11	7	3	2	
Cardiac abnormalities:					
Atrial fibrillation	0	8	0	0	
Acute MI	0	2	0	0	
PFO/ASA	0	1	0	0	
Endocarditis	0	3	0	0	
Aortic dissection	0	1	0	0	
Location of infarcts:					
(i) Carotid circulation of both hemispheres	17 (41.5%)	4 (26.7%)		1 (25%)	NS
(ii) One carotid circulation and vertebrobasilar circulation	5 (12.2%)	5 (33.3%)		1 (25%)	
(iii) Both carotid circulations and vertebrobasilar circulations	19 (46.3%)	6 (40%)		2 (50%)	
Location of infarcts:					
Deep only	22 (53.6%)	0	9 (50%)	1 (25%)	<0.0001
Deep + cortical	16 (39%)	11 (73.3%)	9 (50%)	1 (25%)	
Cortical only	3 (7.3%)	4 (26.6%)	0	2 (50%)	
MRA findings:					
(i) Cervical carotid stenosis/occlusion	0	0	9 (50%)	0	<0.0001
(ii) Intracranial stenosis (>50%)	16 (39%)	9 (60%)	9 (50%)	0	
(iii) Minor irregularities/no stenoses	20 (48.8%)	4 (26.6%)	0	3 (75%)	
	4 mm to 2.5 cm	0.5 to 5 cm	Multiple	2–8 cm	<0.0001
Size of infarcts	<2 cms: 39	<2 cms: 6	small		
	>2 cms: 2	>2 cms: 9	(0.5–1 cm)		

Table 1: Continued.

	No obvious cause on initial evaluation	Cardiac	Border zone infracts	Hematological	*P* value
	Group 1	Group 2	Group 3	Group 4	
Number of infarcts	2-3: 32 patients 4–8: 9 patients	2-3: 6 patients 4–6: 9 patients		2-3: 3 patients 4: 1 patient	NS
Number of patients with chronic small vessel disease seen on MRI FLAIR images	38 (92.6%)	14 (93.3%)	18 (100%)	0	<0.0001
Mean arterial pressure (MAP) (mm Hg)					
At presentation:	101.5 ± 22.6	110.1 ± 23.7	101 ± 96	91 ± 14.4	NS
Number of patients with low or normal BP at presentation	16 of 41 patients had low or normal BP	1 of 15 patients had normal BP	5 of 18 patients had low or normal BP	2 of 4 patients had low or normal BP	
	Subset of 13 patients with pre- and poststroke BP readings available:				
Prestroke (<11 days): At presentation Poststroke (2 weeks):	113.6 ± 11.3 82.9 ± 13.7 128.2 ± 14.3				
	Remaining 25 patients with high BP:				
At presentation	117.6 ± 15.1				

NS: not significant. Hematological causes found: protein S deficiency, lupus-associated coagulopathy, thrombotic thrombocytopenic purpura. Borderzone infarcts were assessed on typical topographic pattern [5, 6] (Figure 1(f)). PFO: patent foramen ovale, ASA: atrial septal aneurysm,

cortical regions in 16 patients (39 percent) (Figures 1(a)–1(e)). As a percentage of all infarcts located in deep regions, infarcts were located in corona radiata/centrum semiovale in 35 percent, putamen/internal capsule in 25 percent, thalamus in 10 percent, pons in 12 percent, cerebellum in 14 percent, and corpus callosum in 4 percent. The size of the infarcts varied from 4 mm to 2.5 cms. Small infarcts (<2 cms) located in deep white matter were significantly more common in Group 1 ($P < 0.0001$) (Table 1). Most patients (80 percent) had 2 or 3 infarcts. 92.6 percent of patients had a history of hypertension and 48.7 percent had a history of diabetes. No patient had evidence of cardiac disease. EKG and echocardiography did not reveal any significant abnormality in any patient. Chart review did not reveal any current or past episode of paroxysmal atrial fibrillation. MR angiography revealed >50% stenosis of intracranial vessels in 16 patients and either a normal study or minor vessel wall irregularities in 20 patients. Abrupt cutoff of arteries suggestive of embolism was not seen. Extensive, chronic small vessel ischemic changes were seen on MRI FLAIR images in 92.6 percent of patients. None of these patients had evidence of malignancy or vasculitis, which have been linked to multiple infarcts [11, 12].

Group 2. All 15 patients (19.3%) had a cardiac embolic source. There were 6 men and 9 women with an average age of 74.4 years, with a range of 53–86 years. Eight patients had atrial fibrillation, 3 patients had endocarditis, 2 patients had acute myocardial infarction, 1 patient had an aortic dissection, and 1 patient had a patent foramen ovale with atrial septal aneurysm. The size of infarcts varied from 0.5 to 5 cms (6 patients had infarcts <2 cms and 9 patients had infarcts >2 cms). Infarcts were located in both deep subcortical white matter and cortical regions in 11 of 15 patients and 4 patients had only cortical infarcts. On MR angiography, 9 of 15 patients had significant stenoses of intracranial vessels and 4 showed minor irregularities. Old cerebral infarcts were seen on MRI FLAIR images in 93.3% of patients.

Group 3 with 18 patients (23.1%) were assessed as being borderzone infarcts based on the typical topographic pattern of infarcts revealed on DWI imaging (Figure 1(f)). There were 10 men and 8 women, with an average age of 62.6 years, with a range of 47–85 years. Infarcts were located in deep subcortical regions in 9 patients and in both deep and cortical regions in 9 patients. On MR angiography cervical carotid stenosis or occlusion was found significantly more commonly than in other groups (9 of 18 patients) and severe intracranial (carotid, MCA, and ACA) stenosis was seen in 9 patients. There were no significant cardiac abnormalities. Old infarcts were seen on FLAIR images in all patients.

Group 4. It had 4 patients (5.1%) with infarcts due to hematological causes (protein S deficiency, thrombotic thrombocytopenic purpura, and lupus associated coagulopathy). There were 2 men and 2 women with an average age of 38 years with a range of 26–55 years. Infarcts were located in cortical

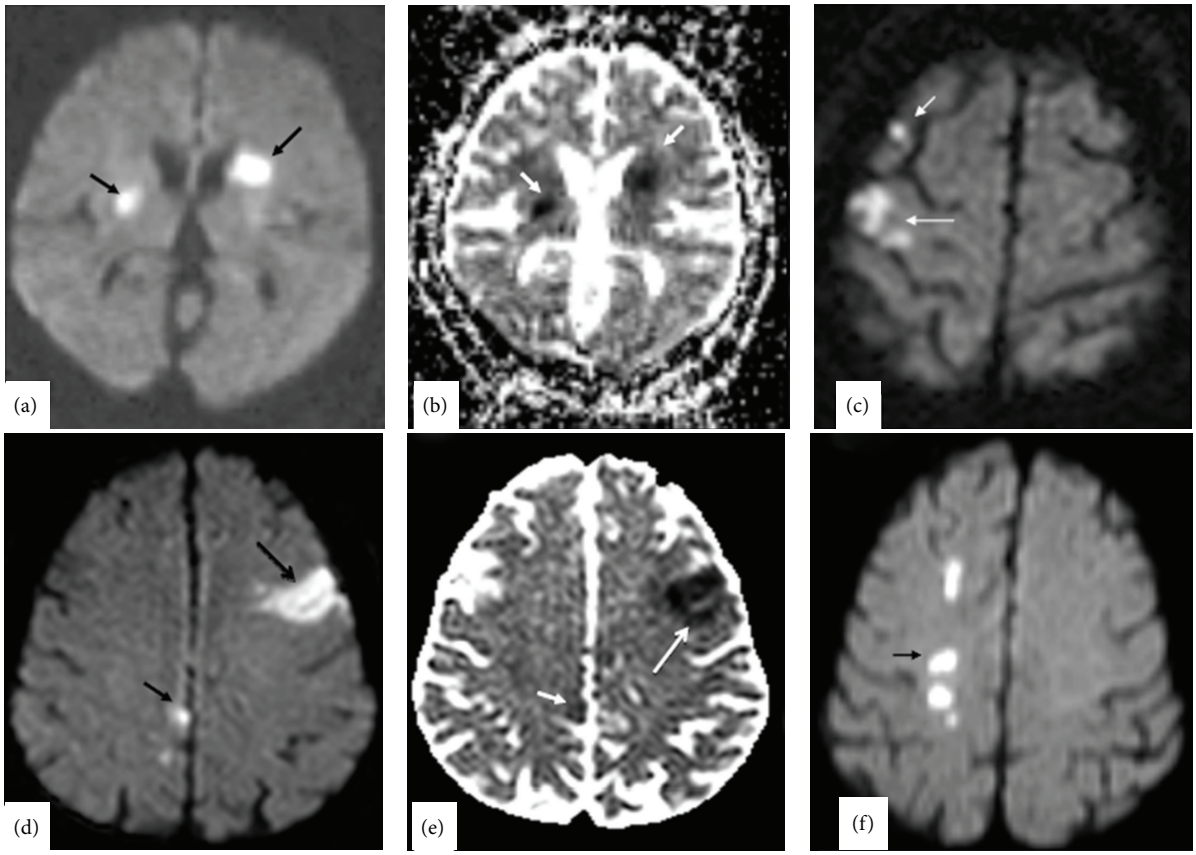

Figure 1: Representative brain MRI (DWI) scans of patients with multiple acute infarcts. (a) and (b) Group 1: *Patient 1*: deep infarcts: left corona radiata and right internal capsule infarcts on DWI and ADC map. Cranial and neck MR angiogram was normal. (c)–(e): Group 1: superficial cortical infarcts. *Patient 2*: (c) right frontal infarcts; the patient also had a small superficial acute infarct in right cerebellum (not shown). *Patient 3*: (d) and (e) left inferior frontal and right cingulate gyrus acute infarctions. MR angiography showed minor irregularities. (f) Group 3: *Patient 4*: representative borderzone infarcts. MR angiography showed severe stenosis in right cavernous internal carotid (not shown).

regions in 2 patients, in both deep and cortical regions in 1 patient, and only deep regions in 1 patient. The size of the infarcts ranged from 2 to 8 ms. EKG and echocardiography were normal and MR angiography was normal in the 3 patients. No patient had old infarcts on MRI FLAIR images.

3.1. ADC Values. The average ADC value of infarcts was $401 \pm 71 \times 10^{-6}$ mm^2/sec (range 242 to 501). In normal white matter, mean ADC value was $862 \pm 65 \times 10^{-6}$ mm^2/sec.

3.2. Clinical Features of Group 1. All patients presented to the emergency room with sudden onset of neurological symptoms. The most common clinical features at presentation were hemiparesis, unilateral facial weakness, hemisensory loss, loss of balance, difficulty walking, or dysarthria (34 patients). Many infarcts were located in clinically silent areas. Seven patients presented with confusion or stupor without obvious focal neurological abnormalities.

3.3. Blood Pressure (BP) at Time of Presentation in a Subset of Group 1 (16 Patients). Sixteen patients, all with a history of chronic hypertension and taking multiple (2–4) antihypertensive medications, had low or normal BP on presentation (initially recorded in the emergency room and then confirmed after admission). These readings were 60/40, 76/43, 97/53, 108/81, 108/65, 115/71, 115/60, 118/65, 121/66, 121/71, 122/83, 127/56, 128/66, 130/87, 132/70, and 132/67 mm Hg. The three lowest readings were in patients with hypovolemia secondary to vomiting/diarrhoea and dehydration.

3.4. Higher BP Readings Preceding Stroke (13 Patients). In 13 of these 16 hypertensive patients, blood pressure recordings were available from clinic visits or in hospital recordings, one to eleven days before the stroke. MAP (calculated as diastolic pressure plus one-third pulse pressure) using the last reading before the stroke was 113.6 ± 11.3 mm Hg. At time of stroke presentation MAP in these patients was 85 ± 11.4 mm Hg, a mean drop of 25.1 percent (range 11 to 44 percent). There was no obvious cause for this fall in BP other than the use of anti-hypertensive medication. Anti-hypertensive treatment was withheld on admission and after 2 weeks BP had increased to above 160/100 (MAP 128.2 ± 14.3 mm Hg).

The remaining 25 patients in Group 1 had BP recordings at presentation in the hypertensive range (MAP 117.6 ± 15.1). Last pre-stroke BP level (in previous 2 to 13 days), available in 6 patients, was slightly higher (MAP 129.2 ± 15.4 mm Hg), indicating a mean drop in BP of 8.9 percent (range 2.8 to 11.6 percent). In Group 2 one patient had normal BP on admission (124/58). In Group 3, MAP was 101 ± 9.6. Five patients had low or normal BP on admission, 100/49, 114/83, 118/68, 126/52, and 123/69 (MAP 81.6 ± 10.4 mm Hg).

4. Discussion

We found a cardioembolic source in 19.2 percent of patients with multiple cerebral infarcts, within the range reported previously, 15–25 percent, for detecting a cardioembolic source in all ischemic strokes [13]. Previous studies focusing on multiple, acute brain infarcts [14–22] have reported widely variable results, attributing infarcts to an embolic source in 28 to 100 percent, with a cardiac or aortic source found in 18 to 52 percent of patients. In these studies, however, a large proportion (27 to 40 percent) of multiple infarcts have been linked speculatively, to emboli from proximal large artery stenotic lesions [14–22]. However, it is implausible that emboli could arise near simultaneously from different proximal arteries or traverse from one proximal artery to circulations in both hemispheres or from carotid to vertebrobasilar circulation. Emboli are also unlikely, as has been shown by injecting microspheres into carotid arteries of monkeys, to selectively occlude deep penetrating arteries [23]. Data on blood pressure at the time of stroke onset was not provided in any of these studies [14–22]. Only one previous study [24] which reported multiple, small, deep subcortical infarcts in most patients found no embolic source in 9 of 10 patients. In contrast to our study, MRI scans were done an average of 17 days after onset and the authors suggested that infarcts had occurred over several weeks. They proposed a diffuse intrinsic microvascular abnormality as a putative mechanism.

In this study in 41 patients (53% of all patients with multiple infarcts) in Group 1, clinical evaluation, electrocardiograms, cardiac monitoring, and echocardiograms did not reveal any cardiac disease or arrythmias and there was no evidence of a hypercoagulable state or vasculitis. Although TEE, which is superior to TTE in detecting some cardiac embolic sources, was not done in all patients, it is unlikely that cardiac embolic sources were undetected because previous studies have shown that TEE is unlikely to reveal any abnormalities when there is no clinical evidence of cardiac disease and TTE is negative, as in all Group 1 patients [25, 26]. Aortic atheroma is also an unlikely embolic source in our study because none of the 24 patients (in all groups) who underwent TEE in our analysis had evidence of complex aortic atheromas [27], and no patient had evidence of concurrent systemic embolism.

Although the unlikely possibility that the responsible embolus had fragmented and disappeared completely by the time of cardiac evaluation cannot be definitively excluded, we attempted to determine whether there were alternative explanations for the multiple infarcts in Group 1 patients. Transient drop in BP is known to occur in hypertensive patients secondary to orthostasis, nocturnally, post prandially, or following changes or erratic use of anti-hypertensive medications. Brief drops in blood pressure may be significant, as cessation of blood flow, even for a few minutes, can cause infarction of brain tissue. A careful examination of the blood pressure readings showed that 16 of these 41 patients, all of whom were chronically hypertensive and most (93%) with MRI FLAIR evidence of extensive, preexisting chronic small vessel ischemic changes, had low (<120/80 mm Hg) or normal blood pressure at the time of initial presentation with a stroke. Since, typically, a reactive elevation in BP is known to occur following cerebral infarction [28], the low BP at presentation in our patients was paradoxical and likely to be significant. Although all patients were on multiple antihypertensive medications, the chart review did not allow us to establish a definitive cause for the drop in BP in most patients.

One limitation of this retrospective study is the lack of blood pressure data in the immediate time period (minutes to hours) preceding an infarct as all BP recordings were initially taken on arrival at the emergency room. Therefore, although a definitive causal relationship between infarcts and BP levels cannot be made, markedly higher BP readings, within the 2-week period both *before* and *after* the infarct in 13 patients, emphasize the higher baseline BP levels and the likely importance of the recorded drop in BP. Another limitation is the small number of patients (13 of 78, ~17% of all patients with multiple infarcts) in whom the most detailed BP data, including prestroke on presentation with stroke and poststroke, was available. However, these patients may be significant, possibly indicating an important causal factor. We reason that in most of these patients (13 of 16) the drop in BP was not sufficient to result in diffuse cerebral ischemia and syncope or near syncope. We emphasize that unlike the patients described above, the majority of Group 1 patients (~61%) had high BP (MAP 117.6 ± 15.1) on initial presentation. The cause of the multiple infarcts in these patients remains unclear.

Chronic hypertension, age, and diabetes result in remodeling of cerebral arteries and arterioles, increase in wall thickness, and impaired vasomotor reactivity [29, 30]. The autoregulatory curve is thus shifted to the right, and higher systemic BP is required to maintain adequate cerebral blood flow. One study suggests that in chronically hypertensive patients, cerebral blood flow decreases when MAP falls below 113 ± 7 mm Hg [31], significantly higher than the level of 60 mm Hg which is required to maintain adequate perfusion in normotensive individuals. The deep brain structures (white matter and deep gray nuclei) are supplied by perforating arteries that are end arteries. Similarly, although the pial arachnoid circulation on the surface of the brain is connected by anastomoses, once pial arteries and arterioles turn to enter the superficial brain parenchyma they are end arteries [32, 33]. All infarcts in the 41 Group 1 patients (including the 13 patients, in whom the most detailed BP data was available) were located in these two areas, which are especially vulnerable to ischemia (Figures 1(a)–1(e)). The arterial pathology and stenosis responsible for these infarcts are likely to be located in the small arteries and arterioles (less

than ~800 μm diameter) which are below the size which can be visualized angiographically.

By comparison 18 of 78 patients (24%) had typical borderzone infarcts [5, 6] (Group 3), which are well known to occur secondary to decreased perfusion. However, as is typically found in such patients, these patients had severe ipsilateral large vessel stenosis [5, 6]. This suggests that the pattern of infarction triggered by hypoperfusion may be determined by the predominant site of severe stenosis; whether it is located proximally in the large arteries, leading to borderzone infarcts as in Group 3 patients (Figure 1(f)), or distally in small end arteries, leading to small infarcts in the territory supplied by these arteries, as in Group 1 patients (Figures 1(a)–1(e)).

Older clinicopathologic studies of patients resuscitated after cardiac arrest [34] or severe hypotension [35] have reported that hypotensive episodes are not a major cause of cerebral infarction. However, in these studies most patients were either young (<45 years) [35] or had little evidence of severe occlusive vascular disease [34, 35] and moreover, since imaging data was not available, many smaller infarcts may have been missed. In more recent studies assessing the possible effects of tight blood pressure control, it has been reported that the risk of stroke is favorably influenced by low normal (taken as <130 mm Hg) systolic BP [36, 37]. However, this may reflect the fact that most of these patients did not have established symptomatic cerebrovascular disease [38]. In contrast, and in support of our findings, recent studies on stroke risk reduction after aggressively targeting systolic blood pressure in high-risk patients, to below 120 mm Hg [39] or 130 mm Hg systolic [40], suggest no benefit [39] or even harm [41]. In addition, a post hoc observational analysis of 20330 patients with recent noncardioembolic ischemic stroke and systolic BP levels during followup in the low normal (<120 mm Hg) range was associated with an increased incidence of recurrent stroke [38].

In conclusion, although lowering BP in hypertensive patients is of paramount importance to reduce atherosclerotic complications and stroke incidence, the immediate consequence of transient drops in BP may occasionally decrease perfusion in vulnerable areas and possibly infarction. Our study suggests that (a) in a minority of patients (~20% of all patients with multiple acute infarcts in this study), who are already at very high risk because of age, diabetes or hypertension, and severe, chronic small vessel disease (detected on MRI FLAIR images as bilateral, extensive, and confluent periventricular white matter hyperintense lesions), small cerebral infarcts may sometimes occur secondary to a drop in blood pressure; (b) the severity and rate of drop in blood pressure from previous even higher levels may be even more important than the recorded BP on presentation which may, sometimes, still be in the normal range; (c) brain regions minimally perfused through severely stenotic end arteries would be at the greatest risk of infarction during this period of hypoperfusion, which, we speculate, may be brief lasting only a few minutes; (d) cardiac and aortic sources for emboli should first be excluded in all patients with multiple acute infarcts before considering decreased perfusion due to a fall in BP as a causative mechanism. Larger studies to confirm these findings are warranted. Finally we note that the recently proposed phenotypic approach to stroke subtyping, which considers *all* underlying diseases and is based on assessment of atherothrombosis (A), small vessel disease (S), cardioembolism (C), or other causes (O) [41], may provide very useful data for future studies if serial blood pressure data is also included in the evaluation.

Conflict of Interests

The authors declare no conflict of interests.

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