Cerebral aneurysms (CA) are vascular out-pouches that most commonly occur at the branching sites of cerebral arteries, usually around the Circle of Willis. Up to 5% of the world’s population is estimated to harbor CA. Although most CA go unnoticed, initial symptoms are usually caused by sudden rupture, causing subarachnoid hemorrhage (SAH). SAH can be devastating; half of those with SAH die within a year, and perhaps only ≈10% of survivors are functionally and neuropsychologically normal. Given these outcomes, recent interest has focused less on the treatment of SAH and more on prevention of hemorrhage.

A fundamental step in tackling the broad problem of SAH is to understand the determinants of CA formation and rupture. In a study comparing the prevalence of hypertension in 20767 Medicare patients with unruptured CA to a random sample of the hospitalized Medicare patients, hypertension was found in 43.2% of patients with unruptured CA compared with 34.4% in the comparison group. Hypertension was also found to be an independent risk factor for future aneurysm rupture in patients with unruptured aneurysms (risk ratio, 1.46; 95% confidence interval, 1.01–2.11). Thus, current thinking is that chronic hypertension is a strong modifiable risk factor for both CA formation and subsequent (and often deadly) rupture.

It has long been speculated that an acute increase in systemic arterial pressure is the ictus that results in an increase in intra-aneurysm blood pressure, an increase in aneurysm wall tension, and rupture. However, the relationship between an acute increase in systemic blood pressure and intra-aneurysm pressure has not been studied directly. If acute increases in systemic blood pressure result in equivalent changes within the aneurysm, then patients with known unruptured aneurysms (1) might be reasonably advised to avoid activities that increase blood pressure (eg, exercise, sex); (2) be pretreated with antihypertensive agents before such activities; and (3) consider treatment of the aneurysm to prevent future aneurysm rupture during surges of blood pressure. Alternatively, if acute increases in systemic blood pressure do not result in equivalent changes within the aneurysm, acute transient hypertension per se may not greatly increase the likelihood of aneurysm rupture.

Abstract—Formation and rupture of cerebral aneurysms have been associated with chronic hypertension. The effect of transient increase in blood pressure and its effect on intra-aneurysmal hemodynamics have not been studied. We examined the effects of controlled increases in blood pressure on different pressure parameters inside the sac of human cerebral aneurysms and corresponding parent arteries using invasive technology. Twelve patients (10 female, 2 male, age 54±15 years) with unruptured cerebral aneurysms undergoing endovascular coiling were recruited. Dual-sensor microwires with the capacity to simultaneously measure flow velocity and pressure were used to measure systolic, diastolic, and mean pressure inside the aneurysm sac and to measure both pressures and flow velocities in the feeder vessel just outside the aneurysm. These pressures were recorded simultaneously with pressures from a radial arterial catheter. Measurements were taken at baseline and then during a gradual increase in systemic systolic blood pressure to a target value of ≈25 mm Hg above baseline, using a phenylephrine infusion. The dose needed to achieve the required increase in radial arterial systolic blood pressure was 0.8±0.2 μg/kg/min. There was a clear linear relationship between changes in radial and aneurysm pressures with substantial patient-by-patient variation in the slopes of those relationships. The overall increases in systolic and mean pressures in both radial artery and in the aneurysms were similar. Pressures in the aneurysm and in the parent vessels were similar. Peak and mean flow velocities in the parent arteries did not change significantly with phenylephrine infusion, nor did vessel diameters as measured angiographically. (Hypertension. 2015;66:00-00. DOI: 10.1161/HYPERTENSIONAHA.115.05500.)

Key Words: blood pressure ■ diastole ■ intracranial aneurysm ■ phenylephrine ■ pulse pressure
Accordingly, the aim of this study was to establish the relationship between systemic arterial pressure (radial artery) and intra-aneurysm pressure in patients with unruptured intracranial aneurysms.

Methods
The protocol for this prospective observational cohort study was approved by the University of Iowa Institutional Review Board, and informed written consent was obtained from each subject. Twelve adult patients with previously diagnosed unruptured intracranial aneurysms were studied during elective endovascular treatment of their aneurysms. Exclusion criteria included polycystic kidney disease or renal dysfunction, hypotension (any systolic blood pressure [SBP] <90 mm Hg within 2 months of the procedure), and any condition where induction of hypertension would be considered to be potentially dangerous (eg, aneurysm of the ascending, thoracic, or abdominal aorta, any history of prior ischemic or hemorrhagic cerebrovascular event, or any cerebral arterio-venous malformation).

During each procedure, a dual-sensor, pressure and Doppler velocity guidewire (ComboWire; Volcano Corporation, Rancho Cordova, CA), and workstation (ComboMap, Volcano) were used to measure changes in intra-aneurysmal pressure. The tip of the 0.4 mm wire contains a piezoresistive pressure sensor and piezoelectrode Doppler device that emits a 45º sonography beam that measures blood flow velocity ≥5 mm beyond the tip. The tip of the microwire was introduced via the femoral artery and was sequentially placed as follows: (1) in the parent cerebral artery (just outside the aneurysm) at baseline systemic blood pressure; then (2) inside the aneurysm dome at baseline systemic blood pressure. The guidewire was then maintained inside the aneurysm throughout the period that systemic blood pressure was increased (see below). Finally, (3) after the target systemic pressure was reached and recording inside the aneurysm dome was completed, the tip of the microwire was withdrawn and placed exactly at the previous location in the parent artery (Figures 1A–C).

After these measurements, the protocol was complete and, the aneurysms were treated as deemed appropriate by the attending surgeon (D.M. Hasan).

Anesthesia Protocol
Before induction of anesthesia, systemic blood pressure was recorded using a noninvasive blood pressure cuff. All patients were monitored with standard noninvasive cardiovascular, respiratory, temperature, and neuromuscular blockade monitors. Patients received a standard-ized general anesthetic, induced with intravenous lidocaine (0–1.1 mg/kg), fentanyl (0–1.7 μg/kg), and propofol (1.1–2.2 mg/kg). Oral endotracheal intubation was facilitated with skeletal muscle relaxation induced by intravenous rocuronium (0.3–0.6 mg/kg). Anesthesia was maintained with sevoflurane in 50% oxygen/50% nitrogen, and mechanical ventilation was adjusted to maintain end-tidal PCO₂ at 35 to 39 mm Hg. After induction, but before study measurements, patients could receive intravenous phentolamine and ephedrine (but no other agent) to maintain systemic arterial pressure at clinically desired levels. However, before recording of baseline (prephenylephrine infusion) arterial pressures, no vasopressor was allowed for at least 5 minutes. Likewise, end-tidal sevoflurane concentration was within the range of 1.3% to 1.7% for at least 5 minutes before baseline pressure measurements. Systemic arterial pressure was continuously measured via a 20 gauge catheter in a radial artery connected to a fluid-filled electronic pressure transducer, interfaced with an Ohmeda S5 Anesthesia monitoring system. The pressure transducer was zeroed at the level of the external auditory meatus. Output from the systemic blood pressure monitoring system was interfaced with the microwire cerebrovascular pressure and flow recording system (Volcano), allowing simultaneous time-synchronized recording of systemic and aneurysm blood pressures.

Preinfusion baseline systemic (radial) and cerebrovascular arterial pressures were obtained with stable values of end-tidal sevoflurane and end-tidal PaCO₂. These did not change during the period of phenylephrine infusion. During the phenylephrine infusion period, no other agent was administered except for a small dose (5 mg) of rocuronium in 2 patients. After recording preinfusion baseline pressure values, a continuous intravenous phenylephrine infusion (100 μg/mL) was started at a rate of 0.2 μg/kg/min, delivered via a constant flow carrier intravenous line (100 mL/min). The phenylephrine infusion rate was increased in increments of 0.1 μg/kg/min at 1 minute intervals until either (1) a target radial systolic pressure 25 mm Hg greater than baseline was reached; or (2) a maximum phenylephrine infusion of 1.0 μg/kg/min had been administered for 1 minute. After the target radial systolic pressure was attained, the phenylephrine infusion rate was adjusted (decreased) to maintain systolic pressure at the target value for all subsequent study measurements. With completion of systemic and cerebrovascular pressure measurements, the protocol was completed and subsequent patient management was directed by the assigned clinical providers.

Comparisons between pressures measured in different locations and between changes in pressures (baseline versus target) were made using paired t-tests. The slopes and intercepts of the radial arterial pressure versus intra-aneurysm pressure (as well as versus parent artery pressure) were calculated using simple linear regression, based on all pressures measured during the graded phenylephrine infusion (not simply baseline versus target).

Results
Patients and Aneurysm Demographics
As summarized in Table 1, 12 patients were enrolled in the study (10 females, 2 males). They had an average age of 54 years (range 33–74). Eleven aneurysms were located in the anterior cerebral circulation and one in the posterior circulation. The average largest diameter of the aneurysms was 8 mm (range, 3–25 mm).

Changes in SBP, Diastolic Blood Pressure, Mean Arterial Pressure, and Pulse Pressure
Preinduction SBP (cuff) ranged between 120 and 180 mm Hg (152±18 mm Hg, mean±SD). During anesthesia, preinfusion baseline systemic (radial) SBP ranged between 86 and 128
mm Hg (107±15 mm Hg). End-tidal sevoflurane concentration (1.4±0.2%) and end-tidal PaCO₂ (36±3 mm Hg) did not differ between preinfusion baseline and target blood pressure conditions. Target systemic systolic (radial) pressure was attained in all patients with phenylephrine infusion rates between 0.4 and 1.0 μg/kg/min (average 0.8±0.2 μg/kg/min), over a period of 4.0 to 9.25 minutes. In no patient did the target radial systolic pressure exceed the preinduction SBP, and there were no study-related (or treatment-related) adverse events.

Table 2 summarizes the changes in systemic hemodynamic parameters and their corresponding changes in the feeder artery and intra-aneurysmal, and Figure 2 shows pressure recordings at baseline and target conditions for a representative patient. Systolic pressures were greater in the radial artery than in either the feeder or the aneurysm, both at baseline and at target, except in one patient (see below). The differences in diastolic and mean pressures in radial versus feeder versus aneurysm were minimal. Pressures in the aneurysm sac and in the feeder vessel were essentially identical during baseline and target conditions. Relative changes in all pressures (target versus baseline) did not differ statistically (eg, radial artery systolic pressure increased by 27.3%±6.4%, compared with an increase in intra-aneurysmal systolic pressure of 31.0%±9.7%). There were no differences in radial versus intra-aneurysmal absolute pulse pressure (PP) changes (15±4 mm Hg versus 13±6 mm Hg respectively) nor in the relative changes (a 33.2%±9.3% increase in the radial artery versus 45.7%±26.5% in the aneurysm).

Within each individual patient, the relationship between radial and intra-aneurysmal pressures (as well as radial and parent vessel pressures) was highly linear (r²>0.9 for each). However, the slopes and Y-intercepts of these relationships varied substantially from patient to patient. For example, for systolic pressure, individual slopes varied between 0.65 and 1.48 mm Hg/aneurysm/mm Hg radial systolic (mean slope

<table>
<thead>
<tr>
<th>Location of Measurement</th>
<th>Time of Measurement</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
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<tr>
<td></td>
<td>Radial</td>
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<td>Pressures, mm Hg</td>
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<tr>
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<tr>
<td>Diastolic</td>
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<tr>
<td>Mean</td>
<td>79±14</td>
</tr>
<tr>
<td>Pulse Pressure</td>
<td>46±9</td>
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All values are mean±SD. Feeder refers to the parent artery just outside the neck of the aneurysm. Aneurysm refers to a location inside the dome of the aneurysm. Both Feeder and Aneurysm pressures were made using the microwire system. Radial pressures were made using a fluid-filled tubing/transducer.
The changes in radial arterial pressures and corresponding changes in arterial pressures both in the parent vessels and within the sacs of CA. Although starting at different absolute values, acute changes in systemic arterial pressures result in nearly equal changes in arterial pressures inside CA. Because the absolute pressure values in the feeder vessel and within the aneurysm are so similar, it is likely that intra-aneurysmal pressures are determined directly by changes in hemodynamics within the Circle of Willis. Finally, neither angiographically determined diameters nor flow velocities within feeder vessels changed with changes in arterial pressure during the infusion.
of phenylephrine (ie, no observable direct vasoconstriction was apparent).

This study was designed to as a prospective observational cohort. The connection between these findings and the hemodynamics associated with aneurysm rupture—or in the longitudinal growth of aneurysms—is unknown. Nevertheless, the finding that intra-aneurysmal pressures follow systemic arterial pressures is consistent with the concern that hypertension, in particular, acute hypertension, will increase both intra-aneurysmal pressures and hence result in an increase in stress seen by the aneurysmal walls. What role this plays in aneurysm formation, growth, or rupture—as distinct from other processes, such as inflammation—remains to be determined. These findings are, perhaps, not surprising because all pressures within the peripheral arterial circulation should track changes in central pressures. Nevertheless, the direct documentation of this relationship in human intracranial aneurysms and the demonstration that there is substantial variation from patient to patient has not been reported previously.

**Differences Between Systemic and Intra-Aneurysmal Pressure Changes**

Pressure differences between intracranial feeder arteries and aneurysms were consistently small (3–5 mm Hg systolic and 2–3 mm Hg mean). However, in contrast, the absolute difference between intra-aneurysmal (and parent artery) systolic pressures and systemic (radial) arterial were much greater (eg, 14–19 mm Hg at target radial pressures). This is, perhaps, expected. In our study, simultaneous pressure differences between parent arteries and radial arteries were quantitatively similar to those observed between central aortic and radial arterial pressures reported by Pauca et al. Augmentation of distal arterial systolic pressure and PP is a well-known phenomenon, which is determined, at least in part, by vascular geometry and vascular stiffness. Because vessels in the Circle of Willis are much closer to the central circulation, they would be expected to be less susceptible to pulse-wave summation. The more important observation is that changes in pressure measured in all locations were similar.

We did encounter one apparent exception to this pattern. In Patient 11, systolic and mean pressures in both the parent vessel and within the aneurysm were consistently greater than in the radial artery. This was the oldest patient in our sample (80 years), who also had the largest aneurysm, and the 2nd largest diameter parent vessel (5.1 mm). She also was sensitive to phenylephrine, reaching target pressures at a dose of only 0.6 μg/kg/min, had the highest target pressure (>170 mm Hg) in the study, and had the second steepest slope in the radial systolic versus aneurysmal systolic pressure relationship. Whether this pattern was the result of greater generalized vascular stiffness or, perhaps, pulse-wave reflectance/summation within the carotid artery, Circle of Willis, or within the aneurysm, is unknown. It does suggest that there may be individuals in whom systemic hypertension may be associated with an exaggerated increase in intra-aneurysmal pressures.
Chronic Hypertension and Cerebral Aneurysms

The role of chronic hypertension in CA formation and rupture is not well defined. Few authors would consider chronic hypertension as a modifiable risk for SAH secondary to ruptured CA.\(^{11-17}\)

Others suggested that although chronic hypertension may be a risk factor for CA formation, its association with the rupture of these aneurysms is unlikely.\(^ {18-20}\) Their suggestion is supported by the fact that prevalence of hypertension among SAH patients seems to be only slightly higher than in the general population.\(^ {12,13,15}\) In a prospective study, hypertension, defined as blood pressure >160/95, was a risk factor for SAH.\(^ {14}\) But, when one adjust for age, sex, cigarette smoking, and alcohol consumption, history of chronic hypertension was not significant for increased risk for SAH.\(^ {12,15}\)

In the opposite, 2 other studies alluded to the fact that chronic hypertension was associated with increased incidence of multiple aneurysms formation.\(^ {21,22}\) One study found that chronic hypertension was an independent risk factor for multiple aneurysms formation with a prevalence of 18% of their study population had multiple aneurysms.\(^ {21}\) In a second study, chronic hypertension and multiple aneurysms were only found in patients aged ≤55 years.\(^ {22}\)

Evidence from human and animal studies suggests that chronic hypertension is associated with inflammation.\(^ {23-25}\) As to whether hypertension activates the inflammatory cascade or vice versa is not well understood. However, Aoki et al elegantly showed that hemodynamic stress activates PGE\(_2\)-EP\(_2\) signaling in the endothelial cells and leads to CA formation.\(^ {26}\)

Transient Increases in Systemic Blood Pressure and CA

The literature is sparse on the association of transient increases in systemic SBP and aneurysm rupture. Are these increases the inciting event that leads to acute aneurysm rupture? If so, how much of an increase is sufficient to fatigue the aneurysm wall and lead to rupture? Our study does not provide any insights.

Pulse Pressure and Cerebral Aneurysms

One consistent observation in our study was that an increase in arterial pressure was associated with an increase in arterial PP (arterial PP=systolic−diastolic) both in the radial artery and within the aneurysm. Although the absolute increases were similar in the 2 locations, the percentage change was numerically (although not statistically) greater in the aneurysm (46% increase versus 33% in the radial artery). Cardiovascular disease, which is increasingly being viewed as an inflammatory disease, has been associated with elevated systemic PP.\(^ {27}\) Inflammation is postulated as a possible mechanism underlying the link between elevated PP and cardiovascular disease. Several recent studies suggested that increases in PP are associated with elevated C-reactive protein levels,\(^ {27}\) elevated levels of reactive oxygen species,\(^ {28-30}\) and increase in the expression of adhesion molecules,\(^ {28,31,32}\) which would tend to promote the inflammatory process involved in atherosclerosis. If the link between PP and cardiovascular disease risk is indeed mediated by inflammation,\(^ {27}\) one might hypothesize that aneurysms that exhibit supranormal changes in intra-aneurysm pressure in response to changes in systemic pressure may, in fact, show evidence of increased local (aneurysm) inflammation. It is now possible to measure inflammation in the wall of CA using ferumoxytol–magnetic resonance imaging.\(^ {33-40}\) In this imaging technique, increased signal in T2\(^ *\) magnetic resonance imaging sequence corresponds to increased uptake of ferumoxytol nanoparticles by macrophages within the wall of CA.\(^ {33-40}\) Using this technique, it should be possible to determine whether increased aneurysmal inflammation is associated with increased intra-aneurysm PP and, thereby, increased potential for acute rupture.

Aneurysm Size and Changes in Systolic and Pulse Pressures

Recent studies showed that even smaller aneurysms (<10 mm) tend to grow (10% to 15%) and possibly rupture.\(^ {41-43}\) Why some smaller aneurysms may grow and others stay stable is unknown? A potential explanation is the variability of these aneurysms in their response to changes in hemodynamic stress (Figures 4B and 5B). Aneurysms with higher PPVI and systolic pressure vulnerability index maybe more prone to grow and possibly progress to rupture. Future studies are needed to confirm this observation and, if verified, to determine the vascular biology of these aneurysms.

Another point of interest would be to suggest that congenital anomalies of the cerebral circulation (such as azygous arteries, fetal origin of arteries, and fenestration) and major occlusion of the cervical internal carotids lead to changes in the flow dynamics and increase shear wall stress. These changes may increase the risk of aneurysm formation and rupture of small aneurysms.

Peak and Mean Flow Velocities in Cerebral Arteries

No changes in peak and mean flow velocities in the parent arteries were observed by recordings using dual sensor microwire during phenylephrine-induced increases in systemic SBP. Because neither flow velocity nor diameter changed, we can conclude that cerebral blood flow also did not change, indicating that (1) these studies were performed within normal autoregulatory ranges and (2) phenylephrine did not induce any detectable degree of cerebral vasoconstriction.

Clinical Implications

The current study suggests that efforts to prevent or limit transient increases in systemic blood pressure using antihypertensive medications and modification of lifestyle may be warranted in patients with asymptomatic unruptured and untreated CA. The observation in one patient (patient No. 3) suggests that there may be a subpopulation of patients with exaggerated aneurysmal pressure responses that would be particularly prone to rupture.

Future studies are needed to confirm this observation and, if verified, to determine the vascular biology of these aneurysms.

Perspective

We demonstrated using invasive technique the relationship between changes in systemic hemodynamic parameters and corresponding hemodynamic changes in the sac of human CA.
Conclusions

There is a close linear relationship between changes in systemic (radial) arterial pressure and intra-aneurysmal pressures. Although the characteristics of this relationship vary from patient to patient, overall, the absolute changes in radial artery and intra-aneurysmal pressure are similar. Changes in peak and mean flow velocities were not significant in parent arteries with increased systemic SBP using phenylephrine.

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Disclosures

None.

References


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**Novelty and Significance**

**What Is New?**

- This is the first invasive study to correlate transient changes in systemic hemodynamic stress to changes in intra-aneurysmal and their parent arteries.

**What Is Relevant?**

- There is a close linear relationship between radial and intra-aneurysmal pressures in individual patients, but with substantial patient-to-patient variation. However, overall the proportional changes in pressures were similar.

**Summary**

- Changes in peak and mean flow velocities were not significant in parent arteries with increased systemic systolic blood pressure using phenylephrine.

This study demonstrates a direct relationship between systemic hemodynamic changes and corresponding changes within the sac of cerebral aneurysm using invasive technique.
Pressure Changes Within the Sac of Human Cerebral Aneurysms in Response to Artificially Induced Transient Increases in Systemic Blood Pressure
David M. Hasan, Bradley J. Hindman and Michael M. Todd

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