**Letters to the Editor**

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**Coxiella burnetii and Atypical Respiratory Infectious Burden in Stroke**

To the Editor:

We have previously reported the seroprevalence of 3 common atypical respiratory pathogens, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*, in case-control studies involving an elderly cohort of stroke/transient ischemic attack (TIA) and medical patients.1 We concluded that the risk of stroke/TIA appeared to associate with the aggregate number of chronic infectious burden of these atypical respiratory pathogens.1

We have now determined the seroprevalence (immunoglobulins, IgG and IgM) of *Coxiella burnetii*, another well-recognized atypical respiratory pathogen in this same cohort of patients. Using commercial enzyme-linked immunosorbent assay (ELISA) kits (PANBIO Ltd), the seropositivity of *Coxiella burnetii* IgG was found in 2 (2.4%) out of the 85 ischemic stroke/TIA cases, and none in the 84 control subjects. None of the 85 cases and 3 (3.6%) of the 84 control subjects were seropositive for *C burnetii* IgM. With such sparse data and zero counts (ie, 0/84 and 0/85), we were unable to estimate any meaningful relative risk; therefore, it was impossible to make any conclusion about association between *C burnetii* infection and stroke.

Nevertheless, the current *Coxiella burnetii* in Elderly Patients with Stroke (C-BEPS) study served as a pilot seroepidemiological survey of *C burnetii* infection in hospitalized elderly stroke/medical patients. Previous studies in the United Kingdom reported a *C burnetii* IgG seroprevalence of 15% to 27% in farm workers, and 4% to 11% in people working in nonfarming sectors.2 We were unable to obtain more detailed occupational/farming history in our cohort retrospectively. Asymptomatic infection or false seropositivity was a possibility. According to the manufacturer’s data, *C burnetii* ELISA had a sensitivity, specificity, and agreement of 72.2%, 100%, and 79.6%, respectively, for IgG, and 97.1%, 84.4%, and 89.8%, respectively, for IgM, when tested against the immunofluorescence reference method. ELISA had been recognized as a useful tool for seroepidemiological studies.1,2

Various microorganisms may contribute to atherogenesis and atherothrombosis through inflammatory/immunological mechanisms.1,4 Among these, *C pneumoniae* is the one most investigated and implicated in the infectious hypothesis of atherosclerosis, an acknowledged inflammatory disease.1,4 Like *C pneumoniae*, *C burnetii* is a Gram-negative, intracellular bacterium that may result in chronic infection and exert a chronic immunological response.1–6 Furthermore, *C burnetii*, *C pneumoniae*, *M pneumoniae*, and *L pneumophila* are all atypical respiratory pathogens that share similar microbiological and clinical features, including vascular inflammation and neurological manifestations.1–3,5,6 Indeed, *C burnetii* infection was reported to associate with cerebrovascular and ischemic heart diseases.6

If the infectious hypothesis of atherosclerosis holds true, it is likely that a large but specific group of microorganisms (specific infectious burden), rather than a selected few, will be discovered to be involved in atherogenesis and atherothrombosis. This concept has implication in the design of future antimicrobial interventional clinical trials in stroke and other atherosclerotic vascular diseases, because subjects infected with a specific infectious burden may be identified and randomized to receive specific antimicrobial/therapeutic agents or even vaccines. Atypical respiratory pathogens can cause up to 50% of cases of community-acquired pneumonia,1 in addition to other systemic manifestations. The development of effective vaccination program in future is becoming a pressing public health issue that will not only prevent atypical respiratory infection but also may clarify if the infectious burden has a causal relationship with stroke and other atherosclerotic vascular diseases.

**Acknowledgments**

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**High-Frequency Transtemporal Sonothrombolysis**

To the Editor:

Clinical trials in the field of transcranial ultrasound thrombolysis used 2-MHz Doppler devices. Available in vitro and animal studies only used ultrasound frequencies in lower ranges. In this context the highest evaluated frequency was 1 MHz,1–4 which was less sufficient when compared with lower frequencies in the kHz range.1,2,5 In our study, ultrasound with a maximum acoustic intensity of 0.72 W/cm² (Food and Drug Administration limit) was used. Clots were focused with B-mode, which was then switched off, and sonication was performed only with 1.8-MHz Doppler ultrasound. The goal was to evaluate if high-frequency ultrasound can lyse clots after temporal bone passage.

Under optimal insonation conditions, up to 10% of the original energy might affect the target. Whether this amount of energy is enough to initiate prothrombolytic processes around the clots surface or at the endothelium cannot finally be answered because our in vitro model cannot mimic endothelium functions and, second, ultrasound impact was analyzed under diffusion condi-
tions. The study revealed that temporal bone attenuated the ultrasound beam significantly so that the thrombolytic effect was lost. According to our data, only 10% of the maximum output intensity hits the thrombus, which comes to an effective energy of ~0.07 W/cm². Data concerning comparatively low levels of energy and their effects on thrombolysis are rare. Kimura et al. showed a significant effect of continuous ultrasound with an intensity of 0.07 W/cm² plus recombinant tissue plasminogen activator, but they used a lower frequency (300 kHz). Recently Basta et al. specifically focused on this problem. They used continuous 2.5-MHz ultrasound with an effective acoustic intensity of 0.099 W/cm². Thereby ultrasound thrombolysis (plus recombinant tissue plasminogen activator, aspirin, heparin) was only effective in clots of coronary artery disease patients when compared with healthy subjects. The authors speculate that this effect was likely caused by chronic use of aspirin and heparin in coronary artery disease patients. We therefore conclude that the effect of high-frequency ultrasound under conditions mimicking reduced flow or constant pressure remains to be evaluated. Apart from this area of vagueness, a major influence of 2-MHz transcranial ultrasound on thrombolysis seems to be questionable, which is supported by clinical findings and cited in vitro studies.

Another study goal was to prove if ultrasound impact can be simply calculated without the effort of studies. We found that calculations implementing ultrasound parameters and tissue barriers were comparable to experimental findings. This suggests that further studies in this field might benefit from extensive calculations. The still remaining key question about crucial ultrasound parameters and their effects on human tissues therefore might be clarified before studies or might at least enable a more efficient selection. However, many biological parameters or tissue-specific constants are not available and deserve attention. For example, what effect is exerted by continuous diagnostic Doppler sonication on human brain tissue when applied over 1 hour? Can negative side effects really be excluded? More basic studies in this field are essential to adapt ultrasound parameters properly. If sonication with ultrasound frequencies lower than 2 MHz might exert the desired impact on thrombolysis remains to be investigated.

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The Risk and Benefit of Endarterectomy In Women With Symptomatic Internal Carotid Artery Disease

To the Editor:

We read with interest the recent article by Alamowitch et al. on the risk and benefit of endarterectomy in women with symptomatic internal carotid artery disease. Whereas women and men with ≥70% symptomatic stenosis had a similar benefit from a carotid endarterectomy, women with 50% to 69% stenosis did not benefit from the procedure. The 30-day perioperative risk of death was 2.3% in women and 0.8% in men, and the combined risk of stroke and death was 7.6% in women and 5.9% in men. Because the data for this study were taken from the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the conclusions must be understood with the design of the NASCET study that involved 50 clinical centers in North America. Patients with high-grade stenosis were enrolled and randomized from January 1988 to February 1991. The parallel study of patients with medium-grade stenosis (30% to 69%) was continued until December 1996. Though patients older than 80 years were excluded before February 1991 for both the moderate and severe parallel studies, older patients were included in the second phase of the NASCET study.

One concern in interpreting the current study is that the moderate stenosis group included older patients than the severe stenosis group, and that the benefit of carotid endarterectomy may be less, in part, from the older age of some patients with moderate carotid stenosis. Because the surgical technique was left to the discretion of the surgeon, it is unclear how different operative techniques affected the results. How many patients had shunts? How experienced were the surgeons who performed the carotid endarterectomies? We know that high volume carotid endarterectomy surgeons and high volume hospitals obtain better outcomes. We believe that the type of closure also affects the outcome, and that women should be closed with a greater saphenous vein patch. Our 30-day perioperative mortality rates with the vein patch closure were 0.5% and 0.4%, the nonfatal stroke rates were 0% and 0.8%, and the combined death and stroke rates were 0.5% and 1.2%, respectively, for male and female patients. We now have performed vein patch angioplasty and carotid endarterectomy for in 300 females with 350 procedures and in 435 males with 491 procedures. Approximately 70% of our patients had the operation for symptomatic moderate and severe internal carotid artery stenosis, and no significant difference in the perioperative risks has been found between asymptomatic and symptomatic patients. A recent study also reports a significant reduction in perioperative complications with a patch closure with a mortality rate of 0.9%, fatal stroke rate of 0.2%, and any stroke or death rate of 2.5%. Because the annual stroke rate for patients with symptomatic moderate internal carotid stenosis has been reported to be 6%, we believe that patients who are symptomatic should be considered for surgical intervention. Low and acceptable perioperative mortality and morbidity rates can be achieved in the symptomatic female with moderate or severe carotid stenosis if vein patch angioplasty and carotid endarterectomy are performed by high-volume vascular surgeons at high-volume institutions.

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**Response:**

We thank Drs Chang and Stein for their comments regarding our comparisons of benefit from carotid endarterectomy (CE) in women and men with symptomatic severe (>70%) and moderate (50% to 69%) internal carotid artery stenosis.1 In their letter, Drs Chang and Stein mistakenly stated that we reported no benefit in women with moderate stenosis. This was only true if women had none or few of the prespecified risk factors for stroke. In the presence of a high risk factor profile, women did receive benefit from CE. We thus concluded that women with a symptomatic moderate carotid stenosis should not automatically undergo CE but should be carefully assessed for additional risk factors that would lead to greater benefit with CE than from best medical care alone.

Drs Chang and Stein suggested that the modest increase in the average age of the group with moderate stenosis (66.4 years old) compared with the severe group (64.3 years old) may have diminished the benefit of CE among the moderates. On the contrary, previous analyses from NASCET showed that the benefit from CE in elderly patients exceeded that found in younger patients. This increase in benefit resulted from having a combination of a higher risk of stroke on medical therapy alone and a lower perioperative surgical risk than the younger patients.2 It must be recalled that at no age were patients enrolled into NASCET who had recent evidence of life-threatening heart disease or evidence of failure of other vital organs.

In regards to the operative procedure itself, NASCET did not include surgeons as participants into the trial unless they demonstrated, by audit, that they had a perioperative rate of stroke and death of <6% in a minimum of 50 consecutive cases accumulated over 2 years. Over the course of the trial, the Surgical Committee of NASCET monitored the surgeons’ performance in each center. Stroke neurologists were responsible for patient assessment and reporting of all outcome events, followed by external adjudication. Although NASCET surgeons were not constrained to follow any standardized surgical technique, other than their normal practice, we are confident that they were experts in the performance of CE. The low perioperative mortality rate of 1.1% and disabling stroke rate of 0.9% attest to this.3

NASCET was not a trial designed to test the relative value of a variety of technical differences in the performance of CE. Nonetheless, details of anesthetic techniques and surgical variations, including the use of intraoperative shunts and patch grafts, were recorded in the Surgical Case Report Form. Among the 1415 patients who were randomized into the surgical arm and received CE, 41.0% had an intraluminal shunt.3 The perioperative stroke and death rate among those who had a shunt was 6.2% compared with 6.7% among those without a shunt (P=0.71). Patch closure was used in 19.8% of the patients. Among those with patching, the perioperative stroke and death rate was 5.0% compared with 6.8% among those who had simple closure (P=0.36). The trend favoring patching is congruent with Drs Chang and Stein’s beliefs of its value to CE. Nevertheless, without trials in which patients are randomly assigned to receive or not receive these technical variations, subgroup analyses and beliefs remain as hypothesis-generating rather than practice-altering certitudes. A recent systematic review of arteriotomy closure is a step in the right direction.4 Even so, it was based on 13 trials of small size and of variable quality. The obvious next step would be to conduct a randomized trial of sufficient size to compare different types of closures and materials, bearing in mind that operative risks are different between women and men, and between symptomatic and asymptomatic patients. Until such a time when this type of trial can be completed, the decision of whether to use a patch routinely will be left to the discretion of the operating surgeon.

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**Organizing Stroke Systems of Care**

*To the Editor:* I read with great interest the American Stroke Association (ASA) policy recommendation entitled Recommendations for the Establishment of Stroke Systems of Care.1 It is encouraging to see that this task force validates the recommendations from the 2 symposia sponsored by the National Institute of Neurological Disorders and Stroke held in 1997 and 2002.2,3 There appears to be consensus on what systems need to be in place to optimally prevent and treat stroke. The challenge lies in effective implementation. Approximately 9 years after the Food and Drug
Administration approved intravenous tissue plasminogen activator (IV tPA), the number of patients treated annually has not increased. It appears that simply agreeing on what should happen does not make it so.

The ASA’s Task Force set forth 5 general recommendations for stroke systems, but there is no clear description of who or what is organizing this comprehensive “systems” approach. The NINDS task force also emphasized the need to link and coordinate the activities of providers, concluding that a stroke system should fundamentally be a single entity that is responsible for organizing the stroke system without helping us understand who that “single entity” is. It is possible that we could fast-forward 9 more years and not have gained much ground.

As with all complex tasks, there is likely to be more than one successful approach. The “top down single entity” model is going to require state and/or federal leadership and support. Florida and New York appear to be headed in this direction. Another approach is to understand the critical elements producing successful outcomes in the “bottom up emergent” regional systems of care and reproduce them in like communities and regions.

The stroke team at the Mid America Brain and Stroke Institute (MABSI) at Saint Luke’s Hospital in Kansas City, Missouri has been active in organizing a systems approach to stroke treatment and prevention since 1993. In 2004, 513 patients with ischemic stroke were admitted to Saint Luke’s Hospital. Of those, 144 received tPA (28%). This was an increase of 80% over the previous year when 80 patients were treated. Seventy percent of the patients who received tPA were referred from one of 47 referring hospitals in the region, and half of the patients who received IV tPA had therapy initiated in the referring hospital, usually by an emergency medicine physician in consultation with the MABSI stroke team neurologist. Thirteen of the 47 referring hospitals were in the Kansas City metro area and 34 were within a 150-mile radius around the city. What is working for our region can certainly be replicated in other parts of Missouri and in other states, but we need to understand how and why the network succeeds.

There is a risk that the ASA Task Force Recommendations of 2005 may not drive the progress we need in stroke systems unless there is support for qualitative study of models that work, be they “top down” or “bottom up.”

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Response:
We applaud the efforts of Dr Rymer’s group and those of many others across the United States who have worked so hard to improve the quality of acute stroke care in their communities. Such efforts have a significant impact in their region and offer considerable benefit to nearby patients. Although single hospital systems or communities have been able to organize and implement improvements in stroke care, including increased treatment with tissue plasminogen activator, broader changes are required to expand access and ensure the highest quality of stroke care across the spectrum of services. Ultimately, a stroke system of care will be successful through effective establishment of interconnected core components, including: (1) primary and primordial prevention; (2) community education; (3) notification and response of emergency medical services; (4) acute stroke treatment, including the hyperacute and emergency department phases; (5) subacute stroke treatment and secondary prevention; (6) rehabilitation; and (7) continuous quality improvement activities. Implementing this continuum of care is the best way to reduce mortality and improve quality of life for all stroke patients. The American Heart Association and American Stroke Association (AHA/ASA) have made a goal of reducing the burden and risk of heart disease and stroke by 25% by 2010. This commitment is reflected in a recent re-organization across the entire affiliate infrastructure that includes the development of specific state-level stroke goals based on the blueprint laid out in the Recommendations for the Establishment of Stroke Systems of Care.

The AHA/ASA is partnering with its volunteer members and key organizations such as the Joint Commission on Accreditation of Healthcare Organizations, the Centers for Disease Control and Prevention, and State health departments and legislatures to form state-specific collaboratives to oversee the implementation of stroke systems of care. This process is playing out in different ways across the country: some states have chosen a DPH-based model (Mass, NY); others are pursuing state legislative models (Fla, NM, NC), and still others are leveraging federal programs like the Paul Coverdell National Acute Stroke Registry (Mass, NC, Ill, Ga). The leadership for implementation of system change will vary from state to state, and the stakeholders may be different, but as we have emphasized the locus of change should be at the state or regional level to be most effective at providing services to all citizens—not just those fortunate enough to live within the catchment area of large metropolitan hospitals. Geographically large states or those with significant rural populations will likely need to leverage access to specialists through the use of telemedicine, aeromedical transport, and interstate collaborations.

The effort to provide federal funds to support further implementation of systems at the state or regional level continues with the re-introduction in Congress of the STOP Stroke Act, a bill to “amend the Public Health Service Act to strengthen education, prevention, and treatment programs relating to stroke.” We urge all those interested in improving stroke care to enlist the support of their elected congressional representatives to pass this vital legislation.

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The Risk and Benefit of Endarterectomy In Women With Symptomatic Internal Carotid Artery Disease
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