ICP compared to trimethaphan. No difference in ICP was found with either drug when the patients were hypocapnic. 

Because of the potentially deleterious effect on intracranial dynamics, it may be wise to use either SNP, nitroglycerine or diazoxide unless ICP is being monitored, since all of these drugs have been shown to cause increases in ICP. 

It is unclear to us whether the patients who do poorly with HTE do so because of their disease or treatment. Because of its lack of direct effect on cerebral vessels, trimethaphan may be safer to use initially in HTE, as it would not be expected to increase CBV and brain edema and hence ICP.

References


The author replies:

I agree with Drs. Egol, Snyder, and Grenvik that increased intracranial pressure (ICP) is a serious factor in hypertensive encephalopathy (HTE). As indicated in my article, the reversal of the process producing edema requires the reduction of systemic arterial pressure, an urgent measure in the treatment of HTE.

Reported studies of the cerebrovascular effects of sodium nitroprusside (SNP) provide conflicting results. Stullken and Sokoll found no increase in ICP when SNP was administered to normotensive cats, in contrast to trimethaphan which did produce an increase in ICP. However, they found an increase in ICP when vasopressin was given to animals following systemic hypotension induced by either drug. As noted by Marsh’s studies such as those by Stullken and Sokoll persuaded some anesthetists to change from trimethaphan to SNP for blood pressure control during induction. Other studies have demonstrated elevation in ICP with SNP. Differences in studies undoubtedly result from factors such as species differences, variations in the nature and extent of brain swelling, level of systemic blood pressure, the method of injecting the test drug, extent of blood pressure drop with hypotensive therapy and paco2.

Care and caution must be exercised when administering any of the major hypotensive drugs. They must be used in a setting which enables constant monitoring of vital signs, but I do not agree that attempts should be made to monitor ICP in all patients with HTE.

Although it is obvious that controlled clinical data are unavailable, it is my opinion that patients with HTE did more poorly when there were no drugs such as SNP at hand to lower blood pressure effectively. Further studies in both animals and man, may lead to a better understanding and more general agreement about the modes of action of SNP.

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Mitral Valve Prolapse and Risk of Stroke

To the Editor:

Considerable difficulty exists in reconciling the rather frequent occurrence of mitral valve prolapse (MVP) in stroke patients (particularly young stroke patients), and the rarity of stroke in MVP patients in clinical series. 1 This paradox is clearly presented in a recent issue of the Journal. 2 One explanation, expressed in an editorial opinion by Hurst and Easton, is that the frequency of stroke due to other causes is low in the younger patients with MVP thereby allowing the relation of stroke to MVP to be clearly seen. Among older persons, they suggest, the stroke associated with MVP is overshadowed by the more frequent occurrence of stroke of all types. 3 We suggest that selective bias is the explanation for the phenomenon, operating in case “selection” in neurological patient series.

A classic study of how a collection of clinical cases reported from a teaching hospital differs from findings derived from a population is that of Crawford and Morris. 4 Noting wide variation in the reported frequency of age, sex and anticoagulant use in cases of ruptured ventricle a population of London, 1957-1958. The Table summarizes their findings. While overall, ventricular rupture occurred equally in men and women in teaching hospitals, there appeared to be a predominance of stroke of all types.

Mitral Valve Prolapse and Risk of Stroke

Table 1: Spontaneous Rupture of Cardiac Ventricle London 1957-1958

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
<th>Coroners' mortality</th>
<th>Average annual incidence per 1000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-54</td>
<td>10</td>
<td>7</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>55-64</td>
<td>10</td>
<td>7</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>65-74</td>
<td>5</td>
<td>1</td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td>70-74</td>
<td>3</td>
<td>2</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>75-84</td>
<td>4</td>
<td>3</td>
<td>29</td>
<td>43</td>
</tr>
<tr>
<td>80-84</td>
<td>4</td>
<td>3</td>
<td>18</td>
<td>38</td>
</tr>
<tr>
<td>85+</td>
<td>2</td>
<td>1</td>
<td>17</td>
<td>32</td>
</tr>
</tbody>
</table>

nance of males under 70. Ventricular rupture was thus thought to be a disease of men under 70 and strongly related to anticogulation since 7 of the 15 men in this age group were taking anticogulants. Examination of the coroners' cases yields quite a different picture. Comparison of annual sex and age incidence rates discloses that while rates are higher in men than in women in middle age, there is little difference above age 70. There were so many more old women than old men in the population at risk in London that a greater number of female cases in old age merely produces near equal rates. Furthermore, none of the coroners' cases were taking anticogulants; use of this therapy was in vogue for acute MI in teaching hospitals at this time.

This feature of a population study rather than a collection of clinical cases obtained through a series of selective referrals, illustrates the way epidemiologic study of disease in populations can help to correct and complete the clinical picture of a disease and its natural history. Once the association of MVP and stroke was detected and confirmed by clinicians a more accurate estimate of the true frequency of MVP and of subsequent stroke risk will probably be obtained by systematic longitudi- nal study in a defined population. Such a prospective investigation is underway in the Framingham Study.5

It is quite likely that the reported coincidences of stroke and MVP in young stroke victims without evidence of carotid and other predisposing cardiac lesions are exaggerated. Under these circumstances MVP would be intensively sought out. By contrast, in MVP cases, which are commonly encountered in cardiology practice, strokes are seldom encountered, more likely reflecting the true situation.

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References

Doctors Hart and Easton reply:

We agree with the sentiment expressed by Dr. Wolf and colleagues that the role of mitral valve prolapse (MVP) in causing cerebral ischemia has probably been exaggerated in the recent literature. The bandwagon phenomena with its unconvincing "confirmatory data" which so often follows the initial description of such clinical associations is in full swing. Recently, MVP has been proposed as etiologic in a man who suddenly began laughing and shouting at 3:00 A.M.1 Because of meth­ odologic flaws, the three articles relating MVP and stroke which accompanied our editorial offer only weak support for this association (al­ though of interest in addressing other aspects of the issue).2-4 However, critical review of all available data do support an important relationship of MVP to unexplained stroke in young adults.

Wolf et al offer two separate criticisms of the data linking cerebral ischemia to MVP: 1. potential selection bias operative in referral-based populations and, 2. more intensive efforts to identify MVP in stroke patients compared to controls or normal populations. These criticisms must be considered separately.

Potential selection bias limits the generalizability of the data linking MVP and stroke to those patients referred to academic centers, whose population may or may not reflect the general population of all stroke patients. Such bias potentially limits the value of studies such as Barnett et al5 and Sandok and Gullian in establishing the quantitative importance of MVP-related cerebral ischemia. One population-based study (albeit retrospective and vulnerable to criticism #2) is available and confirms that young patients with unexplained stroke have a much greater than expected prevalence of MVP.6 Not surprisingly, this study showed that the prevalence of MVP-linked stroke was lower than that reported from referral-based populations, perhaps better reflecting the overall importance of MVP-related stroke.

The second criticism has been addressed by the studies of Barnett et al,5 DeBono and Warlow,6 and Scharf et al7 who studied patients and controls with equal intensity, demonstrating a clear increase in prevalence of MVP, albeit in referral populations of stroke patients.

We certainly agree that epidemiologic studies offer invaluable data clarifying many aspects of disease and we eagerly await such data concerning MVP and stroke. Data from epidemiologic studies, howev­ er, are not always generalized to people who are seen by physicians (ie, patients). For example, the natural history of asymptomatic bruits in the population from the Framingham studyn8 may not represent the natural history in patients seen by neurologists, internists and surgeons.9 Both epidemiologic and other types of clinical data are useful. Based on aggregate data from an abundance of clinical studies of variable quality, we predict that a properly designed epidemiologic study with sufficient numbers of patients will confirm that: 1. The prevalence of MVP in all young adults with cerebral ischemia is only modestly (two times) increased over age-matched controls. 2. The prevalence of MVP will be markedly increased (5-10 times) in young adults with unexplained stroke. 3. The occurrence of stroke in unselected young adults with MVP will be quite low (perhaps 1/5000/yr) but about 5 times that of age­ matched controls without MVP. 4. The paradox noted by Wolf et al and Jones et al8 is explained by the infrequency of stroke in young adults.

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References
8. Wolf PA, Kannel WB, Sorlie T: Asymptomatic Carotid Bruit and

Doctor Jones replies:

We emphatically agree with the major point of Dr. Wolf's et al letter suggesting that selective bias may account for the differences in frequency of stroke in relationship to mitral valve prolapse in our two populations. This was one of the basic purposes of our report, i.e., to emphasize that the risk of stroke appears to be very small in the large general population of patients with well recognized mitral valve prolapse (MVP).

We acknowledge that MVP was "intensively sought out" in young stroke victims without evidence of carotid and other predisposing cardiac lesions. However, within this very small subset population, i.e., the young patient with stroke, the importance of MVP may not be "exaggerated" as well defined by Barnett et al.1 Because some of these patients may have multiple cerebral ischemic events, the identification of this source has obvious therapeutic implications.

The essential question for future studies is the identification of pathophysiologic mechanisms which uncommonly predispose a very few patients with MVP to the risk of stroke. One mechanism that does appear to be documented to date is that of subacute bacterial endocarditis such has been documented in 10% of those in one large series of patients with MVP and stroke.2 Other than for the appropriate prophylaxis for SBE we continue to advocate a conservative management of the asymptomatic MVP patient.

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References

Whole Blood Viscosity and Cerebral Blood Flow

To the Editor:

In a recent issue Grotta and coworkers reported on whole blood viscosity parameters and cerebral blood flow (CBF).3 Their results were further commented on in an editorial by Thomas.2 This report on blood viscosity and CBF deserved further comments.

Changes in hematocrit and blood viscosity may induce simultaneous changes in the blood's oxygen release capacity which has to be taken into account. Grotta and coworkers hardly discuss changes in oxygen release capacity in their paper, but seem to consider the effects as largely due to viscosity changes. Thomas on the other hand mentions that there is some debate on the relative importance of blood viscosity and blood oxygen carrying capacity for the flow changes.

First, it should be pointed out that the blood oxygen release capacity is not a simple function of its oxygen binding capacity but is also heavily influenced by shifts of the oxyhemoglobin dissociation curve. Thus, a shift to the left of the oxyhemoglobin dissociation curve results in a higher oxygen saturation at a given oxygen tension and less oxygen can then be released in the tissue if its oxygen tension has to be maintained unchanged. A shift to the left of the oxyhemoglobin dissociation curve, thus results in a CBF increase.3 Changes in hematocrit result in blood viscosity, in oxygen release capacity and in CBF changes. The oxygen tension in jugular venous blood remains constant following acute decrease of the hematocrit in patients with normal or with high hematocrit.4 Here the oxyhemoglobin dissociation curve also remains constant. But, in patients with chronic changes in hematocrit it is known to shift; e.g. to the right in anaemia.

Grotta and coworkers performed multivariable analysis and demonstrated that the serum fibrinogen concentration and in addition to the hematocrit seems of importance for the CBF. They interpreted this to changes in viscosity which very well may be the case. However, as the oxyhemoglobine dissociation curve is shifted to the right in anaemia, this would per se result in a slightly lower CBF. If such data had been available their multivariable analysis of fibrinogen concentration and hematocrit might well have yielded another result. Thus, caution must be exercised in the interpretation of these results.

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Doctor Thomas replies:

It is now generally agreed that under normal circumstances in patients with high hematocrit, the main reason for their having a low CBF is the higher oxygen carrying capacity of their blood. That the high viscosity, which accompanies high hematocrit, has any influence on CBF at all has been questioned. The paper from Grotta et al is valuable because it shows that factors, like fibrinogen, which raise blood viscosity, but apparently have no effect on oxygen carrying capacity or the oxygen dissociation curve, are associated with lower CBF. Furthermore, the position of the oxygen dissociation curve does not change after venesecion.2

There may be differences between CBF measurements immediately after venesecion and after a few days when the circulation is in a more stable state. In the acute phase, Henriksen et al showed a small rise in the oxygen delivery capacity (CBF x arterial oxygen content) which failed to reach significance in their 6 cases. They also showed a small rise in the cerebral metabolic rate for oxygen. Wade2 measured CBF several days after serial venesecions in 20 cases and found that this rise in O2 carrying capacity (approximately 8%) was significant. He did not measure jugular venous pO2 on ethical grounds because of the higher risk of thrombotic complications in patients with low flow and high haematocrit so he was unable to confirm that the CMRO2 also increased.

Clearly, in patients with high hematocrit the brain is not frankly hypoxic even if CBF is low. However, the low flow may be potentially dangerous, especially if another factor tending to reduce flow or to enhance thrombus formation is introduced. An important point to reassure the caution is that after venesecion oxygen delivery seems to rise slightly, rather than fall. Whether venesecion proves to be of value in preventing thrombotic complications remains to be shown.

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Mitral valve prolapse and risk of stroke.
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