The Effect of Intra-arterial Papaverine on the Regional Cerebral Blood Flow in Patients with Stroke or Intracranial Tumor

BY JES OLESEN, M.D., AND OLAF B. PAULSON, M.D.

Abstract: The effect of intracarotid injection of 10 mg of papaverine on regional cerebral blood flow was measured in 27 patients. Most of the patients had cerebral infarction or intracranial neoplasm. The intra-arterial 133Xenon injection method was used and 16 or 35 regions of the diseased hemisphere were monitored. In patients without focal flow abnormalities an average flow increase of 93% followed the injection. In patients with focal abnormalities of cerebral blood flow the intra-arterial injection of papaverine produced a decrease in focal flow or less increase in flow than normal. It is concluded that vasodilator therapy presumably decreased flow in pathological tissue and that such treatment should not be employed in the therapy of cerebrovascular disease.

ADDITIONAL KEY WORDS

vasodilators vasoconstrictors 133Xenon increased intracranial pressure

Vasodilator drugs have been recommended from time to time in the treatment of patients with cerebral infarction. Although it may be logical to increase the cerebral blood flow (CBF) in areas of focal ischemia, the results of treatment with drugs which produce vasodilatation have been controversial.

This lack of beneficial effect might be due to inadequate increase in CBF resulting from the intravenous administration of the agents used. In the last five years evidence has, however, appeared that even a potent vasodilator (CO₂) will not significantly increase the cerebral blood flow in an area of ischemic brain tissue but that there may be an actual decrease in blood flow; the so-called intracerebral steal effect. The mechanism of this effect is probably as follows: Ischemic brain tissue produces acid metabolites which causes dilatation of blood vessels with ensuing abolition of vasomotor reactions to other stimuli—vasoparalysis. In this situation, administration of a drug which causes vasodilatation would only produce further dilatation in the peripheral healthy blood vessels and thus shunt blood away from the vasoparalytic areas because of a decrease in blood pressure in the smaller intracerebral arteries coupled with an increase in intracranial pressure.

This study is designed to inspect the possibility that pharmacologically induced vasodilatation might or might not produce an "intracerebral steal" similar to that reported during inhalation of CO₂. We measured the regional cerebral blood flow (rCBF) in patients with acute cerebrovascular disease, intracranial tumor and a few cases of nonfocal cerebral disease before and after an intracarotid injection of papaverine. This route of administration was chosen to secure a large increase of cerebral blood flow. For the clear-cut demonstration of the regional effects of papaverine, smaller changes as caused by intravenous injection might not suffice. However, qualitatively the changes induced by both routes of administration are probably the
### Effect of Papaverine on the Regional Cerebral Blood Flow

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1. CBF<sub>initial</sub> values are indicated. When tissue peaks are present rCBF<sub>initial</sub>/rCBF<sub>second minute</sub> values are indicated.
2. The numbers indicate channels with abnormal response to papaverine. The focal areas in the resting state were determined as areas with abnormally high or low flow and were not always completely coextensive with the areas showing abnormal papaverine response.
3. Patients studied with the 16-channel instrument. The others were studied with the 35-channel instrument.
4. In these cases both a hyperemic and an ischemic focus were seen in the resting state.
5. In these cases no focus was observed in the resting state but only after papaverine injection.
6. Abnormal curve configuration was in this case observed in most of the hemisphere, but in the central part taken to be the focus, the curve configuration and papaverine response were distinctly most abnormal.

**MCO:** With occlusion of the middle cerebral artery.

**TIA:** Transient ischemic attack (no arterial occlusion).

**IH:** Intracerebral hematoma.

**WO:** Without arterial occlusion.
same. Therefore, information regarding regional changes in rCBF resulting from intravenously or perorally administered papaverine may also be deduced from the present study.

Methods
A total of 27 patients were studied. Fourteen had cerebrovascular disease, nine had intracranial tumor, one had psychoneurosis, two had presenile dementia, and one had encephalitis. Some of the observations concerning the diagnosis and CBF studies are listed in table 1. Two patients had increased intracranial pressure at the time of rCBF study (cases 4 and 26). In case 26 the intracranial pressure was 59 mm Hg one day before the rCBF study. The other patient had papilledema, but the intracranial pressure was not measured. None of the other patients had papilledema. Eleven of the 14 patients with cerebrovascular disease were studied within 24 hours after the onset of symptoms. Except for the one patient with a transient ischemic attack, all individuals with cerebrovascular disease had severe hemiparesis, while several had aphasia, homonymous hemianopia or focal sensory involvement at the time of the study.

In all 27 patients the regional cerebral blood flow (rCBF) was measured in the resting state and after an intracarotid injection of papaverine. Usually the rCBF was also measured during other functional tests, e.g., during changes of the arterial blood pressure or of the arterial P_{CO_2}.

The 133Xe intra-arterial injection method was used for the rCBF measurements. Theoretical and practical aspects of this method have been reported in previous papers. It shall, therefore, be only briefly summarized.

After local anesthesia and premedication with atropine 0.5 mg and pethidine (meperidine) 25 mg I.M., a small polyethylene catheter was
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placed in the internal carotid artery by means of the Seldinger technique. Two to three mc of $^{133}$Xe dissolved in 1 to 4 ml of isotonic saline was injected rapidly (one to two seconds) through the catheter, and the clearance of the isotope was followed by multiple small scintillation detectors placed externally over the ipsilateral hemisphere (fig. 1). During each flow measurement, a blood sample was drawn through the catheter for determination of $P_{aCO_2}$ and the intracarotid blood pressure was measured with an electromanometer.

The time interval between the single flow measurements was at least 15 minutes. Ten milligrams of papaverine dissolved in 10 ml of isotonic saline was injected through the catheter during five to ten seconds immediately before the rCBF measurement. The injection caused only minor side effects: One patient complained of hemicrania of short duration and some were restless for several seconds.

After the CBF studies, arteriography was usually performed through the catheter already inserted.

Nine patients were studied with a previously described 16-detector equipment, whereas 18 patients were studied with a newly developed 35-channel apparatus consisting of 35 scintillation crystals 10 mm thick and 12 mm in diameter. They are collimated in the same way as in the previously described 16-channel instrument, i.e., with cylindrical lead tubes, 43 mm long and 12 mm in diameter. In the new instrument, the detectors are packed closer than in the 16-channel unit. They are arranged in five rows and seven columns to form a rectangular box, with the peripheral detectors directed a little centrally and the central units pulled a little backward to form a head-fitting shape of the "detector's head" (fig. 1). Each detector has its own ratemeter which displays through a multiplexer the clearance curve onto an oscilloscope screen. On the screen the 35 traces correspond to the position of the probes over the hemisphere. The oscilloscope screen is photographed by a Polaroid camera. The sweep of the scope is set to picture two minutes of the clearance curves. Thus, two minutes after the $^{133}$Xe injection both a positive and a negative

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CASE 25: GLIOMASTOMA

In this patient there is observed in the resting state a frontal hyperemic focus with peaks in the clearance curves. This focus corresponds to the site of the tumor. After papaverine injection no focal abnormalities are seen and all areas are equally perfused.

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*Manufactured by Meditronic Inc., Engelsborgvej 50, 2800 Lyngby, Denmark.
photographic picture are ready for interpretation and the planned functional tests (change of arterial blood pressure or PaCO₂) or pharmacological investigations can be changed according to the individual results.

To localize the position of the probes, two small lead pieces were taped on the head of the patient corresponding to marks on the box containing the detectors, and a lateral x-ray projection of the cranium was taken (fig. 2).

Calculations

The blood flow can be calculated from the first two minutes of the logarithmically displayed clearance curve:

\[ rCBF_{\text{initial}} = 2.3 \cdot \lambda_g \cdot D_{\text{initial}} \text{ ml/100 gm/min} \]

where 2.3 is the conversion factor from base ten to natural logarithm, \( \lambda_g \) the tissue to blood partition coefficient of gray matter which is about 0.87, and \( D_{\text{initial}} \) is the slope of the initial part of the clearance curve as measured in percent of a decade per minute. With this value of \( \lambda_g \), the formula is reduced to:

\[ rCBF_{\text{initial}} = 2 \cdot D_{\text{initial}} \text{ ml/100 gm/min} \]

In normal cases, the logarithmically recorded \(^{133}\)Xe clearance curves are essentially monoexponential for the first two minutes; but, as previously described, the two-minute clearance curves may in pathological cases be multieponential with initial “tissue peaks” representing fast flow components. Consequently, it is sometimes necessary to report two “flow values” for the first two minutes of the clearance curve, one calculated from the slope of the initial part of the curve and the other from the slope of the curve during the second minute (after the tissue peak):

\[ rCBF_{\text{second minute}} = 2 \cdot D_{\text{second minute}} \text{ ml/100 gm/min} \]

It has to be stressed that the “\( rCBF_{\text{second minute}} \)” value is merely a slope index and not a strict flow value. Thus, it does not represent the flow of any specific compartment. Normally \( rCBF_{\text{initial}} = rCBF_{\text{second minute}} \) since the first two minutes of the clearance curve are monoexponential. These equations allow direct reading of the \( rCBF \) values from the curves by simply measuring the slope of the curves. This is easily done on a turntable disk with parallel lines and a zero point. The normal value of \( rCBF_{\text{initial}} \) is 65 ml/100 gm/min, SD 9 ml/100 gm/min.19

In previous studies with the 16-channel instrument it was found that in patients without focal cerebral diseases the interchannel coefficient of variation of the \( rCBF_{\text{initial}} \) was 10.6% with a standard deviation of 2.6%.16 Thus, an interchannel coefficient exceeding 10.6% + 2 \times 2.6% = 15.8% could be considered abnormal with a “fairly” high degree of certainty (p < 0.05). Furthermore, it was found that the \( rCBF_{\text{initial}} \) value decreased about 13% after repeated studies due to remaining activity and to buildup of recirculating activity in the extracranial tissues.10

With the 35-channel instrument the interchannel coefficient of variation was 8.2% and the standard deviation was 1.2%, resulting in a 5% confidence limit of 8.2% + 2 \times 1.2% = 10.6%, i.e., smaller than that previously found with the 16-channel instrument.19 This means that the change from a recording system with tape recorder and playback to a Polaroid camera system and the increased number of detectors has apparently increased the accuracy.

By repeated \( rCBF \) measurements in a group of demented patients the intrachannel coefficient of variation was found to be 4.9%. This coefficient indicates the reproducibility of a hemispheric \( rCBF \) pattern, e.g., it “means that” an area with high flow in one study also will have a high flow in subsequent studies in steady state conditions. Since the intrachannel coefficient of variation 4.9% was less than the interchannel coefficient of variation 8.2%, true differences in the flow pattern within a hemisphere probably exist. This is in accordance with the findings of others.20

Results

Blood pressure, arterial PaCO₂, and blood flow
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CASE 8: MIDDLE CEREBRAL ARTERY OCCLUSION

A patient with stroke, where an ischemic focus is observed in the posterior part of the hemisphere. After papaverine this area shows almost no increase in rCBF, whereas blood flow increases much more in the nonfocal regions.

channels at more than one functional test are factors which must be considered together when the focus is determined. If a focus is small, the technical quality of the clearance curves is very important. Thus, a focus is defined as an area represented by one or more neighboring channels which show abnormalities in the resting state and/or at the functional tests.16

EFFECT OF PAPAVERINE IN PATIENTS WITHOUT FOCAL FLOW ABNORMALITIES

This group consisted of one patient with intracerebral hemorrhage, four of the seven patients having apoplexy without arterial occlusion, two cases of dementia, one with encephalitis and one with psychoneurosis (indicated in table 1 as having 0 channels with focal abnormalities). Intracarotid injection of 10 mg papaverine resulted here in a uniform increase of rCBF\textsubscript{init} averaging 93%. The first part of the clearance curves was rectilinear, indicating that the vasodilatation took place very rapidly. A delayed onset of the effect would have given a bending of the curves with a first slow and a later more rapid part. The action was short lasting, since after 15 minutes the resting flow level was re-found in practically all cases.

Due to the marked increase in CBF after injection of papaverine, a change in the shape of the clearance curves occurred. The rectilinear part of the logarithmically displayed curves lasted in the resting state approximately two minutes, but at high flow the curves usually bent after a shorter time (one to one and one-half minutes). This phenomenon has been previously described,21 and the smooth bending of these curves should be distinguished from the sharper bending due to “tissue peaks” with abnormal fast flow components. The phenome-
Non is not due to a transient effect of papaverine, since the same effect is seen during continuous inhalation of CO₂.

**EFFECT OF PAPAVERINE IN PATIENTS WITH FOCAL FLOW ABNORMALITIES**

This group consisted of the five patients having cerebral infarction with proved arterial occlusion, three of seven patients judged to have cerebral infarction without arterial occlusion, one patient with a transient ischemic attack, and all nine patients with intracranial neoplasms.

In the patients with cerebrovascular disease (14 individuals), "tissue peaks" were small and encountered only in three instances. In all the patients flow values were subnormal in the entire hemisphere. In many, an ischemic focus was observed where the response to papaverine was decreased or abolished (fig. 3). In one instance (patient 17) a clear-cut "intracerebral steal" syndrome was observed, i.e., a reduction of the flow in the focal area simultaneous to a flow increase in the nonfocal areas (fig. 4). The nonfocal areas in the patients with cerebrovascular disease reacted similarly to what was observed in patients without focal flow abnormalities, that is, with a large increase in CBF.

Six of nine patients with intracranial neoplasm had multiexponential two-minute clearance curves with fast flow components (peaks) corresponding to the localization of the tumor in the resting state (figs. 2 and 5). These "tissue peaks" disappeared or diminished associated with the injection of papaverine, and often the curves became monoexponential. In three patients no peaks were encountered. A decrease in focal rCBF ("intracerebral steal" syndrome) was frequently observed after the injection of papaverine.
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CASE 26: ASTROBLASTOMA

![Image](image-url)

FIGURE 5

A marked parietal hyperemic focus is noted in this patient corresponding to the site of the tumor. After papaverine injection the flow in this region is markedly reduced, i.e., a steal syndrome. Even in the nonfocal region the blood flow decreases somewhat after the papaverine injection (see text also).

(figs. 2 and 5). The nonfocal areas in the patients with intracranial neoplasm had a variable reaction secondary to the injection of papaverine—a reaction ranging from a decrease of 14% to an increase of 91% (table 1). Papaverine under certain circumstances may decrease the rCBF in an entire hemisphere. This is illustrated by case 26 (fig. 5), where the flow decreased by 55%/48%

\[
\left( \frac{rCBF_{initial}}{rCBF_{second minute}} \right)
\]

in the focus and 14% in the other portions of the hemisphere. This patient was the only one having papilledema. The other patients with a decreased reaction to the injection of papaverine, outside the focus, had very large neoplasms although there was no papilledema. Since increased intracranial pressure was suspected, lumbar puncture was not performed and the intracranial pressure is not known.

Patient 27 had a large meningioma. There was slight change in rCBF after the injection of papaverine with a decrease in the CBF in the focus and an increase outside the focus. However, peaks in the focus became steeper associated with the injection of papaverine while in all other patients the peaks decreased.

It is conceivable that focal abnormalities in response to vasodilator therapy in patients having foci of ischemia might be better demonstrated in the later phases of the clearance, that is, from eight to ten minutes. This is suggested by the data concerning patient 19. There was cerebral metastasis and a biexponential clearance curve appeared in one channel, over the focal region, after papaverine injection. The fast component showed nearly the same flow as the surrounding nonfocal regions, whereas the slow component showed a "steal" phenomenon. This is probably an example of diseased and nondiseased tissue.
being represented in the same counting field, the diseased tissue having the lowest perfusion after the injection of papaverine.

Discussion

The spatial resolution of the $^{133}$Xe method is rather poor. This fact is of significance in evaluating the data obtained in this investigation. The counting field of one detector may be represented by a truncated cone transsecting the entire hemisphere, and it must thus be assumed that both diseased and healthy brain tissues in a variable proportion will be present within the counting field of each single detector. Because areas of high perfusion receive more $^{133}$Xe than ischemic areas, these latter tissue components exert but little influence on the clearance curves, especially on the first part of them. If a substance tends to decrease the flow in some part of a counting field, that area will get less $^{133}$Xe and the clearance curve will be dominated by the other tissue components. Since papaverine causes a marked increase in CBF in normal brain tissue, these areas may easily mask a flow decrease in other parts of the same counting field, and thus a steal syndrome may in fact be present in the diseased area but not be observed in the clearance curves. This is especially important when large areas are necrotic as in cases of severe stroke, because the CBF in these areas presumably is minimal.

FREQUENCY OF "INTRACEREBRAL STEAL"

The main finding of the present investigation is that the injection of papaverine into the internal carotid artery produces a definite increase in CBF (vasodilator action) when there is no focal pathology and is associated with a number of abnormal reactions when there is focal pathology.

In patients with cerebrovascular disease the focal areas of damaged brain showed a marked decrease in the reaction to the injection of papaverine; however, "intracerebral steal" was observed in only one instance (patient 17).* This patient was one with transient ischemic attacks and presumably had little, if any, irreversible focal brain damage. Further-

*Since this paper was submitted, the authors have investigated one patient whose anterior cerebral artery was clipped during an operation for an aneurysm. In this case a clear-cut intracerebral steal was observed after papaverine injection.

more, it was the only cerebrovascular case which had a hyperemic focus and thus a good $^{133}$Xe supply to the vasoparalytic focus.

Patients with intracranial neoplasm had a focal decrease of the rCBF after the injection of papaverine ("steal syndrome") in seven of nine instances. It is, therefore, apparent that a true "steal" syndrome, i.e., a decrease of flow focally secondary to the injection of papaverine, was produced in most patients with intracranial tumors. One may question, however, whether a true "steal," i.e., a decrease of flow focally, had been provoked by papaverine in the bulk of our cerebrovascular patients—all we found was a smaller increase in the focus than outside it. The question is crucial in relation to the discussion of vasodilator treatment of apoplexies. The fact that focal vasoparalysis exists is generally accepted. However, collaterals to an ischemic vascular bed might be localized outside the acidotic and vasoparalytic focus and thus be fully responsive to papaverine and other vasodilator agents. The fact that the small precapillary arterioles dominate the vascular resistance speaks against this concept. In animal studies the "existence" of intracerebral steal has frequently been demonstrated. Here carbon dioxide diminished flow in the ischemic cerebral cortex distally to the occluded middle cerebral artery, and the blood pressure in the occluded vascular tree also decreased. By serial angiography in man, papaverine has been observed to erase the collateral supply to an ischemic area distal to an arterial occlusion.

MECHANISM OF "INTRACRANIAL STEAL"

Previous studies with the $^{133}$Xe method, using carbon dioxide as the vasodilating substance, demonstrated a much more pronounced steal phenomenon in patients with intracranial neoplasm than was seen in the present study after injection of papaverine. Since the percent flow increase after papaverine and carbon dioxide in the amounts used is roughly the same, factors other than the vasodilatation possibly contribute to creating the steal phenomenon. On the basis of human studies,
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several authors have discussed the importance of the intracranial pressure for the steal phenomenon. Since carbon dioxide dilates the vessels of both hemispheres, it will also increase the intracranial pressure more than papaverine given in one carotid artery.

In one patient with a transient ischemic attack (case 17), the intracranial pressure was recorded during the rCBF study. In the resting condition (horizontally lying on the back) the intracranial pressure was 18 mm Hg and rose to 19.1 mm Hg after injection of papaverine and to 25 mm Hg during CO₂ inhalation. A focal steal was observed in this patient after papaverine injection, but during CO₂ inhalation this abnormal flow response was much more marked (fig. 4).

In another patient (case 26) with an astroblastoma and increased intracranial pressure (papillary edema), blood flow decreased in the entire hemisphere, especially in the region of the neoplasm, after injection of papaverine (fig. 5). In a patient (case 4) with encephalitis and with raised intracranial pressure (59 mm Hg measured one day before the rCBF study), the same paradoxical response was observed during carbon dioxide inhalation, but following papaverine a uniform increase of 75% occurred in the entire hemisphere. These examples seem to demonstrate the different effect on intracranial pressure of papaverine and of carbon dioxide and the importance of the intracranial pressure for the intracerebral steal phenomenon.

PAPAVERINE AS A FUNCTIONAL TEST

The increase in CBF caused by the intracarotid injection of papaverine might be used as a functional test to detect focal vasoparalysis during rCBF measurements. Our results suggest that it can be employed successfully to demonstrate a vasoparalytic region, particularly in patients with intracranial neoplasm and occlusion of a major cerebral vessel. The distribution of the ¹³³Xe bolus follows the distribution of the rCBF, and focal areas where the flow increases less (questionably vasoparalytic areas) than in other regions after papaverine will, therefore, get a lower counting rate due to the change in bolus distribution. This effect of papaverine might be eliminated if the drug were injected immediately after ¹³³Xe instead of before ¹³³Xe. In six instances we tested the influence of the distribution of the ¹³³Xe bolus by injecting papaverine after ¹³³Xe. The findings were not significant and factors such as spontaneous fluctuations of the arterial blood pressure and of PaCO₂ obscured the effect of a possible change in the ¹³³Xe bolus distribution. Considering all of these complex factors, it is our belief that a small vasoparalytic area is better demonstrated by using a test of autoregulation or of changed PaCO₂ rather than by using the intracarotid injection of papaverine.

Clinical Comments

Some years ago, the use of papaverine for treatment of patients with cerebrovascular disease was quite widespread. Some optimistic reports of the beneficial effect of that drug appeared, but many reports were negative and, moreover, these studies lacked a comparable control group (see review by Gottstein). In 1966 Gilroy and Meyer reported a controlled investigation of the effects of papaverine given intravenously in large doses. No difference was found between the treated and untreated group with regard to mortality and usual clinical judgment. By a scored neurological examination, a minor difference in favor of the treated group was demonstrated. On the basis of the studies referred to above and the absence of any beneficial clinical effect in our 14 cases of cerebrovascular disease, we are of the opinion that significant clinical evidence of a beneficial action of papaverine is still not available.

Considering the physiological basis of treatment with vasodilators in cerebral infarction, the rationale of such treatment is open to serious doubt. In patients with cerebrovascular disease without arterial occlusion, no hindrance for the arterial inflow to the diseased tissue is present. In such instances it is therefore unlikely that vasodilatation would have any beneficial effect even if flow was increased in the focal region. Distal to an occluded cerebral artery the tissue is ischemic, and an increased blood flow to such areas would presumably be beneficial. However, treatment with vasodilators can produce a steal syndrome with decrease of the focal rCBF and, as discussed above, this paradoxical reaction probably occurs frequently.

To further illustrate the issue, previous studies have demonstrated that aminophylline has a short-lasting beneficial effect on selected
cases of recent cerebral infarction. The mechanism of this action is a cerebral vasoconstriction in nondiseased brain tissue resulting in an "inversed steal syndrome" with flow increase in the focally damaged area. This flow response can also be obtained during hyperventilation when the arterial P0₂ is lowered.

Thus, two directly opposite therapeutic principles are recommended in the treatment of patients with stroke. However, some physiological investigations have resulted in favor of the vasoconstrictor method and suggest undesirable effects of vasodilator treatment. These physiological arguments may not be significant and the way to evaluate the treatment is by controlled clinical investigations. Therefore, a controlled clinical study of the effect of mechanical hyperventilation of patients with stroke is presently being performed in our clinic.

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EFFECT OF INTRA-ARTERIAL PAPAVERINE


The Effect of Intra-arterial Papaverine on the Regional Cerebral Blood Flow in Patients with Stroke or Intracranial Tumor

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