Differential Reactivity of Neural and Extra-Neural Vasculature

I. Role in the Pathogenesis of Spinal Cord Damage from Contrast Media in Experimental Angiography

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Studies in these laboratories have led to the development of a unified concept of contrast medium injury, clearly delineating dose dependent and concentration dependent toxic actions. Using a canine aortography model to explore the therapeutics of the concentration dependent effect, Margolis and associates have demonstrated that by pharmacologic induction of altered tonus of the vascular system it is possible to protect the spinal cord from injury, and conversely, to potentiate the neurotoxic action of roentgen contrast agents. These modifying influences of vasoactive agents are explicable only on the basis of the differential reactivity of the splanchnic and somatic vascular beds and the vessels of the central nervous system. The stronger response of peripheral vessels overrides and effaces the primary reactions of the neural vascular bed. Hence the vasopressor drug, levarterenol, inducing a strong increase in resistance of peripheral vessels, will drive an injection mass towards the spinal cord. Conversely, vasodepressor agents, by reducing peripheral vascular resistance, will induce a vascular shunt away from the cord. The sensitivity of this concentration dependent model, and the lability of the target vascular beds are of such magnitude that a 10- to 20-fold difference in neurotoxicity was observed between the extremes of the protective action of vasodepressor agents and the potentiating effects of a vasopressor response, with the direction of shunting being the major determinant of injury.

The significance of these observations for diagnostic angiography is implicit in the commentary of the authors: “If, as has been experimentally demonstrated, intrinsic vascular tonus is the major factor in the production of concentration dependent neurotoxic action, an approach is available towards the protection of the central nervous system from injury in angiography and angi cardiography. If we consider that it is in these procedures that the highest relative incidence of serious clinical complications have been encountered, and that these injuries have commonly involved the spinal cord, brain stem and cerebrum, regions outside the ‘target zone’ of these procedures, the potential value of this information is clearly evident. In the literature on diagnostic angiography, frequent reference is made to the hazards of angiography to organs which have a pre-existing vascular disease. Our studies emphasize the alternate possibility; namely, that in the absence of overt brain disease the central nervous system may be imperiled by functional or anatomical vascular shunts resulting from the conditions leading to the need for diagnostic angiographic procedures. For example, this possibility can readily be envisaged in hypertension where there is a sustained elevation in systemic vascular tonus, in occlusive aortic atherosclerosis where there is a strong collateral circulation via the important lumbar spinal radicles, and in coarctation of the aorta with its multiple major collateral routes, including the spinal branches of the intercostal arteries.”

We are now reporting further studies exploring the phenomenon of differential reactivity of the peripheral and neural vascular beds, and the mechanisms whereby vascular shunts modify the noxious action of contrast agents upon the spinal cord. The findings are based upon results of experiments utilizing
cine-angiography, rapid serial angiography, and blood flow measurements with electromagnetic flowmeters and thermistors.

Materials and Methods

Overtly healthy dogs of both sexes, weighing from 10 to 20 kg., were used for this study. Anesthesia was induced and maintained with a single intravenous injection of nembutal 30 mg./kg. body weight. The animals were intubated and respiration artificially controlled by a positive pressure apparatus. Convulsive responses were blocked with flaxedil. The procedures used followed the same plan reported previously.10

The dogs were positioned laterally on the x-ray table for aortography procedures. We injected 60% hypaque or 60% conray, 2 cc./kg., retrograde into the aorta via a femoral catheter passed to the level of the 3rd lumbar vertebra; cinefluorography films were made. After a lapse of 15 to 20 minutes, 1 mg. of levarterenol or 32 mg. of papaverine hydrochloride were administered via the same route, and 30 to 40 seconds later another injection of contrast medium was given. Again the flow of the contrast agent was recorded.

High speed rapid reversal pan 16 mm. motion picture films were exposed at 60 frames per second. The x-ray equipment used consisted of a 9 inch image amplifier operating at an intensity of .75 ma. and approximately 100 kilovolt peak. Each exposure continued until all visible opaque medium had disappeared.

Because of the low resolution, high grain and poor reproducibility of the cine films, parallel studies were carried out using a roll film cassette with a film size of 9½×9½ inches. Films were exposed for ½ second at ½ second intervals at an intensity of 100 ma., and a kilovolt peak range of from 64 to 70. Conventional x-ray film was used.

The procedures followed for the flow studies were essentially alike. Electromagnetic flowmeters, 1 to 3 mm. in diameter, were placed around the femoral, renal and lumbar arteries. Blood flow in each of these arteries was studied separately, except in a few instances when flows were monitored concurrently in the renal and lumbar vessels. On a few dogs commercially available thermistors mounted within 20 gauge needles were implanted in the kidney and spinal cord and changes in temperature following the use of vasoactive drugs were measured. These data were recorded on a Honeywell Visicorder or a Sanborn 2-channel recorder.

Tone and reflex changes were studied as well as immediate convulsive reactions. The neurological status of the experimental animals was observed for 24 hours, following which the spinal cord was studied for pathological changes.15

Results

Each dog served as its own control. The normal systemic pressure averaged 110 mm. Hg. Normally a smooth progression of the opaque medium through the aorta was seen without evidence of a pulsatile flow unless a slow rate of injection was expressly used. Four to 6 pairs of lumbar arteries were usually visible and the passage of the contrast agent through the aorta and lumbar arteries was rapid, the opacification fading from them in approximately 4 and 5 seconds respectively. None of the dogs receiving hypaque alone developed convulsions, reflex changes or paraplegia.

Circulatory Effects of Levarterenol. Six dogs were used for this study. After 1 mg. of levarterenol had been delivered through the same intra-aortic catheter, the blood pressure was 250 ± 50 mm. of Hg and the aortogram showed certain constant and characteristic changes. The progress of the injection mass was delayed, with arrest of retrograde movement during diastole and a pulsatile short advance during systole (Fig. 1 a and b). The density of opacification of the aorta and lumbar arteries was much greater than normal and the radiopacity persisted in them for approximately 7 and 9.7 seconds respectively following the injections (Table 1). At the height of the systolic thrust the angle of “take off” of the lumbar arteries appeared less acute. It was clearly manifest from these observations that the spinal circulation was exposed to a higher concentration of contrast agent and for a longer period than under normal conditions. Two parallel series of aortographic pictures taken before and after levarterenol demonstrated the striking alterations of hemodynamics which occurred (Fig. 2 a–d).

Circulatory Effects of Papaverine Hydrochloride. Four dogs were used for this study. The aortogram was performed before and after 32 mg. of papaverine hydrochloride had been injected intra-aortically. The blood pressure following papaverine hydrochloride was approximately 80 mm. of Hg compared to the normal of 110 to 120 mm. Hg. The aortographic findings were the exact converse of those seen after levarterenol. The main features illustrated were the rapidity of transit from the aorta and the lumbar arteries (Table 1), the long downward flow of the in-