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Effects of Anesthetics on Cerebral, Renal, and Splanchnic Circulations:

Recent Developments

C. Philip Larson, Jr., M.D., Richard I. Mazze, M.D.,† Lee H. Cooperman, M.D.,‡ Harry Wollman, M.D.§*

Cerebral Circulation

THERE ARE SEVERAL excellent reviews of the regulation of cerebral circulation, cerebral metabolism and the effects of anesthetics on these functions.[1-4] However, the rapid growth of new knowledge and consequent changes in the concepts of regulation of cerebral blood flow and metabolism merit a brief updating.

Two interdependent advances, one conceptual and the other technologic, are the primary reasons for the intense interest in cerebral blood flow and metabolism by clinical neuroscientists. The conceptual advance is the recognition that cerebral blood flow is not uniform throughout the brain and that regulation of flow to ischemic areas of brain may be lost or may be different from that prevailing in normal brain. Studies in man and animals indicate that focally ischemic areas of brain develop localized acidosis. This in turn may cause focal vasodilatation and loss of normal autoregulation or loss of responsivity to changes in arterial carbon dioxide tension, or both. Focal vasomotor nonconformity that results in preferential diversion of blood away from ischemic brain when hypercapnia ensues is called an "intracerebral steal." The reverse event, the preferential diversion of blood toward an area of focal ischemia when hypocapnia is initiated, is called an "inverse steal."

The technologic advance is concerned with measurement of regional cerebral blood flow. Numerous methods that attempt to measure the regional distribution of blood flow within brain have been developed. The method having greatest clinical applicability involves injection of a diffusible isotope into a carotid artery and subsequent measurement of the rate of decay of the isotope using multiple, focally collimated probes placed externally about the head. Although measurement of regional cerebral blood flow (rCBF) by this method is relatively simple, the procedure has not become readily available except in very few hospitals because of the high technologic costs and the lack of firm evidence of its value in the diagnosis and treatment of neurologic abnormalities. For example, intracerebral and inverse steals or loss of autoregulation do not invariably occur in all varieties of focal ischemia or trauma to brain. Ischemic brain, for reasons not yet understood, may show only autoregulatory impairment, only an intracerebral steal, or only an inverse steal, or any combination thereof.

Utilizing the concepts and technology described, investigators concerned with anesthetics and cerebral blood flow have concentrated their recent research efforts in two major areas. The first has been to further define the effects of certain anesthetics on total and regional cerebral blood flow and the mechanisms involved. The second has been to clarify whether anesthetic drugs can convey any protective effects to brain exposed to experimentally induced ischemia. This review considers recent progress in these areas.

* Professor, Department of Anesthesia, Stanford University.

† Associate Professor, Department of Anesthesia, Stanford University.

‡ Associate Professor, Department of Anesthesia, University of Pennsylvania.

§ Professor, Departments of Anesthesia and Pharmacology, University of Pennsylvania.

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Effects of Anesthetics on Flow and Metabolism

Halothane is known to increase cerebral blood flow in a dose-related manner, that is, the greater the dose, the greater the total flow. The mechanism for the increased flow was presumed to be a direct one, wherein halothane acted on cerebral arterioles to produce vasodilatation. Recent studies by Smith, however, suggest that the primary regulatory mechanism may be metabolic.[5] The reasoning for this is: Cerebral flow and metabolism are interrelated (metabolism = flow × arteriovenous oxygen content difference). Previously, Smith had shown that cerebral arteriovenous oxygen content difference varies inversely with anesthetic depth with halothane, enflurane, and isoflurane.[6] Since arterial oxygen content is constant, this means that cerebral venous oxygen content must vary directly with anesthetic depth. Because halothane is readily diffusible, it should cause an instantaneous increase in cerebral blood flow if its effects are directly on arteriolar muscles. Instead, Smith found that in dogs increases in cerebral blood flow lagged one to two minutes behind sudden increases in arterial halothane concentrations.[5] Changes in metabolism and cerebral venous oxygen content followed the slower rate of change of the brain tissue content of halothane. From these studies, Smith postulates that the primary effects of halothane are to decrease cerebral metabolism and to regulate cerebral venous oxygen content to maintain a favorable cerebral tissue oxygen tension. Cerebral blood flow then follows passively. The mechanism whereby halothane alters cerebral metabolism or cerebral venous oxygen content is not known.

Irrespective of the exact mechanism of the increase in cerebral blood flow by halothane, there has been concern that the vasodilatation may cause an intracerebral steal in a patient in whom a focal area of cerebral ischemia exists. Smith and colleagues examined the effects of increasing doses of halothane on rCBF in normal canine brain compared with that made acutely ischemic by ligation of an internal carotid and a middle cerebral artery.[7] Flow was lower on the ligated side than on the intact side, but the changes in flow with changes in anesthetic dose were the same on both sides. The vasodilatation induced by halothane did not cause preferential diversion of blood away from the ischemic area. However, it must be emphasized that this study does not exclude the possibility that halothane may cause intracerebral steals under other circumstances or in man, whose blood supply and collateral flow differ from those of the dog.

It is well established that hypercarbia[8] or other cerebral vasodilators[9] do not invariably cause a steal of blood from ischemic brain, indicating that factors other than selective vasodilatation of responsive vessels may influence the regional distribution of blood flow. One such factor may be the prevailing blood pressure. For example, Keaney and associates have shown that profound hypotension (mean blood pressure = 33 torr) from deep halothane anesthesia causes loss or impairment of autoregulation in baboons.[10] The role of blood pressure in the development of intracerebral steals resulting from halothane is not known.

The increase in the use of morphine as an anesthetic for patients undergoing cardiac surgery has necessitated an evaluation of the effects of large doses of morphine (1–3 mg/kg) on cerebral blood flow and metabolism. In a study in dogs, Takeshita, Michenfelder, and Theye found a progressive decrease in cerebral metabolism with incremental doses of morphine.[11] The maximal decrease was small (15 per cent) but significant, and occurred when the cumulative dose reached 1.2 mg/kg. Additional doses did not produce further changes in metabolism. Morphine also produced a dose–response decrease in cerebral blood flow, the maximum decrease (55 per cent) occurring at the highest dose studied (3 mg/kg). This decrease was due in part to the general decrease in cerebral flow that is known to occur when animals are immobilized for prolonged periods. The decrease may also have been due in smaller part to a decrease in mean arterial blood pressure that accompanied morphine anesthesia. The decreases in flow and metabolism produced by morphine are similar in magnitude but more prolonged in duration than those produced by meperidine

or fentanyl. Small doses of nalorphine (0.3 mg/kg) were effective in reversing the decreases in metabolism and flow produced by relatively large doses of morphine (2 mg/kg).

Protective Effects During Ischemia

Several investigators have reported that anesthetics, namely barbiturates and halothane, may protect the brain from acute hypoxia[12,13] or ischemia.[14,15] However, these studies are subject to criticism for lack of measurement or regulation of one or more of the following: anesthetic dose or duration; arterial oxygenation or carbon dioxide tension; brain or body temperature; level of blood pressure. Both Michenfelder[16] and Smith[17] have re-examined the protective effects of anesthetics using the dog as the experimental model with these variables controlled. Both find that barbiturates afford protection but they suggest different mechanisms.

Michenfelder and Theye observed, in dogs, that thiopental, 15 mg/kg, and, to a lesser extent, halothane, 0.8 per cent, protected brain exposed to acute hemorrhagic hypotension (mean arterial pressure 25–30 torr) or arterial hypoxemia (Pa_{O_2} 4 torr), provided neuronal function, as evidenced by an active EEG, was maintained.[16] They propose that at least in the dog model, the protective effects provided by anesthetics result from a decrease in cerebral metabolism, but in a manner somewhat different from the protection afforded by hypothermia. They suggest that anesthetics protect only neurons, and then only when the neurons are actively functioning. In contrast, they propose that hypothermia provides protection by its ability to decrease the energy requirements of all cerebral functions. This theory would imply that the limits of protection afforded by anesthetics are much more circumscribed than those for hypothermia.

Smith and colleagues found that pentobarbital given in the relatively large doses sufficient to decrease EEG frequency to less than 1 Hertz prevented the development of any neurologic abnormalities from acute, permanent occlusion of an internal carotid and middle cerebral arteries. The dogs were sacrificed a week later, and the magnitudes of infarction of the involved hemispheres ranged from none to 5 per cent. In contrast, all dogs anesthetized with halothane (0.8 or 1.8 per cent alveolar concentration) developed immediate and pronounced neurologic deficits. Upon histologic examination, the magnitudes of infarction of the involved hemispheres ranged from 1 to 58 per cent. The more severe abnormalities were found at the higher halothane dose, irrespective of whether blood pressure was maintained at normal values or not. However, protection could be provided dogs anesthetized with halothane by the administration of thiopental, 40 mg/kg, either immediately before or within 15 minutes after arterial occlusion.

The finding that neither light nor deep levels of halothane anesthesia provided protection from cerebral infarction suggests that anesthesia, *per se*, is not protective. Further, barbiturates must afford protection by some mechanism other than anesthesia or a decrease in cerebral metabolism. Both halothane and barbiturates decrease cerebral oxygen consumption, and certainly both drugs have "anesthetic" effects. Smith theorizes that barbiturates protect brain primarily by decreasing cerebral blood flow and perhaps by decreasing intracranial pressure, although the latter effect has not been well documented.[17] Decreasing blood flow and intracranial pressure might lessen the capillary damage and cerebral edema that develop in the ischemic area while at the same time maintaining an adequate perfusion pressure to the ischemic zone. Smith suggests that any protection derived from metabolic depression is of secondary importance. If correct, this theory would imply that protection from acute ischemia would also be afforded by other drugs that acutely decrease cerebral blood flow or intracranial pressure, *i.e.*, neuroleptanesthetics, opiates, or steroid anesthetics (21-hydroxypregnandione), provided normal arterial carbon dioxide tensions were maintained.[2]

The clinical implications suggested by these laboratory findings are obvious. The barbiturates, opiates, and neurolept agents may be the anesthetics of choice for patients undergoing operations in which the risks of cerebral ischemia or edema are high. In general, neurosurgeons and anesthesiologists

have preferred inhalation agents for these patients because inhaled drugs permit rapid emergence from anesthesia and early postoperative evaluation of neurologic status. If barbiturates or other similarly acting intravenous anesthetics are proved in other laboratory or clinical studies to provide protection from ischemia or hypoxia, the desire for rapid emergence may become a secondary consideration in some cases.

Renal Circulation

The kidneys are made up of a number of separate anatomic zones, each of which makes a specific contribution to renal function. Renal blood flow (RBF) appears to have a distinct relationship to the function of each zone. Blood flow to the renal cortex in man[18–20] and experimental animals[21–23] is approximately 400 ml/100 g/min. This greatly exceeds the requirements of renal cortical tissue for oxidative metabolism but is appropriate for its excretory function.

The ability of the kidneys to concentrate urine is dependent upon the presence of a hypertonic medullary interstitium, the osmolality of which varies from 300 mOsm/kg at the corticomedullary junction to 1,200 mOsm/kg at the inner medulla. The countercurrent arrangement of tubules and blood vessels in the renal medulla, and the relatively low inner medullary blood flow of less than 50 ml/100 g/min,[20] are necessary for the establishment and maintenance of this osmotic gradient. Recognition of the differing blood flow requirements of the renal cortex and medulla has served as the stimulus for recent investigations into the intrarenal distribution of blood flow.

Intrarenal Blood Flow

Indirect methods for measurement of intrarenal blood flow were developed in the late 1950's and have been applied clinically within the last ten years. Kramer *et al.*,[21] studying dogs, and Reubi *et al.*,[19] in studies of man, employed dye-dilution techniques to demonstrate rapid blood flow in the renal cortex and much slower flow in the renal medulla. Although quantitating differences in flow, this technique gave no information about the distribution of blood flow within the medulla itself.

The isotope-washout technique for measurement of renal blood flow permitted the distinction between the inner and outer medullary regions. With this technique, a quantity of isotope is injected into the renal artery and an external counter is used to measure the diminishing radioactivity in the kidney. The disappearance curves can be separated into several exponential curves, corresponding to blood flow rates through different regions of the kidney. Thorburn *et al.*,[23] using ^{85}Kr in conscious dogs, localized four regions, *i.e.*, cortex, outer medulla, inner medulla, and hilar and perirenal fat. Ochwadt,[24] using labeled erythrocytes and plasma in isolated dog kidneys, and Ladefoged and Pedersen,[20] employing ^{133}Xe in man, obtained results similar to those of Thorburn *et al.*[23] Isotope-washout techniques employing ^{85}Kr or ^{133}Xe are in most common clinical usage today. Compared with conventional clearance techniques, they have the added advantage of measuring renal blood flow independent of urine flow, permitting study of renal hemodynamics during oliguric or anuric states. Table 1 presents a summary of the results of various studies of intrarenal blood flow. Recent interest in medullary blood flow warrants separate discussion of this area.

Medullary Blood Flow

The straight limbs of the vasa recta are the primary blood supply of the renal medulla. They are derived from the efferent arterioles of the juxtamedullary glomeruli and are arranged in bundles in the outer zone of the medulla.[25]

Blood flow to the outer and inner medulla, per unit of tissue weight, is much lower than in the cortex (table 1), accounting for only 6–7 per cent of total RBF. The inner medulla receives only 1 per cent of total RBF and has the lowest flow in the kidney.[21] Low medullary flow is not due to a poorly developed vascular bed, but probably is the result of the high resistance to flow created by the extraordinary length of the medullary vasa recta.[26]

TABLE 1. Comparison of Intrarenal Hemodynamic Measurements

Species	Method	Area	Reference	Renal Blood Flow			Vascular Volume (Per Cent)
				Per Cent	ml/100 g Tissue/Min	ml/100 g Kidney/Min	
Dog	Dye dilution	Cortex	21	93	458	321	73
		Outer medulla	22	6	112	22	27
		Inner medulla	21	1	29	3	
	Isotope washout	Cortex	24	79			58
			23	80	472	354	
		Outer medulla	24	18			16
			23	16	132	20	
		Inner medulla	24	3			26
			23	2	17	2	
Man	Dye dilution	Cortex	19	80–93			52–78
		Outer medulla		7–20			22–48
		Inner medulla					
	Isotope washout	Cortex	20	92	538		46
		Outer medulla		7	50		
		Inner medulla		2			

The medullary circulation plays an important role in the counter-current mechanism by controlling the rate of solute removal from the interstitium. In so doing, medullary circulation determines medullary osmolality, which in turn influences the ability of the kidney to concentrate urine. The vasa recta participate in this function as a counter-current exchanger. Their hairpin arrangement, extending into the inner medulla, favors the passive exchange of solute and water across their walls. Water passes out of the descending limb of the vasa recta and enters the more hypertonic ascending limb, short-circuiting the inner medulla.[27,28] At the same time, medullary solute is moving in the opposite direction, going from the hypertonic ascending limb of the vasa recta to the interstitium and from there into the relatively less concentrated descending limb. This arrangement favors the development of an osmotic gradient within the renal medulla, with osmolality as high as 1,200 mOsm/kg at the tip of the renal papilla.

TOTAL RENAL BLOOD FLOW

Measurements of intrarenal blood flow during anesthesia have not been made. Rather, total renal blood flow has been measured, most commonly by determining the clearance of para-aminohippurate (PAH) by the kidneys. This method is based upon a simplification of the Fick principle and makes the assumption that PAH concentration in the renal veins is negligible. In actuality, the extraction of PAH (E_{PAH}) usually averages about 0.90, with E_{PAH} 0.95 in the outer cortex and 0.82 in the deep venous drainage returning blood from the inner cortex and medulla.[29] Furthermore, E_{PAH} may vary, particularly in renal failure, when it declines to close to zero[30] or during loading of the circulation with Ringer's solution, mannitol, or plasma, when it may decrease by as much as 20 per cent.[31] Because E_{PAH} has not been measured during studies of renal hemodynamics in anesthetized patients, the validity of intra-anesthetic RBF measurements[32–42] is open to question. Decreases in RBF during anesthesia of as much as 50–70 per cent have been reported, with the greatest decreases occurring in patients deeply anesthetized with drugs that cause catecholamine release, such as cyclopropane and diethyl ether.[32–35] Lesser changes in RBF have been observed in lightly anesthetized[34,36,37] and fluid-loaded patients.[35,37,38,41] Balanced anesthetic techniques employing

drugs with alpha-adrenergic blocking properties, such as droperidol, are said to cause no depression of RBF.[42] Generally, decreases in glomerular filtration rate (GFR) have been less than decreases in RBF, so that the filtration fraction increases. This has been interpreted as representing an increase in renal glomerular efferent arteriolar tone. However, another possible explanation is that the E_{PAH} decreases during anesthesia result in exaggeration of the actual decrease in RBF. Only the most general comparisons can be made among the various studies of intraanesthetic renal hemodynamics because of differences in premedications, depths of anesthesia, and fluid regimens employed.[32-42]

Control of Renal Blood Flow

The renal circulation is subject to two types of regulation: 1) extrinsic neural and hormonal regulation, and 2) intrinsic autoregulation. The changes in renal blood flow during anesthesia occur as a result of these controlling factors. Recently there has been considerable interest in extrinsic hormonal regulation of renal blood flow.

Epinephrine and norepinephrine, when present in small and moderate amounts, produce an increase in blood pressure accompanied by a decrease in total RBF and no change in GFR. Thus, it appears that constrictions of afferent and efferent arterioles are approximately equal. When epinephrine and norepinephrine are administered in high doses, and especially when they are infused intravenously, they cause precipitous decreases in both RBF and GFR. Studies with ^{85}Kr and selective renal arteriograms have demonstrated that almost all of the change in RBF following epinephrine infusion is due to abolition of superficial cortical blood flow, with little or no change in medullary flow[43] (fig. 1).

An additional hormonal pathway capable of affecting renal function is the renin–angiotensin system. Renin is a proteolytic enzyme produced by the juxtaglomerular cells of the afferent arterioles. Renin reacts with an alpha-2 globulin of plasma to form angiotensin I. This substance is ultimately converted into angiotensin II, a strongly pressor and renal vasoconstricting substance. Angiotensin-II activity is one of the major factors governing the release of aldosterone. Control of renin release is influenced by several factors which are in turn affected by administration of anesthesia.[44] Sodium content of tubular fluid, catecholamine levels, sympathetic nerve impulses, and intraluminal pressure of afferent arterioles are probably all involved. Angiotensin, when present in small amounts, reduces RBF without affecting GFR. When it is present in large amounts, both RBF and GFR decrease, with a redistribution of intrarenal blood flow similar to that seen following epinephrine infusion.[45] Reduction of RBF during hemorrhagic hypotension has been shown to be the result of increased concentrations of circulating catecholamines and angiotensin, as well as increased sympathetic nervous system activity.[46,47] It is likely that these hormonal factors also contribute to the changes in total RBF and intrarenal distribution of flow present during other forms of severe stress.

The prostaglandins, a group of lipid compounds found in seminal vesicles, lungs, brain, pancreas, and renal medulla, have marked vasodepressor and antihypertensive activity in animals and man[48]: they act directly on peripheral arterioles.[49] It is likely that these compounds are also involved in regulation of intrarenal blood flow. Prostaglandin infusion produces natriuresis independent of changes in GFR, an increase in cortical blood flow, and a decrease in medullary blood flow.[50,51] The response to prostaglandin infusion is consistent with the general observation that increased blood flow to outer cortical nephrons, with their short loops of Henle, results in diuresis and natriuresis, while increased blood flow to juxtamedullary nephrons, with their long loops of Henle, results in sodium retention.[51] The exact role of the prostaglandins in the control of intrarenal blood flow and in the regulation of sodium and water balance must await the development of more sensitive methods of prostaglandin measurement. There is no evidence to suggest that other vasoactive hormonal substances in physiologic concentrations, such as vasopressin or serotonin, affect total RBF or produce changes in intrarenal distribution of blood flow.

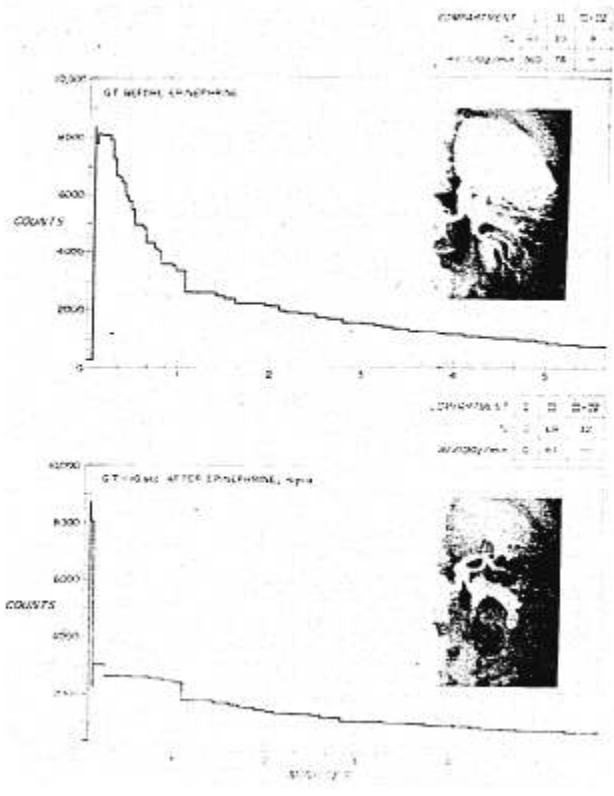

FIG. 1. Effects of epinephrine on the selective renal arteriogram and xenon washout in the normal kidney. Note that after of epinephrine, 6 μg, injected into the renal artery, both the cortical vasculature as seen in the arteriogram and very rapid early disappearance of xenon in the tracing are unrecognizable. (Reproduced with the permission of N.K. Hollenberg and *Medicine*.[43])

Autoregulation of RBF is of interest because it appears to be abolished during general anesthesia. Autoregulation refers to the maintenance of a relatively constant RBF despite changes in mean arterial blood pressure within the range of 80–180 torr.[52] Resistance changes appear to be wholly controlled by the kidney, since RBF is constant in innervated, denervated, and isolated kidneys and during alpha-adrenergic blockade of intrarenal ganglia with phentolamine and phenoxybenzamine.[53–55] Moreover, not only is RBF autoregulated, but GFR is autoregulated, as well, suggesting that the resistance elements are located in the preglomerular vascular segments.[53] Autoregulation of RBF in

these studies is in contrast to its absence during general anesthesia in man and animals. Decreased RBF was observed in all of the studies measuring intra-anesthetic renal hemodynamics referred to above, although arterial blood pressure rarely decreased below 80–90 torr.[32–42] Recently, Leighton *et al.*[56] showed that administration of methoxyflurane to dogs resulted in a 35 per cent decrease in RBF, while mean blood pressure fell from 125 to 102 torr. Other non-anesthetic drugs that paralyze smooth muscle, such as potassium cyanide and papaverine, also abolish autoregulation, suggesting that autoregulatory resistance changes are related to tangential wall tension of the arteriole.[57]

Acute Renal Failure

Although there is still a lack of complete agreement on the mechanism of sustained oliguria and azotemia in acute renal failure, the question appears to be closer to a solution than ever before. Renal micropuncture experiments in which pressure measurements were made in the proximal tubules and efferent arterioles of rats treated with methemoglobin[58] or mercuric chloride[59] indicated that intratubular obstruction by interstitial edema or intratubular casts may be a contributing factor. Other studies have shown that excessive back-flow of filtrate across denuded or damaged tubules may also be involved.[60] However, the majority of investigators studying acute renal failure agree the most common factor in the pathogenesis of the syndrome appears to be suppression of glomerular filtration.[58,61,62] Since light and electron microscopy of glomeruli generally fail to reveal structural abnormalities,[63,64] it is likely that reduced glomerular filtration is due to a vasomotor phenomenon. Total RBF is reduced to about a third of normal in patients with acute oliguric renal failure, but similar reductions in total RBF are common in chronic renal failure without oliguria. Thus, changes in total renal perfusion alone cannot account for the functional changes of acute renal failure.

Hollenberg *et al.* have employed the ^{85}Kr isotope-washout technique and renal arteriography to measure intrarenal distribution of blood flow in patients with renal failure.[43,65,66] They demonstrated that the rapid flow compartment, thought to represent superficial cortical blood flow, was markedly reduced or absent in patients with acute oliguric renal failure secondary to hypotension, but was only reduced in proportion to total RBF in patients with chronic renal failure.[43] In other studies, they showed similar disproportionate decreases in superficial cortical blood flow in patients with acute renal failure due to nephrotoxins[18] (fig. 2); in patients undergoing acute renal allograft rejection[65]; and in a patient with irreversible acute renal failure following methoxyflurane anesthesia.[66] They suggested that sustained preglomerular vasoconstriction, causing a persistent homogeneous reduction in renal cortical perfusion sufficient to induce the cessation of glomerular filtration, may be the pathogenetic final common pathway in acute renal failure.[18]

It is not clear from their studies how reduction in cortical perfusion is induced or sustained. There is some evidence to suggest that a local intrarenal vasomotor mechanism, controlled by a vasoactive mediator such as the renin–angiotensin system, is the predominant factor in the changes in distribution of renal perfusion. As long as 30 years ago, hypertrophy of cellular elements of the juxtaglomerular apparatus was observed in the kidney tissue of patients with acute renal failure related to the crush syndrome.[67] It was postulated that a vasopressor substance was released from this area, resulting in altered RBF, decreased GFR, and finally, renal failure. More recently, elevations in plasma renin levels have been observed in both clinical[68] and experimental acute renal failure.[69] However, the finding of increased renin levels in acute renal failure is not a consistent one, and it is not known whether increased renin activity, when it occurs, is a consequence rather than a cause of acute renal failure. Perhaps the most serious defect of the concept of increased renin–angiotensin activity as the common mediator of renal vascular changes in acute renal failure has been the inability to reverse adverse changes in renal function with drugs that block angiotensin's effects, such as hydralazine and acetylcholine, despite producing improve-

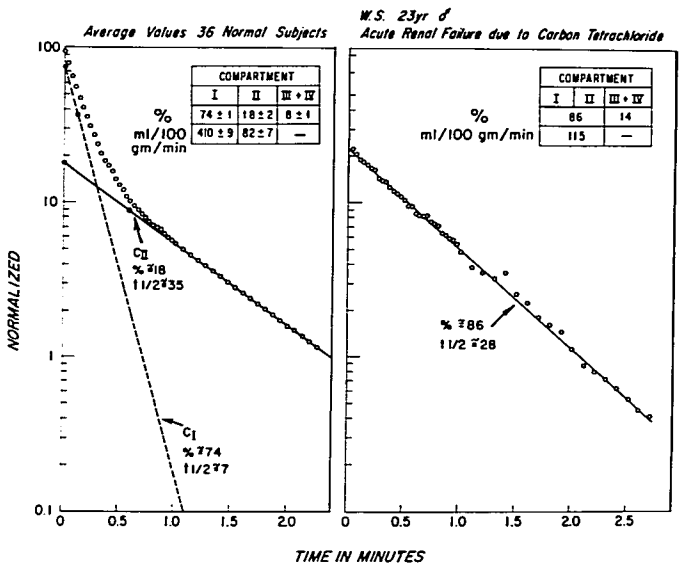

FIG. 2. Average values for the two early rapid-flow components of xenon disappearance from the kidneys of 36 normal subjects (*left*), compared with xenon disappearance from the kidney in a patient with acute renal failure after exposure to carbon tetrachloride (*right*). Note that the two early components have been replaced by a monoexponential with a half-time resembling that of the second component (C-II) more than the first (C-I). (Reproduced with the permission of N.K. Hollenberg and *New England Journal of Medicine*.[18])

ments in renal blood flow and cortical perfusion.[70] Future investigations will, no doubt, determine the factors controlling alterations of intrarenal distribution of blood flow during acute renal failure.

Splanchnic Circulation

After a period of limited interest in anesthetic effects on the splanchnic circulation, the past decade has witnessed a number of careful studies in this area. The renewed activity was spurred in part by technical advances permitting relatively easy and exact measurements in man. Another factor was the heightened interest in hepatic effects of general anesthetics, although in retrospect changes in splanchnic blood flow (SBF) seem unrelated to so-called "halothane hepatitis." Nevertheless, the data have been collected and are complete enough to provide a reasonable picture of SBF during anesthesia.

Initial studies by Price, Epstein, and coworkers indicated that cyclopropane and halothane anesthesia each halved SBF, compared with the awake state.[71,72] These measurements and their subsequent ones were made in healthy male volunteers not undergoing concomitant operation. The mechanism for this decrement during cyclopropane is heightened sympathetic nervous activity and splanchnic vasoconstriction. This constriction, and thus the decrease in SBF, can be prevented by administration of a ganglionic blocker. The

decrease during halothane anesthesia probably results from systemic vasodilation and decreases in both splanchnic perfusion pressure and cardiac output, with no change in splanchnic vascular resistance. When hypercarbia was established during halothane studies, splanchnic vasodilation and increased SBF were observed, suggesting that halothane blocked at least some of the vasoconstrictor actions of CO_2. Thus, the idea that halothane plus hypercarbia decreased SBF sufficiently to produce hepatic damage became untenable.

Methoxyflurane anesthesia is similarly associated with an approximate halving of SBF.[73] In this instance, the mechanism is a combination of decreased perfusion pressure and active splanchnic vasoconstriction. In fact, celiac-artery arteriograms taken during methoxyflurane anesthesia indicated that the constriction is specific for the bed served by the hepatic artery. Other branches of the celiac axis are unaffected by this anesthetic.

The only other general anesthetic studied was nitrous oxide. Epstein first observed that this drug supplemented by thiopental and succinylcholine during normocarbia caused little disturbance of SBF.[74] With hypercarbia, produced by addition of exogenous CO_2, there was splanchnic vasoconstriction (unlike during halothane anesthesia), with a variable response in SBF. This response depended upon changes in arterial pressure, there being a direct relation between the two. A subsequent study employing *d*-tubocurarine, hyperventilation, and hypocarbia as the anesthetic technique showed a marked reduction in SBF.[75] This was due in part to the hypocarbia, for when sufficient CO_2 was added to the inspired gas mixture to produce normocarbia there was a partial return of SBF towards control values. Thus, the mechanical effects of hyperventilation must have caused some of the reduction in SBF.

The effects of spinal anesthesia have recently been studied by Kennedy and coworkers in work that supplements studies performed 20 years earlier by Sancetta.[76,77] Both groups found decreases in SBF of about 25 per cent during high spinal anesthesia. As in the case of halothane, this reduction is a result of splanchnic vasodilation and greatly decreased perfusion pressure. A subsequent study examined the effects on SBF of epidural block with and without epinephrine in the local anesthetic.[78] As might be expected, the effects of epidural anesthesia without epinephrine are somewhat similar to those during subarachnoid block; there is a comparable decrease in SBF. However, Kennedy noted only a slight decrease in arterial pressure and an increase in calculated splanchnic vascular resistance. He suggests that systemic absorption of local anesthetic (lidocaine) produces some cardiovascular stimulation, which counteracts the sympathetic blockade. The addition of epinephrine (1:200,000) to lidocaine resulted initially in stable SBF, the result of increased cardiac output and decreased splanchnic vascular resistance. As the compensatory beta stimulating effects diminished, the typical decrease in SBF of about 25 per cent was noted.

One question that Price and colleagues tried to answer was whether the reduction of SBF accompanying anesthesia was harmful.[79] Measurements of hepatic venous P_{O_2} and splanchnic production of excess lactate, indices of organ hypoxia, were made. But none suggested that hepatic hypoxia was occurring in these healthy individuals. However, there were some differences among the anesthetics. Halothane, cyclopropane, and high spinal anesthesia were associated with somewhat comparable reductions in both SBF and splanchnic oxygen consumption. Nitrous oxide and methoxyflurane, however, caused disproportionate decreases in SBF compared with splanchnic oxygen consumption, a less desirable change than that with the other three anesthetics. This may indicate that, while no anesthetic clearly causes harm, some may be preferable to others, especially for the patient with impaired splanchnic circulation.

We may now be entering another period of inactivity in studies of effects of anesthetics on splanchnic circulation. In part this is due to the fact that direct damage due to splanchnic underperfusion during anesthesia has not been clearly demonstrated. In part it is due to the fact that measure-

ments of splanchnic blood flow, oxygen consumption, and lactate metabolism have uncovered no critical change, and no mechanism of toxicity.

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Cerebral Circulation

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