JOURNAL OF SURGICAL RESEARCH 42, 101–115 (1987)

CURRENT RESEARCH REVIEW

Blood Flow Measurement in the Canine Pancreas

J. G. N. STUDLEY, FRCS, R. T. MATHIE, PH.D., AND L. H. BLUMGART, M.D.

Department of Surgery, Royal Postgraduate Medical School, London, England

Submitted for publication April 21, 1986

INTRODUCTION

There are two distinct types of preparation for studying blood flow and perfusion in the canine pancreas. The first is the *in vivo* gland which can be examined in either anesthetized or ambulant dogs. Both flow and perfusion are under the influences of changes within the pancreas and of external stimuli, including nervous and hormonal factors. Investigators have evaluated blood flow and perfusion in the gland and the changes that occur in various metabolic states or following the administration of hormones or drugs. In the second type of preparation blood flow is controlled artificially, so as to allow measurements of other parameters in the *in situ* or *ex vivo* gland. In 1926 Babkin and Starling [4] described preparations of both an *in situ* and an *ex vivo* gland. Since then many modifications have been developed of both the preparation of the model and the maintenance of flow or perfusion [1, 9, 19, 34, 35, 38, 39, 49, 50, 55, 60, 66, 74]. This review is entirely concerned with evaluation of the intact gland in the living animal. No further consideration is made of preparations in which blood flow has been maintained artificially.

Methods of measurement of blood flow evaluate either total blood flow to the gland or tissue perfusion. Blood flow is a measure of the amount of blood passing through an organ, but does not indicate if all or only part of the volume recorded is available for tissue perfusion. Any blood passing through an arteriovenous shunt will be included in the measurement although it does not pass through the capillary bed. Tissue perfusion indicates the volume of blood which actually passes through the capillary bed and therefore represents tissue perfusion. It does not include any flow that passes through an arteriovenous shunt. If, however, the entire blood flow to an organ participates in tissue perfusion, measurements of "flow" and "perfusion" will have equal value.

To measure flow in the canine pancreas it is essential to be familiar with the anatomy of the blood supply which has been demonstrated to be from three main sources (Fig. 1) [17, 35, 42]. The superior pancreaticoduodenal artery, one of the two end-arteries of the gastroduodenal artery, supplies the head of the gland and part of the body and uncinate process. Branches of the splenic artery supply a portion of the body and tail, and the inferior pancreaticoduodenal artery, arising from the superior mesenteric artery, supplies part of the uncinate process [35, 42]. The degree to which each artery supplies an area is variable and anomalies occur. It is important to be aware that part of the flow from the superior and inferior pancreaticoduodenal arteries supplies the duodenum through the vascular connections between the head of the gland and the duodenum.

This review examines blood flow and perfusion measurements in the canine pancreas—first in anesthetized dogs and subsequently in ambulant animals. It is difficult to compare

0022-4804/87 $1.50

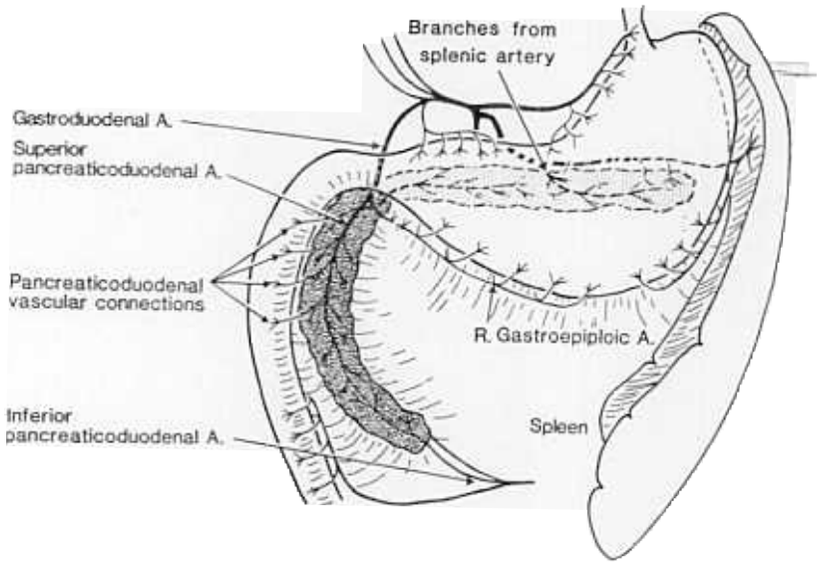

FIG. 1. Blood supply of canine pancreas.

some recorded measurements of blood flow with others, as flow has been variously expressed in ml/min, ml/min/100 g pancreas, and ml/min/kg body weight. Some authors have expressed pancreatic flow as a percentage of the cardiac output to eradicate any discrepancies that may be due to differences in the cardiac output; unfortunately not all authors have measured this value, precluding the comparison of pancreatic flow in these reports with that in others.

1. ANESTHETIZED DOGS (TABLE I)

Measurement of Blood Flow

Plethysmography. This was the first method used for assessing blood flow in the pancreas [24]. The technique measures the volume of the pancreas by placing it in a flexible fluid filled container. Changes in blood flow are then assessed by measuring changes in volume of the gland. Several authors have used the technique and recorded changes in blood flow, although no specific values were given [2, 16, 24, 48].

There are several drawbacks to the technique: the measurements are of the volume of the gland and not flow [14] and the interpretation of changes in blood flow following changes in organ volume can be difficult [3, 73]. In addition, the pancreas, due to its anatomical configuration, is not an ideal organ for volume measurement [48].

Stromuhr. This technique measures flow by directing the blood into a chamber of a known volume. The time to fill the chamber is noted and the blood is then permitted to flow back into the animal. This method has been used by several workers [5, 8, 11, 26, 67]. Herrick and Baldes [37] described flow measurement with a thermostromuhr. The principle used is that when heat is applied to the blood in a vessel the temperature increases—flow can be calculated from the rate of change in temperature which is measured with a differential thermocouple applied to the outside of the vessel [62].

There are several drawbacks to the technique. Eichelter and Schenk [17] point out that the measurements are qualitative, indicating direction of change, and are not susceptible to accurate calibration and quantitation. Also, substantial surgical manipulation of the gland is necessary [14].

Measurements taken by plethysmography and the stromuhr allowed early workers to gain

TABLE 1

MEASUREMENTS OF PANCREATIC BLOOD FLOW AND PERFUSION IN ANESTHETISED DOGS

Technique	Date	Authors		ml/min	ml/min/100 g	PBF/CO (%)[d]
Venous outflow	1968	Hermreck *et al.*	?	—	51	—
	1969	Mandelbaum and Morgan	[a]	9–25	—	—
	1970	Frogge *et al.*	[b,c]	—	87	—
	1972	Pissiotis *et al.*	[a]	22–24	—	—
	1972	Lau *et al.*	[a–c]	—	44.3	—
Electromagnetic flow meters	1966	Eichelter and Schenk	[a]	21.4	—	—
	1971	Rappaport *et al.*	[a–c]	—	10–15.6	—
	1973	Papp *et al.*	—	22.1	—	—
	1974	Lefer and Spath	[a–c]	—	45–50	—
	1975	Fischer *et al.*	—	57–63	200	—
	1978	Donaldson *et al.*	[a]	43.9	—	2.9
	1982	Studley and Schenk	[a]	33.8	—	1.28–2.67
	1982	Studley *et al.*	[a]			
	1982	Wells and Schenk	[a]	—	—	1.4–1.8
	1983	Wells *et al.*	[a]	—	—	1.65
	1983	Knol *et al.*	[a–c]	42.7–62.7	—	—
Isotope fractionation	1958	Sapirstein	—	—	100	1.6
	1965	Gilsdorf *et al.*	—	—	46.8	—
	1966	Delaney and Grim	—	17	61	0.65
	1966	Papp *et al.*	—	22	75.9	0.87
	1969	Goodhead	—	14.3	63.2	0.62
Radiolabeled microspheres	1974	Wulff and Sjöström	—	—	22	—
	1975	Sjöström and Wulff	—	—	44	0.6
	1979	Becker *et al.*	—	—	33	—
	1980	Gurll *et al.*	—	—	42	0.8
	1982	Becker *et al.*	—	—	35	—
	1982	Shatney *et al.*	—	—	31.5–45.8	—
	1983	Lindblad and Bergqvist	—	—	36–44	—
Hydrogen desaturation	1969	Aune and Semb	—	—	42.8	—
^{133}Xe clearance	1974	Glazer and Needham	—	—	120	—
	1974	Ercan *et al.*	—	—	106.8	—
^{85}Kr clearance	1986	Studley *et al.*	—	—	99.4	—
			[a]	—	85.0	—
			[a–c]	—	88.4	—
			Means:	29.8	66.1	1.28

[a] Vessels ligated in preparation.
[b] Pancreaticoduodenal vessels divided.
[c] Part of the pancreas removed or isolated.
[d] Percentage of cardiac output distributed to the pancreas.

some insight into pancreatic blood flow, but the methods would now be regarded as rather primitive and clumsy.

Venous outflow. This method was initially described by Anrep in 1916 [2] who measured the venous outflow by counting the drops of

blood that escaped from a pancreatic vein. Both Anrep [2] and Weaver [75] observed changes in rates of flow but no numerical values were given for actual volume flow.

Kanazawa *et al.* [40] measured flow from the superior pancreaticoduodenal vein in the heparinized dog. Control flows varied from 0.69–1.22 ml/min/kg body weight. As the flow is recorded in relation to body weight it is difficult to compare the measurements in this experiment to those in subsequent investigations.

Hermreck *et al.* [36] measured the venous outflow from the head of the pancreas after it had been isolated from the duodenum. Operative details were not given, but flow was recorded as 44–59 (mean 51) ml/min/100 g in eight control dogs, the measurements being taken over a 4-hr period. Mandelbaum and Morgan [47] measured flow by collecting blood from the superior pancreaticoduodenal vein. Once the measurement was completed the blood was reinfused into the femoral vein. To ensure all venous outflow occurred through the superior pancreaticoduodenal vein, a splenectomy was performed and the inferior pancreaticoduodenal and "pancreatic veins" were ligated. No specific mention was made of the pancreaticoduodenal vascular connections. Mean flow in different groups of dogs was recorded from 9 to 25 ml/min. No measurements of pancreatic weight or cardiac output were made—it was therefore not possible to express the flow in ml/min/100 g or as the percentage of the cardiac output distributed to the pancreas. Pissiotis *et al.* [56] measured flow using the same preparation and found mean control values to vary from 22 to 24 ml/min in different groups of animals. No measurements of pancreatic weight or cardiac output were made.

Frogge *et al.* [25] recorded a mean flow of 87 ml/min/100 g. In their preparation flow was measured by collecting blood from a cannula placed in the superior pancreaticoduodenal vein after excluding the uncinate process, neck, and tail of the pancreas, leaving the head of the gland alone. Vascular connections to the duodenum were ligated and divided. Lau *et al.* [44] measured flow from the superior pancreaticoduodenal vein after dividing the body of the pancreas from the head and uncinate process. Vascular connections between the head and duodenum were divided and the inferior pancreaticoduodenal vein was ligated. Mean flow was 44.3 ml/min/100 g.

Advantages of this technique are that it is a direct measurement of flow; multiple estimations can be taken in each animal, which can therefore act as its own control. The equipment required is simple and inexpensive.

The disadvantage of the venous collection method is that considerable manipulation of the pancreas may be required [14]. In addition, the internal venous drainage may be affected not only by manipulation of the gland, but also by ligating part of the venous outflow, which may alter the normal blood flow pattern within the gland, a criticism which could be applied to all the preparations described. The technique may also determine only a part of the total flow from an unknown fraction of the organ [14], although this problem may have been reduced in the model described by Frogge *et al.* [25].

Electromagnetic flow meters. Flowmeters work on the basis that an electric field is induced when a conductor (such as blood) passes through a magnetic field. The electric field induced is proportional to the magnetic field and to the velocity of the substance passing through that magnetic field. The voltage produced can then be amplified and measured. To use this technique in the canine pancreas, a "cuff"-type probe has been placed around the vessel supplying the gland. Within the cuff a magnetic field is produced between opposite poles on either side of the vessel—at 90° to the field there are electrodes which measure the voltage produced. This voltage can then be converted to a volume flow rate by taking into account the diameter of the vessel.

Eichelter and Schenk [17] were the first investigators to use this method for measuring blood flow in the canine pancreas. Difficulty with this technique arises because the pancreas is not an end-organ and receives arterial blood from three sources, two of which also supply the duodenum through the pancreaticoduodenal vascular connections, as previously de-

scribed. It is therefore necessary to isolate specific vessels and regions of the pancreas for study. The degree of isolation of the blood supply has varied greatly between workers. Eichelter and Schenk [17] recorded normal flow as 12.0–33.5 (mean 21.4) ml/min, or 0.46–1.37 (mean 0.85) ml/min/kg body weight. These values were achieved by placing a flow probe around the superior pancreaticoduodenal artery. Accessory vessels, which included the inferior pancreaticoduodenal artery and branches from the splenic artery supplying the pancreas were ligated. They did not devascularise the duodenum from the head of the pancreas. Cardiac output was not measured. Donaldson *et al.* [15] used a similar preparation, the only difference being that blood flow through the superior pancreaticoduodenal artery was measured with a probe placed around the gastroduodenal artery, the right gastroepiploic artery being ligated. In addition, cardiac output was assessed with a flow probe which was placed around the ascending aorta. Mean pancreatic flow was 43.9 ml/min, representing 2.9% of the cardiac output. Using the same preparation, the mean percentage of the cardiac output being distributed to the pancreas in different groups has been reported as 1.62–2.67% [68] and 1.28–2.27% [69]. Absolute pancreatic blood flow was not documented in these two publications, but from the original data in 42 dogs the measurements ranged from 12 to 80 (mean 33.8) ml/min. The same model has been used by Wells and his associates—in two groups of dogs the percentage of cardiac output distributed to the pancreas was 1.4 and 1.8% [76] and a mean value of 1.65% in five groups [77].

Rappaport *et al.* [61] removed the body and tail of the pancreas and divided the vascular connections to the duodenum, leaving the uncinate process supplied by the inferior pancreaticoduodenal artery and drained by the superior pancreaticoduodenal vein. Flow was measured with an electromagnetic flow probe on the artery which gave values from 10.0 to 15.6 ml/min/100 g. Cardiac output was not measured.

Papp *et al.* [53] measured flow with a probe on the superior pancreaticoduodenal artery. No vessels in the preparation were ligated, but a cannula was placed in the gastroduodenal artery for administering drugs. Cardiac output was not measured. Pancreatic flow was recorded as 14.7–29.6 (mean 22.1) ml/min. Fischer *et al.* [22] measured flow using the same experimental preparation as Papp *et al.* [53], but without a cannula in the gastroduodenal artery. Mean flow in three groups varied from 57 to 63 ml/min. From preliminary measurements of vascular diameters they calculated that over 90% of the superior pancreaticoduodenal arterial flow reached the pancreas and that 58 ± 2% of the pancreatic wet weight was supplied by the vessel. From these questionable calculations they determined flow to be 200 ml/min/100 g.

Lefer and Spath [45] measured flow through the superior pancreaticoduodenal artery after occluding the superior mesenteric artery and the pancreaticoduodenal vascular connections. No part of the gland was removed, but a clamp was placed across the body of the gland, thus isolating the distal part of the body and tail from the rest of the gland. Flow was recorded in two different groups of animals as 45 and 50 ml/min/100 g. Knol *et al.* [42] measured flow with a probe placed around the gastroduodenal artery after ligating the right gastroepiploic and inferior pancreaticoduodenal arteries as well as the paraduodenal collaterals. The body and tail of the pancreas were excised. In two different groups of dogs flow was recorded as 42.7 and 62.7 ml/min.

The advantage of the electromagnetic flowmeter technique is that flows can be recorded accurately and continuously in ml/min. In addition, each animal acts as its own control. No manipulation of the gland is required after the preparation has been completed. Once the equipment has been acquired there is little further expense.

In discussing their preparation, Eichelter and Schenk [17] commented: ". . . blood flow measurements are neither the entire pancreatic flow, nor is all the flow measured delivered to the pancreas." In many of the preparations the pancreaticoduodenal vascular connections were not divided [15, 17, 22, 53, 68, 69, 76, 77]. Electromagnetic flow measurement of

blood flow to the pancreas has been studied before and after ligation of these vessels in eight dogs [71]: mean pancreatic flow fell from 33.8 ml/min to 24.8 ml/min after the dissection procedure, indicating an error of approximately 35% if the pancreaticoduodenal vessels are not ligated. Consequently, the results of the investigations described above in which these vessels have not been interrupted, must be interpreted with great reservation.

In the preparations in which accessory vessels had not been ligated, the measurements may also be erroneous as the gland will receive blood through the accessory vessels [22, 53]. Other drawbacks include the suggestion that ligation of part of the arterial supply may affect perfusion within the gland. Eichelter and Schenk [17] injected contrast medium into the pancreaticoduodenal artery after isolating the pancreas by their technique and found that this sole artery supplied the whole gland. Elliott [18] reported that the pancreas in the dog could survive on the superior pancreaticoduodenal artery and vein with very little scarring when observed over a period of 2 to 6 weeks. However, Hermon-Taylor [35] suggested that perfusion through the coeliac axis alone could lead to inadequate perfusion of some parts of the gland, due to variations in vascular anastomoses within the gland and anomalies of the blood supply to the body and tail. Knol *et al.* [42] stated that perfusion in the body and tail of the gland fell when the splenic vessels were ligated. No operative details of their investigation were given. Perfusion in different regions of the gland has been measured with an inert gas clearance technique and this investigation is described fully later in this review [72]. However, it was demonstrated that if the accessory vessels were ligated varying amounts of the body and tail of the gland became macroscopically ischemic. In addition, perfusion in the uncinate process was reduced when the inferior pancreaticoduodenal artery was divided. Therefore the evidence indicates that perfusion in certain areas of the gland is reduced by ligating part of the arterial supply. It is possible that this, in turn, may affect the accuracy of the electromagnetic flow measurement, which would be a further criticism of many of the preparations [15, 17, 42, 45, 61, 68, 69, 76, 77].

Other disadvantages which are applicable to all the preparations described are that considerable operative manipulation is required in preparing the model; during the dissection the pancreas is handled and could be damaged. Vascular occlusion was necessary for calibrating the earlier designs of flow probes, but this is not necessary with the more modern equipment. As the technique measures only arterial flow to the pancreas, any arteriovenous shunt flow within the organ leads to an overestimation of blood flow to the tissue.

Measurement of Tissue Perfusion

Thermocouples

This method requires a heated thermocouple, maintained at a certain temperature, to be inserted into the pancreatic tissue. The temperature of the needle is dependent on tissue perfusion—increased perfusion cools the needle, whereas reduced perfusion allows it to heat up. An assessment of perfusion can then be made from the change in temperature of the needle [27]. Measurements using this method record changes in tissue conductivity rather then giving numerical values of perfusion [51–54].

A serious disadvantage of this technique is that it gives only relative measurements of blood flow [3]. The gland may also be damaged by the thermocouples.

Indicator Fractionation

Radioactive tracers. This method assesses cardiac output, organ blood flow and perfusion by measuring the distribution of radioactive indicators. The principle used is that when an indicator is injected into the left ventricle, it will be distributed to the organs of the body in the arterial system in proportion to the flow to each organ. Cardiac output can be calculated from the dilution curve of the changing concentrations in arterial samples. Organ blood flow can be calculated by killing the animal during the first circulation of the indicator and measuring the amount of indicator that is present in the organ. Blood flow can then

be calculated from the fraction of the indicator in the organ as compared to the injected volume, and expressed as ml/min or as a fraction of the cardiac output. Most authors using this technique have expressed flow in ml/min/100 g pancreas, and so the method may be regarded as a means of determining pancreatic perfusion.

Sapirstein [63] initially employed this method in the canine pancreas using Potassium-42 (^{42}K). Cardiac output was recorded as 170 ml/min/kg and mean pancreatic perfusion as 2.7 ml/min/kg body weight, or 1.6% of the cardiac output. Perfusion of the pancreas was quoted as 100 ml/min/100 g. Gilsdorf *et al.* (28), using the same isotope, found mean perfusion to be 46.8 ml/min/100 g; cardiac output was not reported. Delaney and Grim [14] using both ^{42}K and Rubidium-86 (^{86}Rb), recorded a mean pancreatic perfusion of 61 ml/min/100 g. Mean blood flow was 17 ml/min, and mean cardiac output 2.7 l/min, of which 0.65% was distributed to the pancreas. The authors noted that their perfusion measurements were nearly half those reported by Sapirstein [63] and considered that this might be due, in part, to the relatively greater weight of the pancreas in Sapirstein's dogs.

Papp *et al.* [51], using ^{86}Rb, found that the mean value of perfusion in the pancreas was 75.9 ml/min/100 g (22.0 ml/min); 0.87% of the cardiac output was calculated to be distributed to the pancreas. To confirm the validity of ^{86}Rb clearance as a measurement of perfusion, they also compared ^{86}Rb clearance with venous outflow from part of the gland and found that the measurements were similar. Goodhead [32] used the technique with ^{86}Rb—mean pancreatic flow was 14.3 ml/min or 63.2 ml/min/100 g. This flow represented 0.62% of the cardiac output.

The major advantage of this technique is that no operative manipulation of the gland is required prior to measurement of the flow. A possible source of error that applies to all the experiments outlined is that only a single measurement is taken and this is estimated over a very brief span of time. Care must be taken to avoid recirculation of the isotope, which could also lead to inaccurate results. Another limitation is that only a single measurement can be made in each animal, as the animal must be sacrificed to allow analysis of the isotope content of the tissues [3, 56]. Therefore each animal cannot act as its own control in subsequent measurements during the experiment.

Radiolabeled microspheres. This technique works on the same theory as isotope fractionation, in that an indicator is injected into the circulation of an animal, following which organ perfusion can be calculated from the fraction of the indicator in each organ. Whereas in the isotope fractionation method the animal must be killed during the first circulation of the isotope, it is not always necessary when measuring perfusion with radiolabeled microspheres. Once injected, the microspheres become trapped in the organs, allowing readings to be taken after organ excision. Further readings can be taken by injecting microspheres with a different radioactive label.

Wulff and Sjöström [78] measured pancreatic perfusion with this method using radiolabelled microspheres with three different labels, 15–50 μm in diameter: Chromium-51 (^{51}Cr), Strontium-85 (^{85}Sr), and Cerium-141 (^{141}Ce). Cardiac output was measured simultaneously by indicator dilution as previously described. Mean pancreatic perfusion was recorded as 22 ml/min/100 g. Cardiac output was 2.0 l/min. In 1975, Sjöström and Wulff [65], using a similar model, measured tissue perfusion as 44 ml/min/100 g. Cardiac output was 2.9 l/min with 0.6% being distributed to the pancreas. Becker *et al.* [6, 7] measured regional splanchnic perfusion by a similar technique. In the first study [6] pancreatic perfusion was 33 ml/min/100 g and cardiac output 132 ml/min/kg body weight. In the second study [7] perfusion was 35 ml/min/100 g and cardiac output 91 ml/min/kg. Gurll *et al.* [33] measured perfusion with 15 μm diameter microspheres tagged with Scandium-46 (^{46}Sc), ^{85}Sr and ^{141}Ce, 2.4 million being injected for each reading. Mean perfusion was reported as 42 ml/min/100 g, 0.8% of the cardiac output being distributed to the gland. Shatney *et al.* [64], used 35 μm diameter microspheres labeled with ^{46}Sc, Cobalt 57 (^{57}Co), and Tin-113

(^{113}Sn) and 50 μm diameter microspheres labeled with ^{51}Cr, ^{85}Sr, and ^{141}Ce. The number of spheres used for each reading varied between 150,000 and 250,000. Mean perfusion was 31.5 ml/min/100 g after a sham operation, 40.4 one week later and 45.8 three weeks later. Lindblad and Bergqvist [46], using approximately 3 million 15 μm diameter microspheres (^{57}Co, Zinc-65 (^{65}Zn), ^{85}Sr, and Niobium-95 (^{95}Nb)) per injection, recorded baseline pancreatic perfusion as 36 and 44 ml/min/100 g in two groups of dogs.

Advantages of this technique are that minimal, if any, manipulation of the pancreas is required prior to recordings. Further readings can be taken using microspheres with a different radioactive label, although the number of measurements possible is limited by the number of different microspheres available. Disadvantages include the possibility of damage to the gland as microspheres are lodged in the vessels and also the cost of the equipment and microspheres. Buckberg *et al.* [10] have demonstrated that errors in this technique are usually less than 20% if 400 or more microspheres are present in a sampling site, but smaller numbers may cause errors up to 113%. This criticism does not apply to the experiments described above in which the number of microspheres used has been recorded [33, 46, 64], but it is unclear if it applies to those which have not recorded the number per reading [6, 7, 65, 78].

Inert Gas Washout

The inert gas clearance technique is based on the Fick principle, which states that the quantity of a metabolically inert substance taken up by tissue in unit time is the product of the arteriovenous concentration difference and the blood flow. The tracer should be metabolically inert and diffuse between blood and tissue with no significant limitation.

Hydrogen desaturation. Aune and Semb [3] measured pancreatic perfusion by recording the rate of hydrogen desaturation in the gland. To obtain this measurement platinum electrodes were placed in the head and body of the gland. After suitable hydrogen gas concentration was achieved in the tissue, the arterial hydrogen concentration was lowered to zero by stopping hydrogen inhalation. Hydrogen gas then diffused from the tissue into the blood at a rate determined by tissue perfusion. Perfusion was calculated from the electric current produced by hydrogen oxidation of the platinum surface which is proportional to the hydrogen gas concentration. Measurements of perfusion in each dog varied from 16.8 to 74.7 (mean 42.8) ml/min/100 g. There were variations in perfusion in the two areas of the gland in which perfusion was assessed, but these were not consistent. To assess clearance from the gland the value of the partition coefficient for the gas between the tissue and blood should be known. In the calculations the authors assumed the tissue/blood partition coefficient and specific gravity of pancreatic tissue to be unity. No measurements of cardiac output were made.

A disadvantage of this method is that tissue trauma can be caused by placing electrodes in the gland and manipulation of the hydrogen gas concentration in the blood may affect physiological processes within the animal. The equipment required for this technique is expensive. It has not been widely used in pancreatic blood flow investigations.

Xenon-133 (^{133}Xe) amd Krypton-85 (^{85}Kr) clearance. The original gas washout technique was described in 1961 by Lassen and Ingvar, who injected ^{85}Kr directly into the arterial supply of the brain. The theory of this intraarterial technique is that when a single dose of an isotope is injected into an artery supplying an organ, it diffuses into the tissues of that organ from the blood very rapidly, 95% equilibrium being reached within a second [41]. After the passage of the blood containing the isotope through the organ, the arterial blood concentration of the gas will fall to zero and the gas will diffuse from the tissues back into the blood. The clearance from the tissue (measured with a detector held over the surface of the gland) will depend on the rate of perfusion. The isotope is then excreted via the lungs as the solubility of both ^{133}Xe and ^{85}Kr is greater in air than in tissue or blood. In one circulation through the lungs 90–95% of ^{133}Xe

[57] and 95–99% of ^{85}Kr is eliminated [12]—consequently minimal amounts of the gas are retained in the blood for recirculation which could affect perfusion measurements.

Of the two isotopes discussed, ^{85}Kr emits over 99% of its activity as beta emissions with an energy of 695 keV. Mean penetration in tissue is 0.7 mm, with a maximum penetration of 2.6 mm [3]. The principal activity of ^{133}Xe is gamma emissions with an energy of 81 keV [29].

An expression for tissue perfusion using this technique can be derived from the Fick principle and is shown to be:

$$\frac{\log_{e^2} \cdot \lambda}{T_{1/2}} \text{ml/min/g},$$

where λ is the partition coefficient for the inert gas between the tissue and blood and $T_{1/2}$ is the time (in minutes) for the tissue concentration of indicator to fall to one half of its value.

Two groups of workers have evaluated perfusion in the canine pancreas by measuring ^{133}Xe clearance. Glazer and Needham [31] injected ^{133}Xe into the splenic artery near a branch of the artery supplying what they described as the left lobe of the pancreas. From their descriptions it is probable that they were referring to the body and tail of the gland as the spleen was removed in their preparation. Clearance of ^{133}Xe from the tissue was then measured using a scintillation counter. They measured perfusion as 120 ml/min/100 g. A possible error in their calculations is that they assumed the pancreas/blood partition coefficient of ^{133}Xe to be 0.65 following work by Conn in 1961 on various organs [13], although the coefficient for the isotope in the pancreas was not actually measured.

In the same year, Ercan *et al.* [21] measured perfusion as 74.6–169 (mean 106.8) ml/min/100 g by injecting ^{133}Xe into the pancreaticoduodenal artery. Perfusion in the tissue of the head, body and tail of the pancreas was also measured by injecting ^{133}Xe directly into the tissue. Mean results were 62.4, 85.7, and 67.1 ml/min/100 g, respectively, which were not significantly different. It is important to note, however, that these investigators did calculate the pancreas/blood partition coefficient of ^{133}Xe and found a value of 1.2. Although perfusion in the gland calculated by each group of workers was similar, the pancreas/blood partition coefficient used by Glazer and Needham [31] was considerably smaller than that of Ercan *et al.* [21], suggesting a marked difference in their recorded clearance rates.

Studley *et al.* [72] assessed perfusion in the head, body, uncinate process and tail of the gland, using the isotope ^{85}Kr in the intraarterial injection technique. The investigation was performed in eight dogs, initially with all vessels to the pancreas being intact and subsequently after division of the accessory vessels. To ensure the flow was stable for each ^{85}Kr clearance reading an electromagnetic flow probe was placed around the gastroduodenal artery to allow continuous monitoring of pancreatic arterial blood flow (ml/min) on a chart recorder. In the preparation in which all vessels were intact, ^{85}Kr was first injected into the superior pancreaticoduodenal artery and mean perfusion of the head of the gland was recorded as 99.4 ml/min/100 g, and in the body 117.5 ml/min/100 g. No activity was detected in either the uncinate process or the tail of the gland when ^{85}Kr was injected by this route. Mean perfusion was therefore measured in the uncinate process by injecting the isotope into a branch of the inferior pancreaticoduodenal artery (97.8 ml/min/100 g); perfusion in the tail of the gland was assessed following injection of ^{85}Kr directly into the splenic artery (131.3 ml/min/100 g). Comparing these perfusion measurements no difference was identified. The accessory vessels were then divided. The tail and varying degrees of the body of the gland invariably became macroscopically ischemic and no perfusion measurements were made in this region. Perfusion in the other regions was measured by injecting ^{85}Kr into the superior pancreaticoduodenal artery. Mean perfusion values recorded were: head 85.0 ml/min/100 g; body 93.6 ml/min/100 g; uncinate process 70.2 ml/min/100 g. Perfusion values in the head and body of the gland were similar, but measurements in the uncinate process were lower (*P*

< 0.05) than in the head of the gland. Therefore anastomoses within the pancreas between the superior and inferior pancreaticoduodenal arteries were not adequate enough to prevent a decrease in perfusion in the uncinate process.

In this experiment the electromagnetic flow measurements (ml/min) could, in principle, be expressed in ml/min/100 g by using the weight of the gland that had been supplied by the vessel. However, it was not possible to standardize the two measurements in either group for several reasons. If all the vessels supplying the gland were intact it was not possible to determine the weight of the gland being supplied by the superior pancreaticoduodenal artery. In the preparation in which the accessory vessels were ligated, the weight of the gland supplied by this sole artery could be determined after removing the macroscopically ischemic tissue; however, perfusion in the uncinate process was reduced which would cause misleading results. In addition, in both preparations the pancreaticoduodenal vessels were not ligated which would lead to an overestimation of the electromagnetic flow measurement.

To overcome this problem of comparing measurements the authors removed the body, tail, and uncinate process and divided the pancreaticoduodenal vessels, leaving the head of the gland alone supplied solely by the superior pancreaticoduodenal artery and vein. Measurements of ^{85}Kr clearance (88.4 ml/min/100 g) were found to be similar to those taken by the electromagnetic flow technique (95.4 ml/min/100 g), after conversion to the same units using the weight of the head of the gland. The authors felt that this preparation had considerable advantages over those previously described as two measurement techniques were being used, thus allowing confirmation of any flow measurements.

The fundamental advantage of the inert gas technique is that it measures tissue perfusion directly and it is therefore not dependent on whether the organ receives its blood supply from one or several arteries. Once the gas has cleared completely further recordings can be made. Another advantage is that the only surgical manipulation required prior to recording perfusion is the placement of a cannula in a vessel, or its side branch, which allows injection of isotope into the arterial supply of the organ being studied. Arteriovenous shunts do not affect the accuracy of the method. The accuracy of the measured perfusion rate is, however, dependent on knowledge of the tissue/blood partition coefficient of the gas used, and there is uncertainty about the value of this for ^{133}Xe in the pancreas, thus suggesting inaccuracies in one or both of the investigators' measurements [21, 31]. The partition coefficient of ^{85}Kr in the study of Studley *et al.* [72] was estimated from the fat content of the tissue. Interpretation of the clearance curves may not always easily be carried out, but in the preparations in which the electromagnetic flow technique is also used to monitor flow this is not so much of a problem, as a clearance measurement can be made when the flow is demonstrably stable. Activity in adjacent regions may be picked up by external detectors which may also lead to errors in the measurements; this factor is more of a problem with Xenon than with Krypton due to the greater penetration of the gamma emissions of Xenon from surrounding tissues.

2. AMBULANT DOGS

Anesthesia is an abnormal physiologic stimulus which affects hemodynamics [3, 6, 20, 59]. It is for this reason that several investigators have attempted to measure pancreatic blood flow in the ambulant dog.

Measurement of Blood Flow

Electromagnetic Flow Meters

Fischer *et al.* [23] measured pancreatic blood flow in four dogs with the electromagnetic flow technique by placing a probe around the superior pancreaticoduodenal artery. No vessels were ligated and cardiac output was not measured. Mean flows of 50–60 ml/min were recorded from 3 to 8 days postoperatively with the dogs standing in a Pavlov frame.

Studley *et al.* [70] evaluated blood flow in the conscious dog, using electromagnetic flow probes placed on the ascending aorta for mea-

suring cardiac output, and the gastroduodenal artery for measuring pancreatic arterial blood flow. The right gastroepiploic artery, the inferior pancreaticoduodenal artery, and branches from the splenic artery supplying the pancreas were ligated. Vascular connections between the head of the pancreas and the duodenum were not divided. Data reported in the experiment included mean blood pressure, cardiac output, and the percentage of the cardiac output distributed to the pancreas, the measurements being taken 24 hr after preparation of the model. Blood flow was measured following the operative procedure in the anesthetized animal and on both the first and second days postoperatively in the ambulant dog, with the animals lying on their side. There was no difference in mean blood pressure comparing measurements in the anesthetized dogs (118 mm Hg) with those taken 24 hr later in ambulant dogs (107 mm Hg), but after 48 hr the measurement was lower (102 mm Hg). Cardiac output was similar in the anesthetized and ambulant animals. In the anesthetized dog mean pancreatic blood flow was 46.6 ml/min, but was higher after 24 hr (69.0 ml/min) and after 48 hr (74.2 ml/min). Relative pancreatic flow (i.e., pancreatic flow expressed as a percentage of the cardiac output) rose from 1.5% in the anesthetized dog to 2.0% at 24 hr and to 2.1% at 48 hr. There were no differences comparing mean blood pressure, cardiac output, pancreatic flow, and relative pancreatic flow in the ambulant dogs 24 and 48 hr following the operation.

Measurement of Tissue Perfusion

Hydrogen Desaturation

Aune and Semb [3] measured perfusion in the pancreas in 15 dogs by the hydrogen desaturation technique previously described. Perfusion recordings were made with the dogs standing in a Pavlov frame 2–12 days following implantation of electrodes into the gland. After this time the sensitivity of the recordings was reduced or unstable. In the conscious dog, perfusion was 76 ml/min/100 g compared to a value of 49.4 ml/min/100 g in the anesthetized animal.

Radiolabeled Microspheres

Ericsson [20] measured flow by the distribution of ^{85}Sr and ^{141}Ce microspheres (50 μm diameter) in the conscious dog and 30 min after induction of anesthesia. Mean perfusion in the duodenum and pancreas in the ambulant animal was 126 ml/min/100 g and in the anesthetized state 77 ml/min/100 g. This flow represented 2.1% of the cardiac output in the conscious dog and 1.4% in the anesthetized dog.

Polansky and Safaie-Shirazi [58] measured perfusion in the pancreas with radiolabeled (15 μ diameter) microspheres: ^{46}Sc, ^{85}Sr, iodine-131 (^{131}I), and ^{141}Ce. They recorded perfusion as 64 ml/min/100 g. No measurements of cardiac output were made. Becker *et al.* (6) also measured perfusion by the injection of radioactive (15 μm diameter) microspheres. Control measurements were made with the dogs under anesthesia. Readings in the conscious animal were taken 10 days after operation. In the anesthetized animal perfusion was 33 ml/min/100 g compared to 131 ml/min/100 g in the conscious animal. Cardiac output was not different comparing the readings in anesthetized and ambulant dogs. They suggested that anesthesia had interfered with physiological splanchnic flow by changing the distribution and reducing resting flows. It is unclear why the measurements of pancreatic perfusion reported by Polansky and Safaie-Shirazi [58] and Becker *et al.* [6] should vary so greatly. The microspheres were of a similar size and measurements were taken 10 and 14 days following anesthesia. The number of microspheres used by each was not recorded. Polansky and Safaie-Shirazi did not measure cardiac output which could possibly have accounted for some or all the difference.

Measurements in ambulant animals can be awkward to obtain due to difficulties associated with ensuring that the dogs are in a relaxed state. With the electromagnetic flow technique [23, 70] this is not so much of a problem as with hydrogen desaturation [3] or the distribution of radiolabeled microspheres [6, 20, 58] as continuous recordings can be made and measurements taken during stable

periods. As the perfusion techniques take single measurements this is not possible.

In addition to this problem, the disadvantages associated with each technique still exist: studies using the electromagnetic flow method employed two different preparations, one in which no vessels were ligated [23] and the other in which the accessory vessels were divided but the pancreaticoduodenal vessels were intact [70]. Therefore, not only is it difficult to compare the two groups of measurements, but also it is possible that they are both inaccurate. The gland may be damaged in the hydrogen desaturation technique by the electrodes, and physiological processes affected by varying hydrogen gas concentrations. In the microsphere technique the small vessels may be occluded. In both perfusion techniques only a limited number of readings can be taken. Measurements obtained using radiolabeled microspheres indicate a large variation which is difficult to explain.

3. SUMMARY AND CONCLUSIONS

Blood flow in the anesthetized animal has been measured indirectly by plethysmography and directly with the stromuhr, venous outflow, and electromagnetic flow techniques. Tissue perfusion in the gland has been assessed qualitatively with thermocouples and quantitatively by isotope fractionation, the distribution of microspheres, hydrogen desaturation, and clearance of either ^{133}Xe or ^{85}Kr. The results of these investigations have been conflicting as there is a large variation in both flow and perfusion measurements, not only overall but also in the values reported by each technique (Table 1). Taking all methods into account flow measurements have been recorded from 9 to 63 (mean 29.8) ml/min, and 10 to 200 (mean 66.1) ml/min/100 g. The mean percentage of the cardiac output distributed to the pancreas is 1.28. Some of these differences are due to various drawbacks associated with each of the techniques; some are almost certainly due to variations in the surgical preparations, and others are undoubtedly caused by the complexity of the pancreatic circulation. Measurements of perfusion in different regions of the pancreas of individual dogs show no difference if all vessels are intact, but accessory vessel ligation affects perfusion in certain areas.

In ambulant dogs the studies suggest that pancreatic blood flow is higher than in the anesthetized animal. This is probably true despite inaccuracies associated with each of the techniques. In addition to this drawback there is also the problem of obtaining measurements with the dogs in a relaxed state. It is probably for this reason that the majority of investigators have preferred to examine blood flow and perfusion in the canine pancreas in the anesthetized animal.

It is not possible to make a definitive statement regarding the best model and measurement technique available to measure blood flow or tissue perfusion in the canine pancreas. The choice should undoubtedly be governed by the aims of the proposed study.

In studies of tissue perfusion in the intact gland, it is obviously preferable that all vessels should be intact, as division of any vessels supplying the gland has been shown to affect perfusion in certain areas. Measurements in such a preparation could be taken using the ^{85}Kr clearance technique, with a flow probe placed around the gastroduodenal artery to ensure stable flow during measurements. It is difficult to assess total arterial blood flow to the whole gland due to the number of vessels supplying the organ. Although measurements have been made through a single vessel, there are errors associated with this approach: if all vessels are intact the value will be underestimated and if "accessory vessels" are ligated changes in perfusion in some regions are induced, which may affect the accuracy of any blood flow measurement. For studies in which information about both blood flow and tissue perfusion is required, the preparation of the head of the gland alone in which both the electromagnetic flow and ^{85}Kr clearance techniques are employed may be suitable. To allow assessment of flow independent of changes in cardiac output, pancreatic blood flow can be expressed as a percentage of the cardiac output being distributed to the gland; however, the difficulties outlined in measuring blood flow

to the whole gland make this a measurement which is not easy to calculate accurately.

REFERENCES

1. Alteveer, R. J., Jaffe, M. J., and van Dam, J. Hemodynamics and metabolism of the in vivo vascularly isolated canine pancreas. *Amer. J. Physiol.* **236**: 626, 1979.
2. Anrep, G. V. The influence of the vagus on pancreatic secretion (Second Communication). *J. Physiol.* **50**: 421, 1916.
3. Aune, S., and Semb, L. S. The effect of secretin and pancreozymin on pancreatic blood flow in the conscious and anesthetized dog. *Acta Physiol. Scand.* **76**: 406, 1969.
4. Babkin, B. P., and Starling, E. H. A method for the study of the perfused pancreas. *J. Physiol.* **61**: 245, 1926.
5. Barcroft, H. A mechanical stromuhr. *J. Physiol.* **67**: 402, 1929.
6. Becker, H. Manganaro, A., Lazar, H., Mulder, D. G., and Buckberg, G. D. Limitations of studying splanchnic blood flow during anesthesia. *Surg. For.* **30**: 347, 1979.
7. Becker, H., Vinten-Johansen, J., Buckberg, G. D., and Bugyi, H. I. Correlation of pancreatic blood flow and high-energy phosphates during experimetal pancreatitis. *Eur. Surg. Res.* **14**: 203, 1982.
8. Bennett, A. L., and Still, E. U. A study of the relation of pancreatic duct pressure to the rate of blood flow through the pancreas. *Amer. J. Physiol.* **106**: 454, 1933.
9. Broe, P. J., Zuidema, G. D., and Cameron. J. L. The role of ischemia in acute pancreatitis: studies with an isolated perfused canine pancreas. *Surgery* **91**: 377, 1982.
10. Buckberg, G. D., Luck, J. C., Payne, D. B., Hoffman, J. I. E., Archie, J. P., and Fixler, D. E. Some sources of error in measuring regional blood flow with radioactive microspheres. *J. Appl. Physiol.* **31**: 598, 1971.
11. Burton-Opitz, R. Über die Strömung des Blutes in dem Gebiete der Pfortader. *Pflügers Arch.* **146**: 344, 1912.
12. Chidsey, C. A., III, Fritts, H. W., Jr., Hardewig, A., Richards, D. W., and Cournand, A. Fate of radioactive krypton (Kr^{85}) introduced intravenously in man. *J. Appl. Physiol.* **14**: 63, 1959.
13. Conn, H. L., Jr. Equilibrium distribution of radioxenon in tissue: xenon-hemoglobin association curve. *J. Appl. Physiol.* **16**: 1065, 1961.
14. Delaney, J. P., and Grim, E. Influence of hormones and drugs on canine pancreatic blood flow. *Amer. J. Physiol.* **211**: 1398, 1966.
15. Donaldson, L. A., Williams, R. W., and Schenk, W. G., Jr. Experimental pancreatitis: effect of plasma and dextran on pancreatic blood flow. *Surgery* **84**: 313, 1978.
16. Edmunds, C. W. The antagonism of the adrenal glands against the pancreas. *J. Pharmacol. Exp. Ther.* **1**: 135, 1909.
17. Eichelter, P., and Schenk, W. G., Jr. Hemodynamics of pancreatic secretion. *Arch. Surg.* **93**: 200, 1966.
18. Elliott, D. W. Discussion on Hemodynamics of pancreatic secretion. *Arch. Surg.* **93**: 206, 1966.
19. Eloy, M. R., Kachelhoffer, J., Pousse, A., Dauchel, J., and Grenier, J. F. Ex vivo vascular perfusion of the isolated canine pancreas. *Eur. Surg. Res.* **6**: 341, 1974.
20. Ericsson, B. F. Effect of pentobarbital sodium anesthesia, as judged with aid of radioactive carbonized microspheres, on cardiac output and its fractional distribution in the dog. *Acta Chir. Scand.* **137**: 613, 1971.
21. Ercan, M. T., Bor, N. M., Bekdik, C. F., and Öner, G. Measurement of pancreatic blood flow in dog by ^{133}Xe clearance technique. *Pflügers Arch.* **348**: 51, 1974.
22. Fischer, U., Hommel, H., and Schmid, E. Dynamics of canine pancreatic blood flow and of insulin secretion during an intravenous glucose load. *Pflügers Arch.* **358**: 89, 1975.
23. Fischer, U., Hommel, H., and Salzsieder, E. Pancreatic blood flow in conscious dogs after oral administration of glucose. *Diabetologia* **12**: 133, 1976.
24. Francois-Franck, M. M., and Hallion, L. Recherches sur l'innervation vaso-motrice du pancreas. *C. R. Soc. Biol.* **10**: 561, 1896.
25. Frogge, J. D., Hermreck, A. S., and Thal, A. P. Metabolic and hemodynamic effects of secretin and pancreozymin on the pancreas. *Surgery* **68**: 498, 1970.
26. Gayet, R., and Guillaumie, M. Presentation d'un hemorheometre constitue avec des segments vasculaires. *C. R. Soc. Biol.* **103**: 1102, 1930.
27. Gibbs, F. A. A thermoelectric blood flow recorder in the form of a needle. *Proc. Soc. Exp. Biol. Med.* **31**: 141, 1933.
28. Gilsdorf, R. B., Peter, E. T., Pearl, J. M., and Leonard, A. S. Hypothalamic influence on pancreatic blood flow and secretion. *Surg. For.* **16**: 371, 1965.
29. Glass, H. I., and Harper, A. M. Measurement of regional blood flow in cerebral cortex of man through intact skull. *Brit. Med. J.* **1**: 593, 1963.
30. Glass, H. I., Harper, A. M., and Glover, M. M. The measurement of local cortical blood flow in the brain by the analysis of the clearance curve of Krypton-85. *Phys. Med. Biol.* **6**: 65, 1961.
31. Glazer, G., and Needham, T. ^{133}Xenon clearance for repeat assessment of pancreatic blood flow in the anesthetized dog. *J. Physiol. (London)* **240**: 32P, 1974.
32. Goodhead, B. Vascular factors in the pathogenesis of acute haemorrhagic pancreatitis. *Ann. R. Coll. Surg. Engl.* **45**: 80, 1969.
33. Gurll, N. J., Reynolds, D. G., Coon, D., and Shirazi, S. S. Acute and chronic splanchnic blood responses to portacaval shunt in the normal dog. *Gastroenterology* **78**: 1432, 1980.
34. Hashimoto, K., Satoh, S., and Takeuchi, O. Effect of dopamine on pancreatic secretion in the dog. *Brit. J. Pharmacol.* **43**: 739, 1971.

35. Hermon-Taylor, J. A technique for perfusion of the isolated canine pancreas. *Gastroenterology* **55**: 488, 1968.
36. Hermreck, A. S., Smith, E. I., and Thal, A. P. Acute edematous pancreatitis: metabolic and hemodynamic studies. *Surg. For.* **19**: 368, 1968.
37. Herrick, J. F., and Baldes, E. J. The thermo-stromuhr method of measuring blood flow. *Physics* **1**: 407, 1931.
38. Homma, T., and Malik, K. U. Effect of prostaglandins on pancreatic circulation in anesthetized dogs. *J. Pharmacol. Exp. Ther.* **222**: 623, 1982
39. Iversen, J., and Miles, D. W. Evidence for a feedback inhibition of insulin on insulin secretion in the isolated, perfused canine pancreas. *Diabetes* **20**: 1, 1971.
40. Kanazawa, Y., Kuzuya, T., and Ide, T. Insulin output via the pancreatic vein and plasma insulin response to glucose in dogs. *Amer. J. Physiol.* **215**: 620, 1968.
41. Kety, S. S. The theory and applications of the exchange of inert gas at the lungs and tissues. *Pharm. Rev.* **3**: 1, 1951.
42. Knol, J. A., Edgcomb, L. P., Inman, M. S., and Eckhauser, F. E. Low molecular weight dextran in experimental pancreatitis: effects on pancreatic microcirculation. *J. Surg. Res.* **35**: 73, 1983.
43. Lassen, N. A., Ingvar, D. H. The blood flow of the cerebral cortex determined by radioactive Krypton85. *Experientia* **17**: 42, 1961.
44. Lau, T. S., Taubenfligel, W., Levene, R., Farago, G., Chan, H., Koven, I., and Drucker, W. R. Pancreatic blood flow and insulin output in severe hemorrhage. *J. Trauma* **12**: 880, 1972.
45. Lefer, A. M., and Spath, J. A., Jr. Pancreatic hypoperfusion and the production of myocardial depressant factor in hemorrhagic shock. *Ann. Surg.* **179**: 868, 1974.
46. Lindblad, B., and Bergqvist, D. Tissue blood flow and blood flow distribution after administration of dextran 70, dihydroergotamine and their combination. *Acta Chir. Scand.* **149**: 467, 1983.
47. Mandelbaum, I., and Morgan, C. R. Pancreatic blood flow and its relationship to insulin secretion during extracorporeal circulation. *Ann. Surg.* **170**: 753, 1969.
48. May, O. The relationship of blood supply to secretion, with especial reference to the pancreas. *J. Physiol.* **30**: 400, 1904.
49. Meyer, W., Castelfranchi, P. L., Schulz, L. S., Ruiz, O. J., Hendrickx, J., Aquino, C. J., and Lillehei, R. C. Physiologic studies during perfusion of the isolated canine pancreas. *Eur. Surg. Res.* **5**: 105, 1973.
50. Nardi, G. L., Grepp, J. M., Chambers, D. A., McCrae, C., and Skinner, D. B. Physiologic peregrinations in pancreatic perfusion. *Ann. Surg.* **158**: 830, 1963.
51. Papp, M., Varga, B., Acs, Zs, Krasznai, I., and Földes, J. Pharmacological effects on pancreatic blood flow. *Arch. Int. Pharm. Ther.* **161**: 61, 1966.
52. Papp, M., Makara, G. B., and Varga, B. Effets de la bradykinine, de la kallidine, de la serotonine et de l'histamine sur le flux sanguin du pancreas. *Arch. Int. Pharm. Ther.* **165**: 31, 1967.
53. Papp, M., Varga, B., and Folly, G. Effect of secretin, pancreozymin, histamine and Decholin® on canine pancreatic blood flow. *Pflügers Arch.* **340**: 349, 1973.
54. Papp, M., Feher, S., Varga, B., and Folly, G. Humoral influences on local blood flow and external secretion of the resting dog pancreas. *Acta Med. Acad. Sci. Hung.* **34**: 185, 1977.
55. Pascal, J. P., Roux, P., Vaysse, N., Lacroix, A., Martinel, C., and Ribet, A. Respiratory exchanges and acid-base balance during perfusion of ex vivo isolated pancreas. *Dig. Dis.* **21**: 381, 1976.
56. Pissiotis, C. A., Condon, R. E., and Nyhus, L. M. Effect of vasopressin on pancreatic blood flow in acute hemorrhagic pancreatitis. *Amer. J. Surg.* **123**: 203, 1972.
57. Pittinger, C. B., Conn, H. L., Featherstone, R. M., Stickley, E., Levy, L., and Cullen, S. C. Observations on the kinetics of transfer of Xenon and chloroform between blood and brain in the dog. *Anesthesiology* **17**: 523, 1956.
58. Polansky, D. B., and Safaie-Shirazi, S. Simultaneous measurement of pancreatic blood flow, endocrine, and exocrine secretion in conscious dogs. *Surg. For.* **28**: 91, 1977.
59. Priano, L. L., Traber, D. L., and Wilson, R. D. Barbiturate anesthesia: an abnormal physiologic situation. *J. Pharmacol. Exp. Ther.* **165**: 126, 1969.
60. Rao, M. M., and Elmslie, R. G. A modified technic of isolated pancreatic perfusion. *J. Surg. Res.* **10**: 357, 1970.
61. Rappaport, A. M., Kawamura, T., Davidson, J. K., Lin, B. J., Ohira, S., Zeigler, M., Coddling, J. A., Henderson, H., and Haist, R. E. Effects of hormones and of blood flow on insulin output of isolated pancreas in situ. *Amer. J. Physiol.* **221**: 343, 1971.
62. Rein, H. Die Thermo-Stromuhr. Ein Verfahren zur fortlaufenden Messung der mittleren absoluten Durchflussmengen in uneröffneten Gefässen in situ. *Z. Biol.* **87**: 394, 1928.
63. Sapirstein, L. A. Regional blood flow by fractional distribution of indicators. *Amer. J. Physiol.* **193**: 161, 1958.
64. Shatney, C. H., Harmon, J. W., and Rich, N. M. Effects of portasystemic shunting on visceral and portal blood flow in the dog. *Gastroenterology* **83**: 1170, 1982.
65. Sjöström, B., and Wulff, K. E. Influence of long-term anesthesia on regional blood flow distribution and hemodynamics in the dog. *Eur. Surg. Res.* **7**: 1, 1975.
66. Spath, J. A., Jr., Gorczynski, R. J., and Lefer, A. M. Pancreatic perfusion in the pathophysiology of hemorrhagic shock. *Amer. J. Physiol.* **226**: 443, 1974.
67. Still, E. U., Bennett, A. L., and Scott, V. B. A study of the metabolic activity of the pancreas. *Amer. J. Physiol.* **106**: 509, 1933.
68. Studley, J. G. N., Schenk, W. G., Jr. Pathophysiology of acute pancreatitis. Evaluation of the effects and mode of action of steroids in experimental pancreatitis in dogs. *Amer. J. Surg.* **143**: 761, 1982.
69. Studley, J. G. N., Lee, J. B., and Schenk, W. G., Jr. Pathophysiology of acute pancreatitis: evaluation of

the effects and mode of action of indomethacin in experimental pancreatitis in dogs. *J. Surg. Res.* **32:** 563, 1982.

70. Studley, J. G. N., Lee, J. B., and Schenk, W. G., Jr. Effects of indomethacin on blood flow in the normal pancreas in conscious dogs. *J. Surg. Res.* **37:** 464, 1984.
71. Studley, J. G. N., Mathie, R. T., and Blumgart, L. H. An evaluation of blood flow and perfusion in the canine pancreas. *Acta Chir. Scand.* **151:** 551, 1985.
72. Studley, J. G. N., Mathie, R. T., and Blumgart, L. H. Regional pancreatic perfusion. An experimental study in the dog. *Acta Chir. Scand.* **152:** 373, 1986.
73. Tankel, H. I., and Hollander, F. The relation between pancreatic secretion and local blood flow: a review. *Gastroenterology* **32:** 633, 1957.
74. Teufel, H., Hellmann, G., Wismeth, A., and Forell, M. M. The hydrelatic effect of secretin and its inactivation in isolated perfused dog pancreas. *Arch. Mal. Dig. Nut.* **61:** 104c, 1972.
75. Weaver, M. M. Studies on the visceral vasomotor responses to intravenous injection of purified pancreatic secretin. *Amer. J. Physiol.* **85:** 410, 1928.
76. Wells, A. D., and Schenk, W. G., Jr. Beneficial effect of ethamsylate on the relative blood flow in the pancreas in acute canine necrotizing pancreatitis. *Surg. Gynecol. Obstet.* **155:** 673, 1982.
77. Wells, A. D., Imahori, S. C., and Schenk, W. G., Jr. Does edematous pancreatitis exist in biliary-related pancreatitis? *Arch. Surg.* **118:** 1277, 1983.
78. Wulff, K., and Sjöström, B. Influence of acute pancreatitis on central hemodynamic, regional blood flow distribution and arteriovenous shunting in the dog. *Eur. Surg. Res.* **6:** 354, 1974.