Islet Capillary Blood Pressure Increase Mediated by Hyperglycemia in NIDDM GK Rats

Per-Ola Carlsson, Leif Jansson, Claes-Göran Östenson, and Örjan Källskog

This study was performed to measure pancreatic islet capillary pressure under basal conditions and after an acute glucose stimulation of insulin release in normal rats. In addition, the islet capillary pressure was estimated in GK rats, an animal model of NIDDM. Hydrostatic pressure in single pancreatic islet capillaries was determined in vivo by direct measurement using the micropuncture technique. The pancreatic islets were visualized by injection of neutral red. This intravital staining had no effect on islet function, whole pancreatic and islet blood flow, and capillary blood pressure in the exocrine pancreas. Islet capillary blood pressure in normoglycemic Wistar F rats was estimated at 3.1 ± 0.3 mmHg (n = 15). Administration of D-glucose (1 g/kg) doubled this value, whereas no effect was seen after injection of an equimolar dose of the non-metabolizable glucose-derivative 3-O-methyl glucose. In GK rats, basal islet capillary blood pressure was increased (5.7 ± 0.4 mmHg; n = 10; P < 0.001) when compared with the control Wistar F rats. Reduction of blood glucose levels in GK rats with phlorizin treatment showed this increased basal islet capillary pressure in GK rats to be glucose dependent and reversible. In the present study, we have for the first time shown that both acute and chronic hyperglycemia augment islet capillary pressure. The effects of a chronically increased islet capillary pressure on long-term islet function remain to be determined. Diabetes 46:947–952, 1997

The pancreatic islets of rats constitute only 1–2% of the whole pancreas (1,2) but receive a blood supply representing ~10% of whole pancreatic blood flow during normoglycemia (3–6). Animals with an increased functional demand on the islets, e.g., experimental and spontaneous models of NIDDM, have a 50–100% increase in islet blood flow (7–9).

A common denominator for many late complications of diabetes, such as retinopathy and nephropathy, is an altered and functionally insufficient microcirculation. These microvascular abnormalities have been suggested to owe their origin to a hyperperfusion of the organ with an associated increased capillary pressure; the latter is likely to cause the damage to the vascular walls that characterizes early diabetes (10–12). It is unknown at present if the high islet blood flow seen when an increased functional demand is placed on the islets is associated with a rise in pancreatic islet capillary pressure.

In view of the paucity of knowledge in this field, the aim of the present study was to measure basal pancreatic islet capillary pressure with a micropuncture technique in normal rats. Furthermore, we examined the effects of acute glucose administration on islet capillary pressure, as well as the effects of chronic hyperglycemia as seen in the Goto-Kakizaki (GK) rat, a model of NIDDM.

RESEARCH DESIGN AND METHODS

Animals. Male Wistar-Furth (WF) and Goto-Kakizaki (GK) rats aged 14–17 weeks and weighing approximately 350 g were used in all experiments. WF rats were purchased from Møllegaard Breeding and Research Centre A/S (Skensved, Denmark). GK rats were obtained from the local breeding colony (Department of Endocrinology, Karolinska Institute and Hospital, Stockholm, Sweden) established in 1988 with breeding couples from the colony at the Tohoku University School of Medicine (Sendai, Japan). The GK strain originated from normal Wistar rats, which were bred using glucose intolerance as a selection index (13–15).

All animals had free access to tap water and pelleted rat food. The experiments were approved by the local animal ethical committee at Uppsala University.

Pancreatic islet capillary pressure measurements. The animals were anesthetized with an intraperitoneal injection of thiobutabarbital sodium (Inactin, Research Biochemicals International, Natick, MA; 120 mg/kg body wt), placed on a heated operating table maintained at body temperature (38°C), and tracheostomized. Polyethylene catheters were inserted into the left femoral artery and left femoral vein. The former catheter was connected to a Statham P23dB pressure transducer to allow continuous monitoring of the mean arterial blood pressure; the latter catheter was used for continuous infusion (5 ml • h⁻¹ • kg⁻¹ body weight) of Ringer solution to substitute for body fluid loss.

The abdomen was opened by a midline incision, and the pancreas was placed loosely over a hollow cylindrical plastic block, attached to the operating table, for immobilization. The pancreas preparations were continuously kept moist by superfusion with heated (37°C) mineral oil (Apoteksbolaget, Göteborg, Sweden). After allowing for mean arterial blood pressure to stabilize, 0.8 ml sterile-filtered 2% (w/v) neutral red (Kebo Græve AB, Stockholm, Sweden) dissolved in saline was injected intravenously into the left femoral vein to selectively stain the islets within the pancreas (16,17). This technique allows for reliable identification of islets with a diameter exceeding 50–60 μm (17). The animals were then allowed to rest for at least 30 min to minimize the influence of surgical stress and maintain steady pressure values on capillary pressure values.

The hydrostatic pressure in single pancreatic islet capillaries and exocrine capillaries was recorded by an electronic servo-nulling pressure device (18). The capillaries were punctured, in reflected light, with a sharpened glass pipette (outer diameter 2–3 μm) filled with 0.5 mol sodium chloride solution, supplemented with 0.01% Fast Green (Eastman Kodak, Rochester, NY) under a stereo microscope (10X) by the use of a micromanipulator. The pipette was attached to a servo-nulling pressure circuit (Instrumentation for Physiology and Medicine, La Jolla, CA), and the pressure was recorded by a Statham P23Db pressure transducer connected to a Grass amplifier and recorder. Efforts were made to place the pipette tip in the blood stream within the capillaries without attaching to the capillary wall. Since islet capillaries were not readily visible within the islet, the correct location in a capillary was confirmed, after recording the hydrostatic pressure, by observing the flow of an injected Fast Green NaCl solution. Extracapillary placement of the pipette tip led to a diffuse spread of the injected Fast Green NaCl solution, whereas a correct intracapillary position led to the visualization of the islet capillary network.
and venous drainage. The capillary pressure in islets with a diameter exceeding 50 μm from both the head and the splenic parts of the pancreas was examined. In each animal islet, capillaries from 3–11 islets were punctured. When multiple capillaries were investigated within the same islets, the mean of all these capillary pressure values was calculated to obtain the islet capillary pressure. The mean of the islet capillary pressures in one animal was then considered to be one experiment. In the WF rats, capillary pressure values were recorded both before and after an intravenous injection of 1.0 ml of a 30% (wt/vol) d-glucose or 3-O-methyl glucose solution. Blood glucose concentrations were determined with test reagent strips (ExacTech, Baxter Travensol, Deerfield, IL) from samples obtained from the cut tip of the tail.

Some of the WF and GK rats investigated were injected subcutaneously twice daily (8:00 A.M. and 8:00 P.M.) with phlorizin dissolved in propylene glycol (0.4 g/kg body wt per day; Sigma, St. Louis, MO) for 10–14 days. Phlorizin inhibits renal tubular glucose transport, which enhances renal glucose excretion and thereby reverses hyperglycemia in diabetic rats (19). Blood glucose concentrations were determined, as described above, every morning at 8:00 A.M. immediately before administration of phlorizin. Capillary pressure and blood glucose concentrations were determined in the phlorizin-treated animals both before and after an intravenous injection of 1.0 ml of a 30% (wt/vol) d-glucose solution.

**Blood flow measurements.** The effects of neutral red on whole pancreatic and islet blood perfusion were evaluated in separate WF and GK rats with a nonradioactive microsphere technique (3). The animals were anesthetized, placed on a heated operating table, and tracheostomized as described above. An injection of 600 IU of heparin (Heparin 5000 IE/ml, Loven’s Lakemedel, Malmo, Sweden) was given into the left jugular vein. Polyethylene catheters were inserted into the right femoral artery, the right femoral vein, and the ascending aorta via the right carotid artery. The latter catheter was connected to a pressure transducer (TDCH 75; Druck, Groebn, U.K.) to allow continuous monitoring of the mean arterial blood pressure. When this had remained stable for at least 15 min, 0.8 ml of either 0.9% (wt/vol) saline or sterile-filtered 2% (wt/vol) neutral red dissolved in saline was injected into the right femoral vein within 15 s. Approximately 1.5–2.0 × 10^9 nonradioactive microspheres (NEN-Trac, DuPont, Wilmington, DE), with a diameter of 11 μm, were injected 40 min later via the catheter with its tip into the ascending aorta for 10 s. Starting 5 s before the microsphere injection and continuing for 60 s, an arterial blood sample reference was collected from the catheterized femoral artery into a preweighed tube at a rate of approximately 0.50 ml/min. The exact withdrawal rate was confirmed in each experiment by weighing the sample. The animals were then killed, and the pancreas and adrenal glands were counted in a stereo microscope equipped with both dark and bright field illumination (Wild M3Z; Wild Heerbrugg, Heerbrugg, Switzerland). The volume of the islets in each pancreas was also determined in these preparations by a point-counting method (21). The intersections overlapping islets were counted at a magnification of 400 x, and a total of 44.6 ± 1.0 different fields were counted in each WF rat pancreas (corresponding to 5,360 ± 126 points; n = 8) and 48.1 ± 1.8 in each GK rat (corresponding to 5,762 ± 242 points; n = 14). The microsphere contents of the arterial blood reference samples were determined by transferring the samples to glass microfiber filters (pore size 0.2 μm) and counting in transmitted light. The blood flow values were calculated according to the formula:

\[ Q_{ref} = \frac{N_{ref} \times V_{ref}}{N_{cap}} \]

where \( Q_{ref} \) is the withdrawal rate of reference sample (milliliters per minute), \( N_{ref} \) is the number of microspheres present in the organ, and \( N_{cap} \) is the number of microspheres in the reference sample. When the islet blood flow was expressed per islet weight, the latter was estimated by multiplying the pancreatic weight with the islet volume fraction of whole pancreas in each animal. The adrenal glands were used as a control organ to confirm adequate mixing of the microspheres. A difference of less than 10% in blood flow values between the right and left gland was taken to indicate sufficient mixing.

Arterial blood samples were taken from the femoral artery immediately after injecting the microspheres. Blood glucose concentrations were determined with test reagent strips (ExacTech) and serum insulin concentrations via radioimmunoassay (Insulin RIA Kit, Pharmacia-Upjohn Diagnostics AB, Uppsala, Sweden) using a rat insulin standard (Novo Research Institute, Bagsvaerd, Denmark). Blood glucose concentrations were also determined before administration of neutral red or saline.

**Statistical analysis.** All values are given as means ± SE for the number of experiments given in the tables. When multiple comparisons between data were performed, analysis of variance (ANOVA) and Fisher’s protected least-square difference (PLSD) test were used (Statview, Abacus Concepts, Berkeley, CA). When only two groups were compared, probabilities (P) of chance differences between the experimental groups were calculated using Student’s paired two-tailed t test when comparing values from the same animal and Student’s unpaired two-tailed t test when comparing different groups of animals.

**RESULTS**

The islets located at the pancreatic surface became clearly visible after neutral red injection, thereby making it possible to perform micropuncturations of their capillaries. All islets studied had diameters exceeding 50 μm and possessed a tortuous network of capillaries that were wider than the capillaries in the exocrine tissue. After injection of the dye Fast Green via the micropuncture glass pipette tip into an islet capillary, the dye could be seen to drain into adjacent venules. Dye was never seen to drain into capillary plexa in the exocrine tissue following islet capillary injection. The islet capillaries were highly comparable with those of the exocrine pancreas, as manifested by a very rapid entrance of dye into the interstitial space within the islet. No differences in vascular anatomy between pancreatic islets from WF and GK rats could be discerned.

Pancreatic islet capillary pressure in normoglycemic WF rats was estimated to be approximately 3 mmHg (Tables 1 and 2). The capillary blood pressure in the exocrine capillaries, which was measured in some Wistar and GK rats, was 7–10 mmHg and was not influenced by injection of neutral red (data not shown). Intravenous administration of d-glucose (1 g/kg) doubled pancreatic islet capillary pressure, whereas no effect was seen after injection of an equimolar dose of 3-O-
TABLE 2
Pancreatic islet capillary pressure and blood glucose concentrations in anesthetized male GK and Wistar F rats pretreated with an intravenous injection of 0.8 ml 2% (wt/vol) neutral red

<table>
<thead>
<tr>
<th>Islet capillary pressure (mmHg)</th>
<th>Wistar F (n = 15)</th>
<th>GK (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose concentration (mmol/l)</td>
<td>4.9 ± 0.3</td>
<td>11.0 ± 0.5*</td>
</tr>
</tbody>
</table>

Data are means ± SE. *P < 0.001 compared with Wistar F rats using unpaired Student's t test.

Table 3
Mean arterial blood pressure, pancreatic islet capillary pressure, and blood glucose concentrations before and 15 min after intravenous administration of 1.0 ml of a 30% (wt/vol) solution of D-glucose to anesthetized male Wistar F and GK rats pretreated with phlorizin (0.4 g • kg⁻¹ • day⁻¹) for 10-14 days and given an intravenous injection of 0.8 ml 2% (wt/vol) neutral red

<table>
<thead>
<tr>
<th></th>
<th>Wistar F (n = 7)</th>
<th>GK (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial blood pressure (mmHg)</td>
<td>104 ± 3</td>
<td>124 ± 2*</td>
</tr>
<tr>
<td>Pancreatic islet capillary pressure (mmHg)</td>
<td>2.9 ± 0.2</td>
<td>3.4 ± 0.4</td>
</tr>
<tr>
<td>Blood glucose concentration (mmol/l)</td>
<td>5.4 ± 0.3</td>
<td>5.6 ± 0.2</td>
</tr>
</tbody>
</table>

Data are means ± SE. *P < 0.01 and †P < 0.001 compared with the corresponding animals before glucose administration using Student's paired t test. ‡P < 0.001 compared with the corresponding Wistar F rats using Student's unpaired t test.

Discusssion
The pancreatic islets possess a vasculature that is both anatomically and functionally different from that of the exocrine pancreas (6,22). There is at present some debate on how the blood flow is distributed within the islets, namely whether the flow is from the β-cells toward the peripheral non-β-cells or vice versa (cf. 6). A third theory is that blood enters an arterial pole of the islet and then is transported in a regulated fashion through the islet capillaries toward a venous pole (6). The common feature in all these models, however, is the presence of islet capillaries that are fenestrated and have a larger diameter than their exocrine counterparts. Furthermore, there is growing agreement that the islets receive a high blood flow in relation to their fraction of the whole pancreas, i.e., usually 5-10% of the whole pancreatic blood flow (6,22). Changes in the islet vascular anatomy have been observed in animal models of type 1 diabetes (23), whereas only functional changes have been observed in models of NIDDM (22). In the latter, there seems to be a hyperperfusion of the islets (7-9).

All islets investigated in the present study were, for technical reasons (reliable identification of islets), large islets and had diameters exceeding 50 μm (cf. 4). These islets constitute the major part of islet volume (1) and possess a unique vascular organization (see below). They also receive the major fraction of islet blood flow (4). Morphological investigations on larger islets in the normal rat pancreas have demonstrated a vasculature that is both in series and in parallel to that of the exocrine parenchyma (see 24). Capillaries of small islets are drained either by efferent capillaries passing to the exocrine capillary plexa, thereby forming an insulo-acinar portal system, or by collecting venules that empty directly into larger veins (24). The largest islets, in particular, seem to drain directly into venules, without forming any insulo-acinar portal system (24,25). These findings were confirmed by the injections of Fast Green in the present study. Furthermore, the presence of a much lower capillary blood pressure in the islets compared with exocrine capillaries also argues against the presence of an insulo-acinar portal system in these islets, since a reversed flow would occur if this was the case. It should be noted that we were unable to perform measurements of capillary pressure in smaller islets possessing an insulo-acinar portal system in the present study. It therefore remains unknown whether these...
islets have a higher capillary pressure, i.e., similar to that of capillaries in the exocrine pancreas.

The pancreatic islet capillary pressure in normoglycemic WF rats was measured to be ~3 mmHg, and this value doubled after administration of D-glucose. This marked glucose-induced increase in islet capillary pressure was not merely an osmotic effect, since there was no corresponding rise when the same amount of the nonmetabolizable glucose derivative 3-O-methyl glucose (26) was injected. The increase in islet capillary pressure was instead likely to depend on the previously described glucose-stimulated increase in islet blood perfusion (cf. 3, 27, 28). In view of the simultaneous increase in islet blood flow and islet capillary pressure caused by D-glucose, the present findings suggest that islet blood flow is regulated mainly at the precapillary level. If the glucose-stimulated increase in islet blood flow had been due to a decreased postcapillary resistance, a decrease in islet blood capillary pressure would have been observed. The mechanisms behind the islet blood flow increase probably reflect a nervous effect elicited by the hyperglycemia (22) or an increased production of nitric oxide (28).

The GK rat is a nonobese NIDDM model characterized by an intrinsic defect in the glucose stimulus-secretory pathway of the β-cell (29). A markedly increased basal islet blood flow has been observed in these animals (8, 9) without any changes in islet mass (30); these findings were confirmed in the present study. Basal islet capillary pressure in GK rats was approximately doubled when compared with normoglycemic WF rats, i.e., it was similar to the capillary pressure values registered in WF rats after an intravenous glucose load. Interestingly, blood glucose concentrations in the GK rats were also almost as high as those seen after D-glucose administration to control rats.

To investigate if the elevated islet capillary pressure seen in GK rats was glucose dependent and reversible, GK and WF rats were treated with phlorizin subcutaneously for 10-14 days. The efficiency of the phlorizin treatment was evaluated by measuring blood glucose levels every morning at 8:00 A.M. Although GK rats had a slightly higher blood glucose concentration at this time point than did WF rats, their blood glucose values were considered normalized since they represented the maximal concentration during the course of the day (fed rats, 12 h since last phlorizin injection). Actually, the blood glucose concentrations did not differ between phlorizin-treated GK and WF rats when islet capillary pressure measurements were performed later in the day. Furthermore, islet blood perfusion was not affected by a similar degree of hyperglycemia in a previous study (27).

When blood glucose concentrations were normalized with phlorizin treatment in GK rats, the elevated islet capillary pressure was decreased to values seen in WF rats. This suggests that the capillary pressure increase in these animals depends on hyperglycemia and is reversible. To what extent a chronically increased capillary pressure may influence islet function is unknown. It has previously been demonstrated in animal models of NIDDM, however, that the diabetic condition in itself perturbs the metabolic functions of pancreatic islets (31-37). Several mechanisms have been suggested to be

### TABLE 4

<table>
<thead>
<tr>
<th></th>
<th>Blood glucose (mmol/l)</th>
<th>Insulin (pmol/l)</th>
<th>Mean arterial blood pressure (mmHg)</th>
<th>Percent decrease in mean arterial blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wistar F</td>
<td>GK</td>
<td>Wistar F</td>
<td>GK</td>
</tr>
<tr>
<td></td>
<td>0 min</td>
<td>40 min</td>
<td>0 min</td>
<td>40 min</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>4.5 ± 0.2 (10)§</td>
<td>4.6 ± 0.3</td>
<td>4.8 ± 0.1 (9)§</td>
<td>5.0 ± 0.2§</td>
</tr>
<tr>
<td>Insulin</td>
<td>10.4 ± 0.6 (7)§</td>
<td>11.6 ± 0.7§</td>
<td>11.3 ± 0.7 (7)§</td>
<td>11.9 ± 0.6§</td>
</tr>
<tr>
<td>Mean arterial blood</td>
<td>Wistar F</td>
<td>ND</td>
<td>Wistar F</td>
<td>ND</td>
</tr>
<tr>
<td>pressure (mmHg)</td>
<td>173 ± 58 (10)</td>
<td>576 ± 43 (7)§</td>
<td>173 ± 72 (9)</td>
<td>461 ± 58 (7)</td>
</tr>
<tr>
<td></td>
<td>GK</td>
<td>ND</td>
<td>GK</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>127 ± 4 (10)§</td>
<td>112 ± 5*</td>
<td>133 ± 3 (9)</td>
<td>103 ± 3§</td>
</tr>
<tr>
<td></td>
<td>170 ± 4 (7)§</td>
<td>148 ± 9†§</td>
<td>167 ± 3 (7)§</td>
<td>122 ± 12†§</td>
</tr>
<tr>
<td></td>
<td>11 ± 3 (10)</td>
<td>23 ± 2 (9)</td>
<td>27 ± 7 (7)§</td>
<td></td>
</tr>
</tbody>
</table>

Data are means ± SE for the numbers of experiments given in parentheses. *P < 0.05, †P < 0.01, and ‡P < 0.001 when compared with the corresponding animals before treatment. §P < 0.001 when compared with the corresponding WF rats. ||P < 0.05 compared with the saline-treated rats of the same strain. ANOVA and Fisher's PLSD test were used for all comparisons. ND, not determined.
TABLE 6
Pancreatic blood flow
Islet blood flow
Islet volume and whole pancreatic and islet blood flow measured 40 min after an intravenous injection of 0.8 ml of 2% (wt/vol) neutral red or 0.9% (wt/vol) saline in anesthetized adult male Wistar F or GK rats

<table>
<thead>
<tr>
<th></th>
<th>Wistar F (n = 10)</th>
<th>Neutral red (n = 9)</th>
<th>GK (n = 7)</th>
<th>Neutral red (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic blood flow (ml • min⁻¹ • g⁻¹ pancreas)</td>
<td>0.87 ± 0.08</td>
<td>0.92 ± 0.09</td>
<td>1.18 ± 0.18</td>
<td>1.18 ± 0.12</td>
</tr>
<tr>
<td>Islet blood flow (µl • min⁻¹ • g⁻¹ pancreas)</td>
<td>89 ± 11</td>
<td>88 ± 9</td>
<td>144 ± 19†</td>
<td>145 ± 13†</td>
</tr>
<tr>
<td>Islet volume (% of total pancreas)</td>
<td>1.47 ± 0.05</td>
<td>1.54 ± 0.06</td>
<td>1.34 ± 0.08</td>
<td>1.53 ± 0.12</td>
</tr>
<tr>
<td>Islet blood flow per estimated islet weight (ml • min⁻¹ • g⁻¹ islet tissue weight)</td>
<td>6.1 ± 0.8</td>
<td>6.3 ± 0.9</td>
<td>10.7 ± 1.3†</td>
<td>10.0 ± 1.4‡</td>
</tr>
</tbody>
</table>

Data are means ± SE. *P < 0.05 and †P < 0.01 compared with the corresponding Wistar F rats using ANOVA and Fisher’s PLSD test.

responsible for the deterioration of function in long-standing NIDDM, namely a reduction in β-cell mass (38-40), islet amyloidosis (41,42), and an induced insulin secretory defect (36). There is considerable evidence at present to support the bestowal of the well-known fact that NIDDM and essential hypertension in organ such as the retina and kidneys (10–12). It could be speculated that an increased islet capillary blood pressure contributes in a similar way to the decline in islet function seen in NIDDM by damaging the islet endothelium and thickening the capillary walls, ultimately decreasing the islet organ blood perfusion. In line with these notions is the finding that the increased islet blood perfusion seen in younger GK rats has reverted to a decrease when the animals are 1 year old, even though the rats are still diabetic (unpublished observation). Since a high basal islet blood flow is dependent on factors produced by the islet endothelial cells, mainly NO (22,28), damage to these cells, etc., by sheer stress, would be expected to lower islet blood flow.

Mean arterial blood pressure was higher in GK rats than in control WF rats and was not affected by blood glucose normalization. This difference in blood pressure has not previously been described. In earlier studies, anesthesia was induced with pentobarbital (8,43), a drug with a more pronounced hypotensive effect than thiobutabarbital. The higher arterial blood pressure in GK rats is interesting in view of the well-known fact that NIDDM and essential hypertension frequently coexist (44). The reasons for and the significance of the higher systemic blood pressure in GK rats are unknown at present.

For islet capillary blood pressure measurements to be performed, the islets and their capillaries had to be clearly visualized. This was accomplished by administration of the intravital stain neutral red, which selectively stains the pancreatic islets more markedly than the surrounding exocrine pancreas (16). Consistent with previous results on transplanted islets (45), the stain did not affect blood glucose homeostasis. A decrease in mean arterial blood pressure, similar in degree in WF and GK rats, was seen after administration of neutral red, but no effect on either whole pancreatic or islet blood flow could be observed when comparisons were made with saline-injected rats of the same strain. Also, the capillary pressure in the exocrine pancreatic capillaries remained constant at 7–10 mmHg after administration of the dye. In view of these findings, it seems unlikely that neutral red affects islet blood flow or islet capillary blood pressure to any major extent in the present study.

To enable proper fixation of the pancreas during the capillary pressure measurements, we had to elevate it approximately 2 cm above its resting position in the abdomen (animals lying on their back). An effect of this maneuver leading to an underestimation of the true capillary pressure values cannot be ruled out. This fixation was similar in all animals, however, and is therefore unlikely to induce the increase in capillary pressure observed in the GK rats or after D-glucose administration. Furthermore, the present recorded values for the exocrine capillary pressure were similar to those estimated previously by a different technique, which argues against any fixation-induced artifacts (46).

In summary, we have measured islet capillary blood pressure in rats and found that both acute and chronic hyperglycemia augmented islet capillary pressure. The effects of a chronically increased islet capillary pressure on long-term islet function remain to be determined.

ACKNOWLEDGMENTS
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