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Transient Postoperative Stenosis in Small-Vessel Anastomoses

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Using a newly developed Doppler probe, we have found that a standard suture anastomosis in a rat femoral artery is accompanied by significant (30–60%) cross-sectional area stenosis, which dissipates to baseline levels within 24 hours. We hypothesized that spasm, deposition of coagulation products, or the suture technique itself was responsible. Topical vasodilators (papaverine, sodium nitroprusside, lidocaine) and intravenous thromboxane A₂ synthetase inhibitor and receptor blocking agent (Ridogrel, 4 mg/ml), anticoagulants heparin and SC4992 (an experimental platelet inhibitor/arginine-glycine-aspartic acid analogue), were administered. No drug had any significant effect on preventing postoperative stenosis. Varied suture bites affected stenosis measurements. Scanning electron microscopy and light microscopy displayed "bunching" of vessel wall in the suture ties. This was confirmed with methyl methacrylate corrosion casts and microangiography. "Sham" anastomoses also produced stenosis, which was relieved when sutures were removed. We conclude that suture anastomosis of small vessels is accompanied by significant cross-sectional stenosis caused by the physical action of tensioned sutures. This effect dissipates over a 24-hour postoperative period. The mechanism behind these changes and the clinical importance of this effect are still under investigation.

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The use of high-frequency pulsed Doppler ultrasonography (HFDPDU) in the evaluation of arterial hemodynamics has been frequently reported over the past decade. Our own laboratory has reported the use of HFDPDU with a specially designed tandem Doppler probe (TDP) [1]. This two-crystal probe was designed to measure simultaneously the Doppler shift caused by flowing blood at two sites along an artery and compare the two Doppler waveforms. Using the following equation: [2]

$$\% \text{ area reduction} = 100 - [1 - V_p/V_s],$$

where V_p represents prestenotic velocity (by Doppler shift) and V_s denotes stenotic velocity, waveforms can be directly compared and cross-sectional area stenosis assessed.

Recent studies have revealed a cross-sectional area stenosis of 30 to 60% in standard rat femoral artery end-to-end anastomoses at 10 minutes postoperatively. In vivo microarteriography has confirmed this effect (Fig 1). The stenotic effect dissipates to baseline by 24 hours postoperatively. We hypothesized four possible causes for this finding: computer or technical error, spasm, coagulation product deposition, and constriction resulting from the suture technique itself. This study examines each of these possible causes.

Materials and Methods

The TDP is composed of two 1-mm² gold-plated piezoelectric crystals mounted at right angles to each other with a corresponding 45-degree angle to the vessel under study (Fig 2). The probe is held in place by an adjustable micromanipulator (Harvard Bioscience, South Natick, MA) capable of adjustment in three dimensions with an accuracy of 0.05 mm. To perform Doppler readings, the TDP is brought within 1 mm of the study vessel and a drop of saline is applied as a coupling medium. The TDP is connected to a HFDPDU unit (VF-1, Crystal Biotech, Hopkinton, MA), which generates the ultrasound pulses and receives the reflected ultrasound signals. The received signals are fed directly into a monitoring program (Dataflow, Crystal Biotech) on a Compaq 386/25 personal computer. The probe is maneuvered with the micromanipulator until maximum Doppler shift is located as judged by real-time computer-generated waveforms and mean Dopp-



Fig 1. Microarteriogram of standard rat femoral artery anastomosis. Needle was placed before radiograph and points to anastomotic site (arrowheads).

ler shift determinations. The ultrasound unit's Doppler range gate is also used to adjust the intraluminal sample area under study. The data flow computer program is later used to regenerate the Doppler waveforms and conduct analytical and comparative functions.

All rodent experiments used male Sprague-Dawley rats weighing between 350 and 500 gm. Femoral arteries in these rats measured between 0.8 and 1.1 mm in diameter. Anesthesia was achieved with a mixture of ketamine (Ketaset, Aveco, Ft Dodge, IA), 112.5 mg/ml, and acepromazine (PromACE, Aveco), 2.5 mg/ml, given intramuscularly at a dose of 0.07 ml/100 gm body weight. Institutional guidelines for the care and use of experimental animals were adhered to throughout the study.

All anastomoses were performed using a standard groin incision followed by dissection of the artery under study. Spasm was relieved with topical lidocaine (20 mg/ml) after which the artery was placed in a double clamp and transected. The lumen was flushed with heparinized saline (10 U/ml) and the excess adventitia trimmed away. All sutures were either 10-0 or 11-0 monofilament nylon (Ethicon, Somerset, NJ).

Statistical analysis was performed using either the Microsoft Excel Statistical Analysis Package or SAS. Reported errors are standard errors of the mean unless otherwise noted.

Equipment Assessment

The TDP was used to measure the degree of stenosis of four standard, six-stitch, 10-0 nylon,

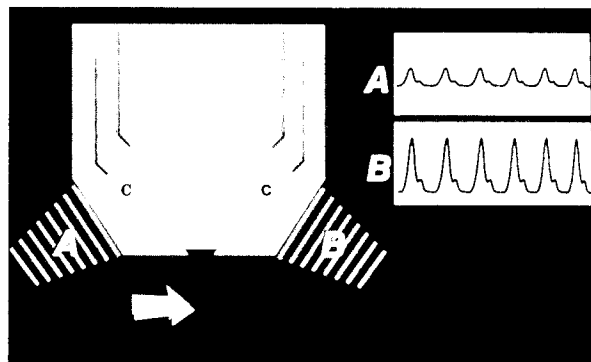


Fig 2. Tandem Doppler probe schematic. (A = pre-stenotic tracing; B = poststenotic tracing; C = piezoelectric crystal).

femoral artery, end-to-end anastomoses. After initial readings at 10 minutes postoperatively, the probe was rotated 180 degrees so that the crystal that had been scanning the stenotic area was now scanning the normal area and vice versa. Additionally, each anastomosis was examined with two different TDP units as well as one commercially built cuff-type probe (Crystal Biotech, HDP-1.0-2.0S). Results were analyzed using a Student's *t*-test.

Spasm Evaluation

Five rat femoral artery anastomoses were performed in standard end-to-end-fashion with six 10-0 nylon sutures. The degree of stenosis was evaluated at 10 minutes postoperatively using the TDP. Three topical spasmolytics as well as one experimental intravenous spasmolytic agent were then applied in succession. The topical agent application followed the regimen described by Cooper [3]. Four milliliters of either papaverine, 1.5 mg/ml, lidocaine, 20 mg/ml, sodium nitroprusside, 0.5 mg/ml, or saline (control) were applied topically and allowed to dwell on the vessel for 1 hour after which TDP readings were repeated. All applications were performed in an anonymous fashion. After each reading, the previous drug was irrigated off the vessel with 50 ml of saline and the next drug applied. After the saline and topical agents, a 2-mg/kg intravenous bolus of thromboxane A_2 synthetase inhibitor and thromboxane A_2 prostaglandin endoperoxide receptor blocking agent (Ridogrel, Janssen Pharm, Beerse, Belgium) was administered, and TDP readings were repeated 10 and 60 minutes

after injection. Results were statistically analyzed by analysis of variance (ANOVA).

Coagulation Product Deposition

Twenty-four rats were divided into three groups of eight and underwent end-to-end anastomosis of either their right or left femoral artery with 10 stitches of 11-0 nylon. Before release of the double clamp after anastomotic repair, a bolus of 0.25 ml of either heparin, 160 U/ml, arginine-glycine-aspartic acid (RGD) (SC = 4992, Searle, Skokie, IL) analogue in saline solvent, 200 gm/ml, or saline (control) was administered. The clamp was then removed. Repeat drug doses were given every 30 minutes. All drugs were given in a randomized, anonymous fashion. TDP readings were taken at 10, 60, and 120 minutes after hemostasis was achieved as well as 24 hours postoperatively. Several animals from each group were also observed for an additional 7 to 30 days. Multiple histological specimens for light microscopy and scanning electron microscopy (SEM) were taken at each Doppler examination period. Statistical analysis consisted of Student's *t*-tests as well as two-factor mixed ANOVA followed by Tukey's honestly significant difference test. All analyses were performed in an anonymous fashion.

Suture Technique

Suture technique was assessed in two parts. In part 1, 18 rats were divided into three groups of 6. Group 1 underwent standard end-to-end anastomosis with six stitches of 10-0 nylon. Group 2 underwent end-to-end anastomosis with large suture bites (approximately 0.5 mm) taken from each vessel edge. Group 3 also had an end-to-end anastomosis, but a single backwall stitch was introduced. TDP readings were taken at 10, 60, and 120 minutes after clamp release as well as 1, 7, and 28 days postoperatively.

In part 2 of this assessment, five rats underwent bilateral exposure of their femoral arteries and sham anastomosis. After dissection and application of lidocaine to relieve spasm, a single bulldog clamp was applied to the artery proximally near the inguinal ligament. This clamp halted most blood flow, but the remaining backflow kept the artery from collapsing. Six suture bites of 10-0 nylon were then taken circumferentially in the same manner that an anastomosis would be per-

formed. The sutures were tied, the clamp removed, and lidocaine applied to relieve any spasm. Doppler readings were taken 10 minutes after clamp removal. The sutures were then cut and removed, and lidocaine was again applied. Repeat TDP readings were taken 10 minutes after the last suture had been removed. Statistical analysis was performed with Student's *t*-test and ANOVA.

Results

Equipment Assessment

Examination of postoperative stenosis showed no change in the degree of stenosis based on which crystal read the stenotic area. Likewise, there was no change in the degree of stenosis if the probes were exchanged or if a commercially available cuff probe was used.

Spasm Evaluation

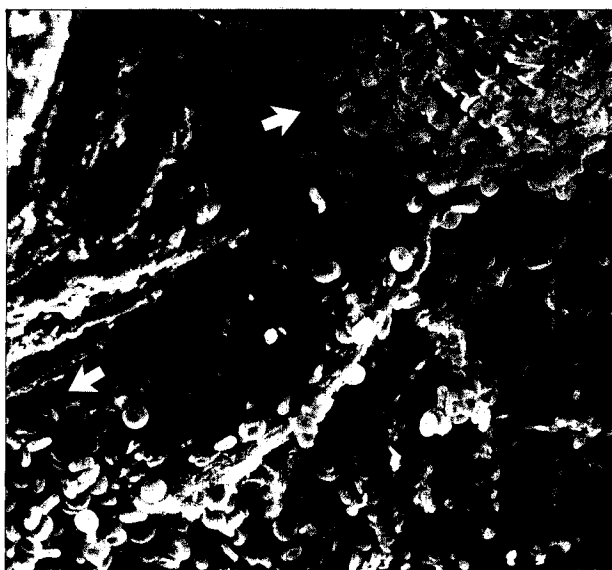
Treatment of the study vessel with spasmolytic drugs revealed no changes in the degree of stenosis during each 1-hour treatment period. ANOVA manipulation done after the experiment likewise revealed no statistically significant differences between the treatment groups or within the same treatment group over time.

Coagulation Product Deposition

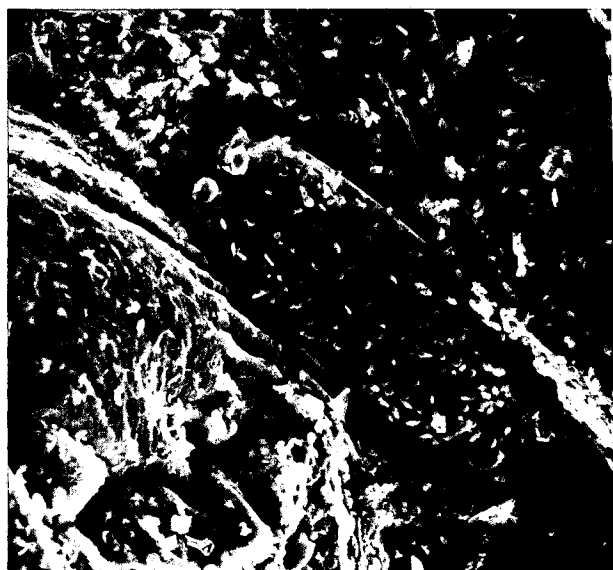
Evaluation of TDP mean waveform values revealed no significant difference between the treated and control groups. The baseline stenosis measurements for the three groups were $2.9\% \pm 3.1$ for the antiplatelet group, $2.3\% \pm 3.4$ for the saline group, and $-1.1\% \pm 4.6$ for the heparin group, producing a mean of $1.4\% \pm 1.2$. These values increased to $36.8\% \pm 9.3$, $32.3\% \pm 8.3$, and $35.3\% \pm 6.3$, respectively, at 10 minutes postoperatively (mean, $34.8\% \pm 1.3$).

Light microscopy using Carstairs' stain for platelets and fibrin demonstrated no significant deposits of platelets or fibrin at the anastomotic site.

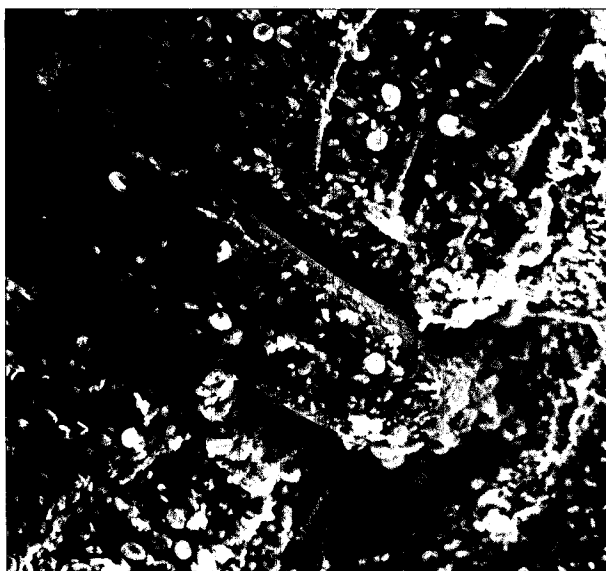
Scanning electron microscopy did reveal changes in platelet, fibrin, and red blood cell deposition, as shown in Figure 3. Figure 3A demonstrates the suture entry and exit areas in a saline-treated animal. Note the deposition of a



A



B



C

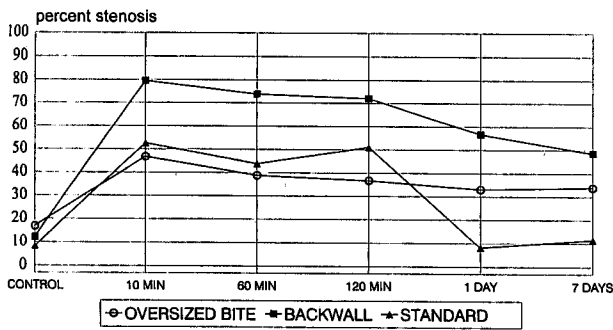
Fig 3. (A) Scanning electron microscopy (SEM) of saline-treated artery 1 hour postoperatively. Note areas of red blood cell, platelet, and fibrin deposition at suture entry and exit points (arrows). (Original magnification $\times 737$, before 34% reduction.) SEMs of arteries treated with (B) heparin (original magnification $\times 716$, before 34% reduction) and (C) RGD analogue (original magnification $\times 638$, before 34% reduction) showing little coagulation product deposition.

meshwork of platelets, fibrin, and red blood cells (arrows) at the points of suture entrance and egress. This deposition is absent in both the RGD analogue-treated (Fig 3B) and heparin-treated (Fig 3C) specimens. These changes, however, were focal and could not account for the degree of stenosis measured.

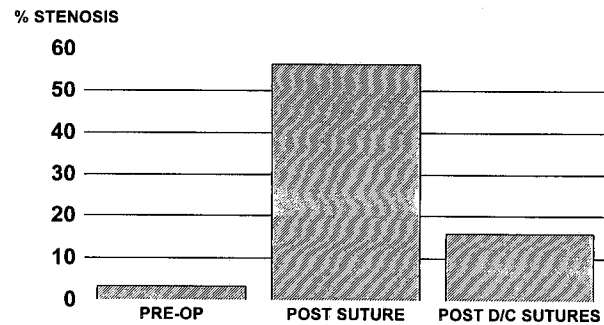
Suture Technique Evaluation

In part 1 of this evaluation (Fig 4A), the backwall stitch group demonstrated the highest degree of stenosis at 10 minutes ($74.9\% \pm 5.3$), which

diminished over time but did not near baseline levels. The stenosis in the large suture bite group was likewise high at 10 minutes ($46.2\% \pm 4.2$) and diminished over time but did not approach baseline levels at 24 hours ($32.7\% \pm 4.5$). The standard end-to-end group, however, registered a 10-minute stenosis value of $52.2\% \pm 9.5$, which dropped to 7.7 ± 3.1 at 24 hours. The stenosis values of the standard anastomosis versus the large suture bite or backwall stitch groups at 24 hours are significantly different ($p < 0.002$ in each case).



A



B

Fig 4. Suture techniques. (A) Stenosis with varied suture bites. (B) Stenosis of "sham" anastomosis; suture in intact artery. (D/C = removal.)

In part 2 of this section (Fig 4B), the 10 arteries had a mean preoperative TDP stenosis value of $3.3\% \pm 2.5$, which increased to $56.4\% \pm 2.0$ after suturing. On suture removal the value dropped to $15.8\% \pm 3.9$. The difference between sutured and suture-removed groups is statistically significant with $p < 0.0001$.

Scanning electron and light microscopy of standard sutured anastomoses displayed a finding of vessel wall "bunching" because of the suture ties. SEM data (Fig 5A) show the vessel wall puckered around the anastomotic line (arrows). Higher power SEM of the same anastomosis (Fig 5B) shows the individual sutures causing a loss of luminal diameter by raising an intraluminal ridge of vessel wall (arrowheads). This effect is diminished by 24 hours postoperatively in a standard end-to-end model as seen in Figure 5C and D. Note the attenuation of the intraluminal ridge (arrowheads) in Figure 5C and D compared with Figure 5A and B. Light microscopy shows a similar effect. Figure 5E shows a slightly oblique cross-section of a standard anastomosis in which one half of the suture line appears while the other half of the artery is a virgin, nonoperated vessel. A comparison of the sutured and nonsutured areas shows the bunching of the vessel wall. Micrometer measurements reveal a 75 to 100% thickening of the vessel wall in between the suture bites. Most of this thickening has been forced into the vessel lumen. Higher power magnification (Fig 5F) displays the actual bending and crimping of the muscle fibers within the suture bites.

Discussion

The use of HFPDU in the evaluation of arterial hemodynamics is well established in the literature; however, few investigations have dealt with the use of HFPDU to evaluate hemodynamics at the site of anastomosis itself [1, 2]. Prior investigations used single-crystal Doppler probes to quantify blood flow and examine pre- or post-anastomotic arterial waveforms [4-9]. Some investigators have used HFPDU in conjunction with fast Fourier transformation algorithms to produce spectral analysis of the measured Doppler signals [6, 7, 10, 11]. This latter technique allows the calculation of cross-sectional velocity profiles, luminal diameter estimations, and vessel blood flow rates. Our technique, although unable to perform these functions, is more reliable in reading mean Doppler shifts at the anastomotic site because it does not use spectral analysis, which is severely affected by the complex distribution of local velocities at an anastomotic site. Previous work in our laboratory [1] and others [4] has demonstrated that HFPDU can be used to measure stenosis reliably on the basis of a pair of Doppler shift readings taken at either the same time at different sites along an artery, as in our case, or at the same site at different times [4]. This latter method, of course, suffers from the possible changes in heart rate, blood pressure, and vascular resistance, which may occur between measurements.

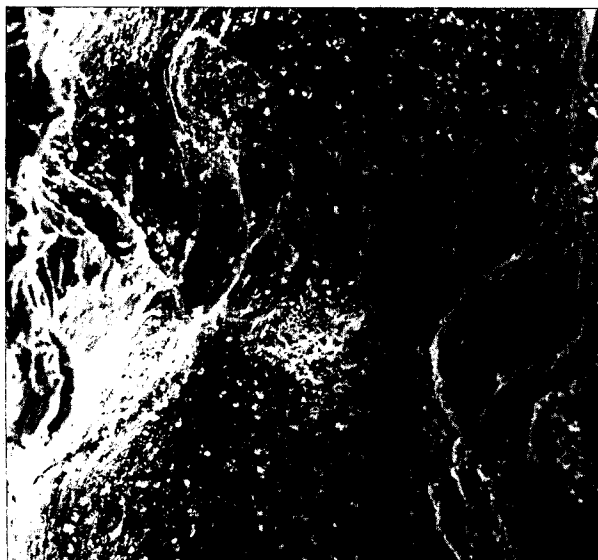
The earlier use of methyl methacrylate castings [1] and the current multiple testing with different probes and crystal orientations demonstrate that



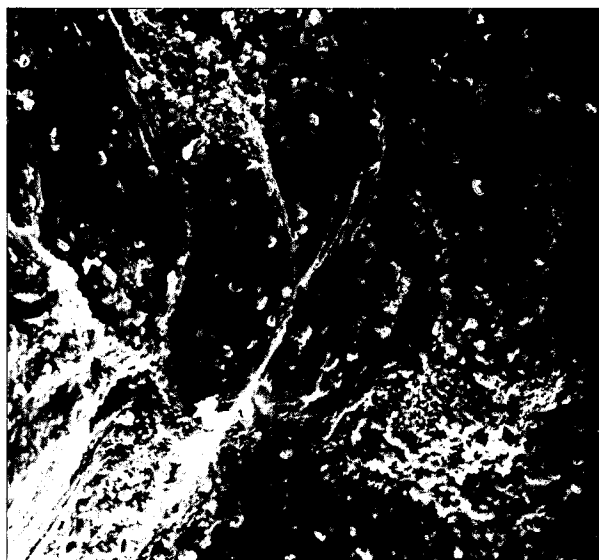
A



B



C



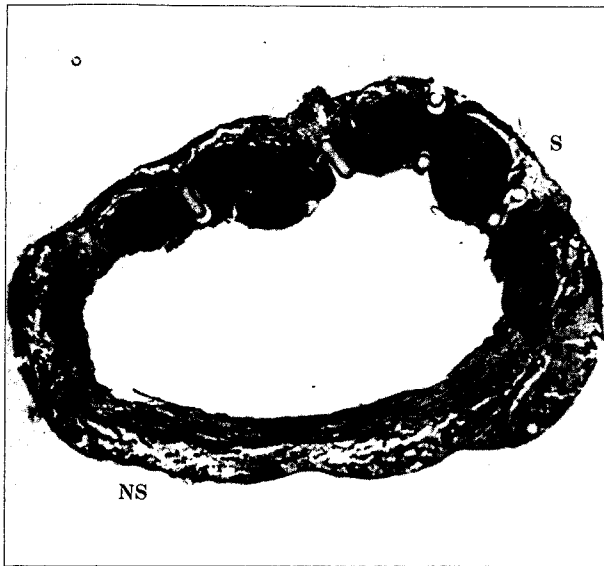
D

Fig 5. (A) Scanning electron microscopy (SEM) of standard anastomosis 1 hour postoperatively. Note vessel wall ridge (arrows). (Original magnification $\times 241$, before 34% reduction.) (B) Higher power (original magnification $\times 346$, before 34% reduction) view of sample in Fig 4B. "Bunching" is clearly visible. (C) SEM of standard anastomosis 24 hours postoperatively. Note the lack of ridges and protrusion of suture loops. (Original magnification $\times 200$, before 34% reduction.) (D) Higher power view (original magnification $\times 376$, before 33% reduction) of Fig 5C. (E) Light microscopy of anastomotic region 1 hour postoperatively. Note thickened, bunched, vessel wall between suture bites. (Carstairs stain, original magnification $\times 200$, before 35% reduction.) (F) Higher power (original magnification $\times 400$, before 50% reduction), view of Fig 5E. Note crimping and deformation of muscle/elastic fibers (Carstairs stain).

the Doppler shift measured with our technique is not merely an artifact of flow aberration at the anastomotic site but is in fact a stenotic jet whose velocity and waveform can be used to calculate stenosis accurately. Although the use of HFPDU combined with spectral analysis in the assessment of the microvascular anastomotic site itself has been avoided by some researchers because of

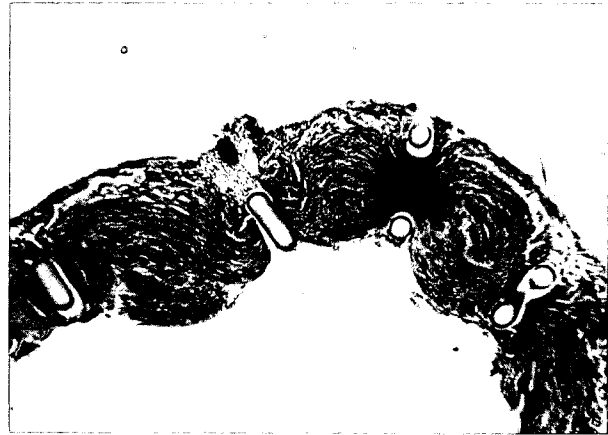
the difficulties in signal interpretation [12] caused by the local flow irregularities, our use of HFPDU without spectral analysis has provided useful data, as previously predicted [13].

The pharmacological interventions used to treat suspected spasm were directed at various parts of the vasoconstrictive mechanism. Papaverine, a commonly used spasmolytic, has direct



E

Fig 5. Continued



F

action on vascular smooth muscle, which experimental evidence links to an inhibition of oxidative phosphorylation and calcium flux during muscle contraction. Although the exact actions of lidocaine are still unspecified, it seems to act on both the vascular smooth muscle itself and its nervous innervation without the involvement of any endothelial factors or prostaglandin metabolites [14]. Sodium nitroprusside causes vessel dilatation by causing smooth-muscle relaxation via the generation of intracellular nitric oxide and the formation of cyclic guanosine monophosphate. Ridogrel acts on the potent endogenous vasoconstrictor thromboxane A_2 at both the synthesis and receptor levels. It additionally blocks prostaglandin endoperoxide receptors. This dual blockade has been shown to inhibit prostaglandin-induced smooth-muscle constriction in rabbit and human models [15]. The lack of any change in the level of postoperative stenosis with any of these treatments forges a good case against spasm as a cause of this phenomenon.

The use of heparin to provide anticoagulation via the magnified effect of antithrombin III on fibrin production did not decrease stenosis as measured by HFPDU or scanning electron microscopy. The arginine-glycine-aspartic acid (RGD) analogue SC-49992, which inhibits platelet aggregation by blocking the platelet glycoprotein IIb/IIIa receptor likewise had no effect on the

stenosis level. Both drugs did, however, display focal anticoagulant effects as seen on SEM (Fig 3).

The changes in TDP stenosis readings based on varied suture technique provided the first evidence of a mechanism behind the stenosis effect. The continued high stenosis readings of the large bite group, contrasted to the return to baseline of the standard group, argues that the inclusion of greater amounts of tissue in a suture bite will lead to significant postoperative stenosis. Likewise, the significant loss of stenosis when tied sutures are cut and removed points to the suture technique as the cause of the stenosis phenomenon. The demonstration of intraluminal bunching and ridges on both scanning electron and light microscopy furthers this explanation.

The return of stenotic anastomoses to normal baseline configurations over 24 hours is as yet unexplained. Research has shown, however, that vascular remodeling is a rapid and dynamic event [16]. Forces such as laminar shear stress and biaxial deformation have been shown to change endothelial cytoskeletal arrangements and realign cell configuration [17] and may thereby account for the changes seen here.

We have found that standard microvascular anastomoses of rat femoral arteries are accompanied by significant postoperative stenosis. This stenosis is caused by the clustering of vessel wall within and between individual suture bites. Al-

though the stenosis caused by this effect did not appear to be thrombogenic in this rat femoral artery model, concern must be given to smaller vessel anastomosis in which the effect may be amplified. This effect may pose a theoretical limit to the size of a vessel that can be successfully anastomosed with standard suture technique.

We thank Ms Lynne Bonavita for her help, Dr Larry P. Feigen for his knowledge, and Dr Joseph N. Cunningham for his support.

Open Discussion

Dr Julian J. Pribaz (Boston): I enjoyed that study. I just wondered for completeness whether it would be worth looking at the effects of a continuous suture technique on this anastomosis and also the use of couplers when technically you should not be able to get any spasm. That may help eliminate any of the potential coagulation problems that can occur at the anastomosis. I also wondered if you have looked at veins; do they undergo the same problems? Finally, is this the reason why in clinical usage end-to-side anastomoses seem to do better than end-to-end anastomoses when you eliminate this spasm factor?

Dr Moskovitz: Regarding continuous sutures and couplers, we had not done any evaluation using continuous sutures, and only recently had we thought of using the coupler. We had done some research using fibrin-glued anastomoses in smaller arteries that tended to have less of an anastomotic stenosis measurement. So the idea of couplers is a valid one, especially in this model. As I said, I have not looked at continuous sutures. Likewise, the measurement of stenosis in veins, using high-frequency pulsed Doppler ultrasonography, is rather difficult because we rely on the waveforms, which in the lower velocity venous system are very difficult to ascertain. As regards the end-to-side anastomosis, especially using an interrupted suture, it actually could be one of the reasons that end-to-side anastomoses do better. On the basis of some of our research, the continuous suture, especially in a continuous end to side, may do better than our interrupted.

Dr Grant Thompson (New Haven, CT): Did you actually measure the cross-sectional area of the anastomoses? You seem to imply that the bunching caused reduction in the cross-sectional area. Did you measure that?

Dr Moskovitz: We did not measure the actual cross-sectional anastomosis using high-frequency Doppler ultrasonography. Is that what you are asking?

Dr Thompson: No. I mean actually measuring it: taking a cross-section of it and measuring it using computer imaging.

Dr Moskovitz: No. The only actual cross-section that we measured was in the light microscopy, which did conform to what we measured with high-frequency ultrasonography.

Dr Thompson: So there was a reduction in the cross-sectional area?

Dr Moskovitz: Yes, as seen on that light micrograph.

Dr Thompson: The other possibility is that there could be just some turbulence caused by the sutures that could reduce your flow as well.

Dr Moskovitz: We looked at turbulence as a possibility, and because we were not using the high-frequency ultrasonography to assess cross-sectional diameter, using a fast Fourier transformation for spectral analysis, this was simply the use of pure velocity as measured by Doppler ultrasonogram. It has been estimated that there should be maybe a 10 to 15% error margin, even caused by turbulence, so we found that earlier studies using methyl methacrylate casts and radiographs corresponded with the degree of 0.96 to that measured by our Doppler ultrasonogram. So the previous study had borne out that this technology is valid.

Dr Scott P. Bartlett (Philadelphia): Dr Moskovitz, did one surgeon do all the anastomoses, strip the adventitia, and do the suturing, or did you have multiple surgeons?

Dr Moskovitz: The vast majority of the study, other than the initial pilot study, was done by one surgeon.

Dr Bartlett: If it is true that you get a relaxation stenosis, if you will, why do you think that occurs at the 24-hour period? Is it necrosis or some other element?

Dr Moskovitz: Several studies done in the past year or 2 on the concept of vascular remodeling

suggest such forces as laminar shear stress and biaxial deformation. These have been shown to cause significant changes in the endothelial structure within the first 6 hours postoperatively. We, therefore, believe that, on the basis of the pulsation of the artery itself, it is probably such things as shear stress and transformation.

Dr Bartlett: Finally, does it make a difference clinically? Do you follow these long term in terms of patency rates or at least until pseudointima was formed or look at flow dynamics, that is laminar or spiral flow in the vessels?

Dr Moskovitz: We did not look at laminar or spiral flow. We followed these out between 7 and 30 days. As I said in our conclusion, these were standard end-to-end anastomoses. We found that there was nothing thrombogenic about this effect. Because a cross-sectional stenosis of 50% is below that of a critical stenosis, we would not expect it to be thrombogenic in this model. Whether it would be more thrombogenic in a smaller artery is another question we hope to address in the future.

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