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Low Pressure Radiofrequency Balloon Angioplasty: Evaluation in Porcine Peripheral Arteries

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Objectives. The purpose of this study was to evaluate the efficacy of radiofrequency-powered thermal balloon angioplasty in an in vivo porcine model.

Background. Various modes of thermal energy used adjunctively during balloon angioplasty have demonstrated the potential to enhance the results of acute lumen dilation.

Methods. In normal pigs, 75 peripheral arteries were dilated with a newly designed, radiofrequency-powered, thermal angioplasty balloon. All inflations were performed at 2-atm pressure for 85 s. Dilations were performed either with (hot) or without (cold) the application of heat. Lumen dimensions and vessel morphology were assessed with intravascular ultrasonography. At the end of each study, dilated arterial segments were harvested for histologic examination.

Results. Single cold balloon inflations resulted in a 12.7% increase in arterial cross-sectional area whereas single hot inflations resulted in a 22.9% increase ($p < 0.03$). Similarly, when multiple cold inflations were compared with multiple hot inflations, two, three and four sequential hot inflations resulted in a significantly greater increase in cross-sectional area than an equivalent number of cold inflations ($p < 0.03$).

Histologic examination demonstrated a temperature-dependent effect on the depth of medial necrosis and extent of arterial wall thinning ($p < 0.001$) as well as evidence for uniform alteration of elastic tissue fibers at temperatures of ≥60°C ($p < 0.03$).

Conclusions. Low pressure radiofrequency thermal balloon angioplasty results in a greater increase in cross-sectional area in porcine peripheral arteries than does nonheated conventional balloon angioplasty. The pathologic basis for this enhanced dilation may be a temperature-dependent effect on medial necrosis, thinning of the arterial wall or alteration of vascular elastic fibers, alone or in combination.

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Over the last decade, percutaneous transluminal angioplasty has become an accepted therapeutic option for the treatment of obstructive vascular disease. Although the primary success rate in both the peripheral and the coronary vasculature exceeds 90%, the procedure remains limited by inadequate primary dilation, abrupt vessel reocclusion and late restenosis. Efforts to deal with these problems have led to the development of adjunctive angioplasty techniques including the mechanical removal of tissue, direct laser ablation of plaque and stenting of the vessel lumen. As yet, however, these methods have not been universally successful in overcoming the limitations of conventional angioplasty.

Recently, attention has been focused on the concept of thermally mediated balloon angioplasty as another potentially useful adjunctive technique. Thermal balloon angioplasty devices employing laser (1) or microwave (2) energy have been developed and tested in both animal and human protocols. These devices have been reported to improve lumen dilation over that achieved with conventional angioplasty and, in the case of laser balloon angioplasty, to seal vascular dissections (3). Most thermal angioplasty studies to date have involved devices that produce tissue temperatures >80°C. Little information is available on the potential utility of thermal angioplasty using lower temperatures.

Radiofrequency energy has previously been used to create surgical anastomoses in vascular tissue (4,5), to ablate cardiac conduction tissue and muscle (6–8) and to recanalize totally occluded vessels. Recently, a new balloon dilation catheter has been designed that employs radiofrequency circuitry and a variable output generator to heat balloon fluid to a temperature that can be individually selected for a variable duration. In the present study we evaluated this device in normal porcine peripheral arteries. Specifically, our aim was to determine: 1) the short-term efficacy of this

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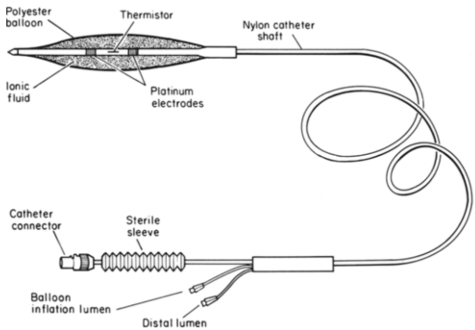

Figure 1. Schematic of the radiofrequency balloon dilation catheter. Radiofrequency energy passes between the two platinum electrodes heating the ionic fluid to a predetermined temperature.

form of thermal angioplasty compared with that of conventional balloon angioplasty, and 2) the pathologic effects and mechanism of action of the technique with a view to identifying the optimal operating temperature for this device.

Methods

Overview of study design. Radiofrequency balloon angioplasty was performed on right and left carotid, femoral and iliac arteries in 18 anesthetized, nonatherosclerotic pigs. Each arterial segment was examined before and after balloon dilation using intravascular ultrasonography to assess arterial dimensions and morphology. All balloon inflations were performed using 2-atm pressure, a balloon inflation time of 85 s and a mean balloon diameter/vessel diameter ratio of 1.31 ± 0.07. Heated inflations employing radiofrequency energy (hot inflations) were performed at temperatures ranging from 40° to 90°C. Balloon inflations performed without the use of radiofrequency energy (cold inflations) served as study controls. At the end of each study, each pig was killed and the dilated arterial segments were pressure perfused and isolated for histologic examination.

Equipment. *The radiofrequency balloon catheter* (Boston Scientific) consists of a 7F, triple-lumen, nylon shaft with a 2-cm polyester balloon at the distal end (Fig. 1). Three catheter lumens are used for passage of a guide wire, for balloon inflation and deflation and as a channel for the bipolar radiofrequency circuitry. A 100-W portable radiofrequency generator (Boston Scientific) allows for a variable output of continuous radiofrequency energy at 640 kHz. The generated current is applied over two wires that terminate in two platinum electrodes, 1 cm apart, located on the catheter shaft within the balloon lumen. Current traveling between the electrodes heats an ionic fluid within the balloon to a preset temperature up to 100°C. Temperature is regulated to within 1°C by a thermistor-generator feedback mechanism. Duration of energy output can be present in increments of 1 s. A standard inflator (Advanced Cardiovascular Systems) was used to inflate the balloon and monitor pressure. This balloon reaches nominal size at 2 atm.

The intravascular ultrasound catheter (Diasonics and Boston Scientific) consists of a 20-MHz, single-element, mechanical imaging device enclosed in a 6F blunt tip sheath. The catheter is connected to a console that displays two-dimensional pictures of the structures surrounding the catheter tip. Images are viewed in real time and stored onto videotape for subsequent review. The system is internally calibrated to permit on-line or off-line measurements with a spatial resolution <0.1 mm.

Animal preparation. Eighteen male or female adult pigs weighing 18 to 20 kg were premedicated with tiletamine/zolazepam (100 mg intramuscularly) and atropine (2 mg intramuscularly), paralyzed with a continuous infusion of succinylcholine and endotracheally intubated. Anesthesia was maintained with enflurane (Ethrane) and ventilation provided by a volume respirator. Both external carotid and femoral arteries were cannulated with 10F hemostatic vascular sheaths by local cutdown. Heart rate and arterial pressure were continuously monitored. Systemic anticoagulation was achieved with intravenous heparin. A bolus infusion of 200 U/kg body weight was given initially followed by 100 U/kg per h. All experiments conformed to the guiding principles of the "Position of the American Heart Association on Research Animal Use," adopted by the Association in November 1984.

Protocol. In each pig, up to six separate arterial segments (the right and left external carotid arteries, right and left iliac arteries and right and left femoral arteries) were studied with the following protocol. The ultrasound catheter was advanced into the vessel and baseline images were recorded. On-line measurements of the lumen diameter and cross-sectional area were made from the systolic still frame demonstrating the maximal vascular dimensions. The intravascular catheter was then removed and a balloon catheter was advanced over a 0.035-in. (0.089 cm) J-tipped guide wire so that the balloon was centered at the site of ultrasound measurement. For all segments, a balloon size was chosen to give a balloon/vessel diameter ratio of approximately 1.3:1. All inflations were performed at 2 atm for 85 s. For heated dilations, radiofrequency energy was applied during the initial 60 s of the balloon inflation; cooling of the balloon occurred over the remaining 25 s before deflation. After deflation, the balloon catheter was exchanged for the intravascular ultrasound catheter and repeat assessments of arterial dimensions and morphology were performed. The vascular sheaths were flushed with heparinized saline solution after each catheter exchange. A typical study, consisting of an ultrasound measurement, a balloon dilation and a repeat ultrasound measurement, was performed in 6 to 10 min.

Three methods were employed to ensure that the same arterial site within each segment was used for all measurements and inflations: 1) Radiopaque rods were positioned under the pig to mark the site of ultrasound measurement; 2) catheter positions were marked on the fluoroscopic screen; and 3) venous structures on the ultrasound freeze frame image served as landmarks.

Four different inflation protocols were employed, one of which was used in each arterial segment, thereby creating four groups for comparison. The *single cold inflation* group included segments in which one nonheated inflation was performed. The *single hot inflation* group comprised those segments in which only one radiofrequency-heated inflation was performed. Within this group, arterial segments were dilated at either 40°, 60°, 70° or 80°C. In the *multiple cold inflations* group, two to seven inflations, none heated, were performed in each segment. In the *multiple hot inflations* group, each segment was initially dilated with a cold inflation that was then followed by one to six heated inflations. The mean temperature of the hot inflations was 50° ± 5°C (range 40° to 90°C). For both the multiple cold and multiple hot inflation groups, arterial segments underwent serial dilation until the cross-sectional area increased by at least 10% or a total of seven inflations were performed.

On completion of the study, death was induced in each animal with intravenous potassium chloride and the arterial segments were excised and pressure perfused with 10% buffered formalin. All dilated specimens were sent for pathologic analysis. After fixation, central, proximal and distal sections of each segment were prepared for hematoxylin-eosin and Verhoeff elastic tissue staining. Sections were examined by two pathologists who did not know the specific dilation protocol or the intravascular ultrasound data.

In five arterial segments not included in these protocols, vessel wall temperature was measured with the use of a needle thermistor. The needle was inserted into the vessel wall before balloon inflation and heating. Simultaneous balloon and thermistor temperatures were then recorded during a heated balloon inflation. Although intramural temperature could be measured, this method did not permit precise localization of the thermistor to either the media or the adventitia.

Data analysis. The short-term impact of heat on the efficacy of dilation was analyzed by comparing the ultrasound-derived initial cross-sectional area, postdilation cross-sectional area and percent change in cross-sectional area in vessels undergoing single hot versus single cold inflations, as well as in those undergoing multiple hot versus multiple cold inflations. For purposes of this analysis, the first inflation in both the multiple hot and multiple cold groups (i.e., a cold inflation) was also included in the single cold data. When analyzing the multiple inflation data, comparisons between hot and cold groups were made after the same number of inflations had been performed in each group (i.e., percent change in cross-sectional area after the second inflation, the third inflation, and so forth, as compared to the baseline cross-sectional area).

All ultrasound measurements were performed by two experienced observers who did not know the specific dilation protocol employed. In addition, all ultrasound recordings were carefully reviewed by two observers to detect the presence of arterial dissections. The incidence of dissection after hot and cold inflations was expressed as the percent of inflations that resulted in dissection.

Pathologic changes in each arterial segment were evaluated according to the following eight variables: intimal damage, internal elastic lamina damage, medial necrosis, dissection, delamination, elastic tissue alteration, compaction or thinning of the arterial wall, and thrombus (Table 1). Delamination refers to the separation of myocyte layers. Elastic tissue alteration refers to the straightening of the normally buckled elastic fibers. For each variable, each segment was given a numeric rank and intermediate grades were assigned a value of 0.5 (i.e., 1+ to 2+ was recorded as 1.5).

Statistics. The results are presented as the mean value ± SD. Comparisons between individual groups for the continuously distributed variables were performed using either an unpaired Student *t* test for the normally distributed variables or a Mann-Whitney test for the variables that were not normally distributed. Comparisons between the multiple temperature subgroups were performed using analysis of variance. For categoric data, either the Fisher exact test or chi-square analysis was used as appropriate. For pathologic variables measured on an ordinal scale, a Kruskall-Wallis analysis or a Mann-Whitney test was used. A p value < 0.05 was considered significant.

To estimate expected errors in intravascular ultrasound cross-sectional area measurements, two cycles from each of 10 arterial segments were analyzed in duplicate (replications) by each of two different echocardiographers (observers). A total of 80 measurements were made and input into the SAS statistical software (9) running on an IBM mainframe computer, using the NESTED procedure. The components of variance of cross-sectional area, expressed here as standard deviations, were estimated to be: cycles 0.0017 cm^2; observ-

Table 1. Criteria Used for Histologic Examination

Grade	Definition
Intimal damage	
0	Absent
1+	Focal
2+	Diffuse
Internal elastic lamina	
0	Present
1+	Focally absent
2+	Diffusely damaged or absent
Medial necrosis	
0	Absent
1+	Involving inner third of media
2+	Involving entire media
3+	Involving entire media and adventitia
Dissection	
0	Absent
1+	Extending to inner third of media
2+	Extending to outer third of media
3+	Extending through media into adventitia
Delamination	
0	Absent
1+	Partial and focal
2+	Full thickness and diffuse
Elastic tissue	
0	Straight
1+	Focally buckled
2+	Diffusely buckled
Compaction (thinning of arterial wall)	
0	Absent
1+	Involving inner third of vessel wall
2+	Involving inner third to half of vessel wall
3+	Involving outer half of vessel wall
Thrombus	
0	Absent
1+	Mural
2+	Partially occlusive
3+	Totally occlusive

Each dilated arterial segment that underwent histologic examination was graded according to these criteria.

ers (interobserver) 0.0009 cm^2, and replications (intraobserver) 0.0016 cm^2. Therefore, the best estimate of error expected in a single cross-sectional area measurement is 0.0026 cm^2.

Results

In 18 pigs, a total of 222 inflations were performed in 75 arterial segments with a balloon/vessel diameter ratio of 1.31 ± 0.07 (range 1.15 to 1.41). Single cold inflations were performed in 47 segments and single hot inflations in 28 segments. In the single hot group, seven segments were dilated at 40°C, eight at 60°C, six at 70°C and seven at 80°C.

In the multiple cold group, 41 inflations were performed in 8 segments, in the multiple hot group, 144 inflations were performed in 30 segments. The mean temperature for the multiple hot inflations was 50° ± 5°C (range 40° to 90°C).

Among the four comparison groups, there were no significant differences in balloon/vessel diameter ratio, initial lumen cross-sectional area or distribution of carotid, femoral and iliac segments. During all inflations the heart rate, cardiac rhythm and systemic blood pressure remained stable.

Quantitative intravascular ultrasound measurements. When single cold inflations were compared with single hot inflations, both postinflation cross-sectional area and percent change in cross-sectional area were significantly greater in the hot group (the respective values were 0.208 ± 0.05 cm^2 vs. 0.229 ± 0.06 cm^2, $p = 0.04$; and 12.7 ± 19.9% vs. 22.9 ± 25.0%, $p = 0.03$). Figure 2, A and B, demonstrates intravascular ultrasound images before and after cold and hot inflations. Although the size of the study group precluded meaningful temperature subgroup analysis, the greatest increase in cross-sectional area was found with the 70°C group (12.7 ± 19.9% vs. 31.2 ± 21.6%). Data comparing single cold and single hot inflations are summarized in Table 2.

When the multiple cold and multiple hot inflation groups were compared, significantly greater values for cross-sectional area and for percent change in cross-sectional area were noted in the hot group, as compared with the cold group, for two, three and four inflations ($p < 0.03$); however, no significant difference was seen for inflations five, six and seven. Multiple cold and hot inflation data are summarized in Table 3.

Incidence of arterial dissections. The incidence of arterial dissections was based on the intravascular ultrasound images of 216 inflations in 75 arterial segments. Six inflations were not included in this analysis because they were performed in a segment after a dissection occurred. Among the cold inflations, there were 3 dissections (3.8%) in 80 inflations as compared with 1 dissection (0.7%) in 136 hot inflations ($p = 0.14$). Balloon/vessel diameter ratios were not significantly different between the hot (mean 1.31 ± 0.07, all inflations) and cold (mean 1.31 ± 0.07, all inflations) groups.

Histologic examination. Histologic examination was performed on a study subset consisting of 8 single cold inflation segments, 24 single hot inflation segments, 8 multiple cold inflation segments and 20 multiple hot inflation segments. Fifteen segments (1 single cold, 4 single hot and 10 multiple hot) were found to be unsuitable for histologic analysis by two pathologists who did not have access to the dilation protocol employed or the intravascular ultrasound data.

Segments subjected to a single cold inflation demonstrated smooth muscle cell necrosis that extended, on the average, into the inner one third of the media (mean grade 1.1 ± 0.5). The outer one third of the media and the adventitia demonstrated no significant evidence of necrosis or disruption, and there was minimal compaction and thinning of the vessel wall (mean grade 0.9 ± 0.5). Of the eight segments, six demonstrated straightening of the normally buckled elastic fibers, five showed diffuse absence of the

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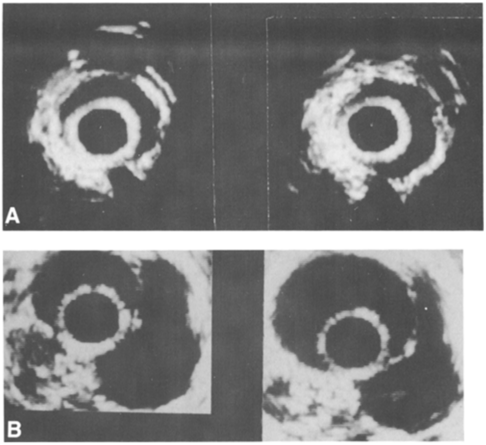

Figure 2. Intravascular ultrasound images of a porcine iliac artery segment. **A,** Effects of a cold balloon dilation. At baseline (**left panel**), lumen cross-sectional area was 0.19 cm^2. After a cold dilation (**right panel**), the cross-sectional area was 0.20 cm^2, a 5% increase. **B,** Effects of a hot balloon dilation. Before heated dilation, lumen cross-sectional area was 0.21 cm^2 (**left panel**). After dilation at 70°C., the cross-sectional area was 0.33 cm^2, a 57% increase (**right panel**). The lumen to the right of the artery is the iliac vein. In both **A** and **B**, the circular white shadow in the vessel lumen represents intravascular ultrasound catheter artifact.

intima, four showed focal damage or absence of the internal elastic lamina and six showed focal or absent delamination. Only one segment was dissected. In five of the eight segments some degree of thrombus was present.

With the application of radiofrequency energy in the single hot inflation group, there was a significant increase in the depth of medial cell necrosis ($p < 0.001$) and vessel wall compaction and thinning ($p < 0.001$) with increasing temperatures. At each successively higher temperature, compaction and necrosis extended deeper into the wall. In general, compaction extended into the inner third of the media at 40°C (mean grade 0.8 ± 0.5), the inner half of the media at 60°C (mean grade 1.7 ± 0.6), and was between half and full thickness at 70° (mean grade 2.2 ± 0.6) and 80°C (mean grade 2.3 ± 0.6). Cellular necrosis involved the inner third of the

Table 2. Single Cold Versus Single Hot Inflations

	Inflations		
	Single Cold (n = 47)	Single Hot (n = 28)	p Value
Inflation temperature			
Cold inflation	47	0	
40°		7	
60°		8	
70°		6	
80°		7	
Balloon/vessel diameter ratio	1.30 ± 0.07	1.31 ± 0.06	NS
CSA (cm^2)			
Before dilation	0.186 ± 0.04	0.188 ± 0.03	NS
After dilation	0.208 ± 0.05	0.229 ± 0.06	0.04
Change in CSA (%)			
Total group	12.7 ± 19.9	22.9 ± 25.0	0.03
40°C		18.9 ± 26.5	NS
60°C		23.5 ± 18.9	NS
70°C		31.2 ± 21.5	NS
80°C		19.0 ± 34.7	NS

All values are expressed as number of inflations or mean value ± SD. CSA = cross-sectional area.

Table 3. Multiple Cold Versus Multiple Hot Inflations

	Inflations		
	Multiple Cold	Multiple Hot	p Value
No. of segments			
Inflation 2	8	30	
Inflation 3	6	20	
Inflation 4	6	17	
Inflation 5	6	14	
Inflation 6	4	11	
Inflation 7	3	9	
Balloon/vessel diameter ratio	1.31 ± 0.06	1.31 ± 0.07	NS
Predilation CSA (cm^2)	0.181 ± 0.03	0.192 ± 0.04	NS
Change in CSA (%)			
Inflation 2	6.38 ± 10.10	21.83 ± 21.78	0.03
Inflation 3	3.00 ± 9.96	20.15 ± 19.60	0.03
Inflation 4	5.00 ± 13.56	28.24 ± 25.76	0.03
Inflation 5	17.0 ± 21.15	32.71 ± 21.08	0.07
Inflation 6	15.25 ± 7.50	31.82 ± 21.28	0.08
Inflation 7	18.0 ± 10.15	34.33 ± 18.10	0.09

All values are presented as number of inflations or mean value ± SD. CSA = cross-sectional area.

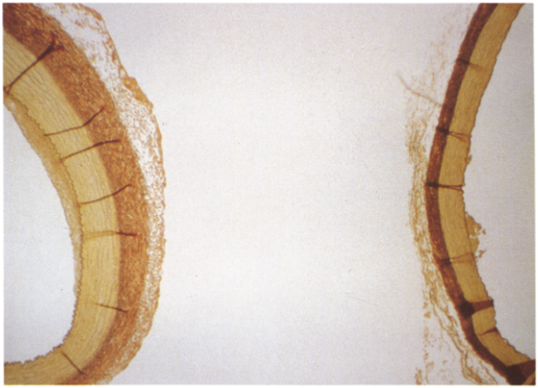

Figure 3. Photomicrographs of porcine carotid arteries demonstrating the effect of a heated inflation on the width of the arterial wall. The specimen on the **right**, which was dilated at 70°C., is compressed and thinned compared with the nondilated control specimen on the left. Verhoeff elastic tissue stain ×60, reduced by 30%.

media at 40°C (mean grade 1.2 ± 0.5), the inner half at 60°C (mean grade 1.6 ± 0.4) and the entire media at 70° (mean grade 2.5 ± 0.6) and 80°C (mean grade 2.7 ± 0.7). Adventitial necrosis was present in both the 70° and 80°C groups, with more extensive involvement at 80°C. There was no adventitial damage in any specimen heated at ≤60°C.

There was also a significant effect of heat on the elastic tissue fibers. With temperatures of ≥60°C, all segments demonstrated straightening of the normally buckled elastic fibers. As compared with the combined cold and 40°C groups, this finding was significant at the $p = 0.03$ level.

With respect to the internal elastic lamina, there was significantly less damage with the single hot dilations (mean grade 0.15 ± 0.4) than with the single cold dilations (mean grade 0.5 ± 0.5) ($p < 0.05$). Intimal damage was extensive in both groups, although there appeared to be less intimal trauma with the single cold inflations ($p < 0.05$). With respect to delamination, dissection and thrombus, there was no significant difference between the single hot and single cold groups.

In general, as compared with the segments that underwent a single inflation, the segments subjected to multiple inflations had a greater degree of internal elastic lamina damage ($p < 0.01$), delamination ($p = 0.01$), dissection ($p < 0.01$) and thrombosis ($p = 0.04$). There was no significant difference between single and multiple inflated segments with respect to degree of intimal damage, effect on the elastic fibers or the extent of compaction or medial necrosis.

Among the multiple inflation segments, there was no significant difference between the heated and nonheated segments with respect to amount of intimal damage, internal elastic lamina damage, delamination, medial dissection, elastic fiber straightening or degree of thrombus. However, as with the single inflation segments, in the multiple inflation group the depth of medial necrosis appeared to increase with increasing temperature ($p < 0.01$) as did the degree of wall thinning ($p = 0.05$). Examples of histologic changes with cold and hot inflations are presented in Figures 3 to 5.

Thermistor data. In the five vessels in which the wall temperature was measured, the intramural temperature remained within 1°C of the balloon temperature throughout the period of heating with a lag time of 1 to 2 s.

Discussion

This study has demonstrated that low pressure, radiofrequency-powered thermal angioplasty of normal porcine peripheral arteries results in a greater increase in lumen cross-sectional area than that achieved with conventional balloon angioplasty. The histologic basis underlying the enhanced dilation appears to be a temperature-dependent effect on the depth of medial cell necrosis, vessel wall compaction and alteration of elastic tissue fibers.

Intravascular ultrasound measurements. It is notable that single hot inflations resulted in an 80% greater increase in cross-sectional area than that of single cold inflations (22.9% vs. 12.7% increase). Although the individual temperature subgroups were too small to precisely determine the optimal temperature for dilation, the effect of heating was most pronounced in the 70°C subgroup, which demonstrated a 146% greater increase in cross-sectional area compared with that in the single cold group (31.2% vs. 12.7% increase).

When multiple inflations were performed, there was a significantly greater dilation with two, three and four hot

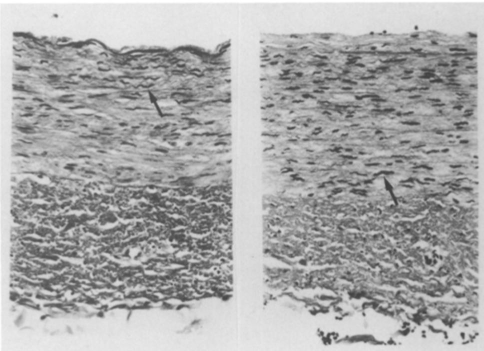

Figure 4. High power photomicrographs of femoral arteries treated with a cold inflation (**left panel**) and a hot inflation at 60°C (**right panel**). Pyknosis and "wrinkling" of the nuclei (**arrows**) is present throughout the heated specimen but is confined to the lumen (**top**) side of the media in the nonheated specimen in which the outer portion appears normal. Hematoxylin–eosin ×625, reduced by 20%.

inflations as compared with an equivalent number of cold inflations. The change in cross-sectional area after five, six and seven inflations did not reach statistical significance. The lack of a significant heat effect with more than four inflations may be due to an effect of multiple dilations that is independent of heating. It may also relate to the small number of segments in these groups.

Evaluation by intravascular ultrasound detected very few dissections even though the balloon was routinely oversized. This may be explained, at least in part, by the fact that these were nonatherosclerotic vessels. No significant difference was found between the hot and cold groups with respect to the incidence of dissection.

Pathologic observations. There are several interesting pathologic correlates to the intravascular ultrasound data. 1) Despite greater dilation with heated inflations, there was no increase in the extent or presence of dissection, the degree of vessel delamination or the extent of internal elastic lamina damage when compared with findings after cold inflations. In fact, heating appeared to attenuate disruption of the internal elastic lamina.

2) The observed straightening of elastic tissue fibers may be associated with a loss of tissue elastic properties. The finding that this straightening was most pronounced in the temperature range at which the greatest dilation occurred (e.g., 60° to 70°C) suggests that improved dilation may reflect an alteration of these fibers. In the multiple inflation group, we did not find a specific effect of heat on elastic tissue straightening. It is possible that multiple inflations have an independent effect on elastic tissue straightening, thereby making it difficult to assess the effect of heat in this situation.

3) The consistent relation found between temperature and depth of wall injury suggests that the ability to regulate balloon temperature may permit precise control of the degree of vascular injury. This concept is further supported by the observation that intramural thermistor-measured temperature closely paralleled intraballoon temperature without a significant time lag. The ability to control injury may be an important and useful property of thermal conduction heating.

4) It is notable that both hot and cold segments demonstrated a significant presence of thrombus after angioplasty, although the amount of thrombus was not affected by heat. With regards to this finding, a previous study (10) has demonstrated a high thrombotic tendency in the porcine angioplasty model, with a 50% incidence of thrombus in conventionally dilated arteries.

Possible mechanisms of radiofrequency-heated angioplasty. Previous studies of conventional, nonthermal balloon angioplasty have ascribed vascular dilation with that technique to stretching of the normal vessel wall and cracking of the atheromatous plaque (11–13). A dilated vessel usually does not maintain the cross-sectional area it attains while the balloon is inflated, implying some degree of immediate recoil (14). The mechanism of this recoil is unclear but may involve rebound of elastic elements (14,15) or vasoconstriction by myocytes (16).

1) Radiofrequency warming of the vessel wall during balloon inflation may improve dilation by attenuating this phenomenon of immediate recoil through several mechanisms. 1) Immediate recoil may be due to the rebound of stretched elastic elements in the vessel wall. Jenkins and Spears (17) has noted that elastic fibers are straightened permanently with laser balloon angioplasty and attributed the decrease in recoil to this phenomenon. In the present study, straightening of the elastin fibers occurred consistently when a temperature of ≥60°C was employed. This pathologic change may be a correlate of a decrease in elasticity and be responsible for the improved dilation seen with the heated inflations.

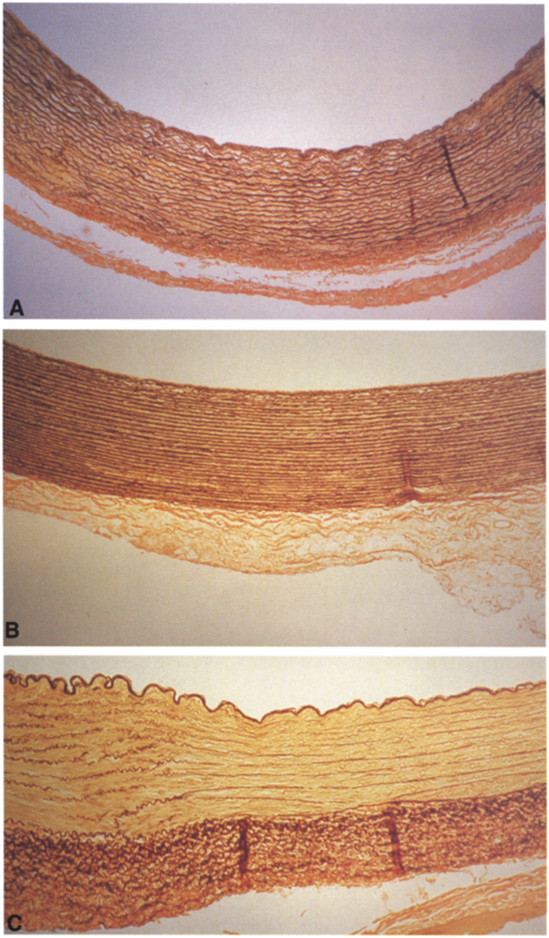

Figure 5. A and B, Medium power photomicrographs of carotid arteries after balloon dilation. A, After dilation at 40°C, this specimen demonstrates buckled and widely spaced elastic laminations (**arrow**). B, After dilation at 70°C this specimen clearly demonstrates straightening and compression of the elastic laminations (**arrow**) compared with those in A. C, Medium power photomicrograph of an iliac artery at the transition zone (**arrow**) between a nondilated, normal segment of the artery (**left side**) and a region dilated at 70°C (**right side**). The effect of heat on compression and straightening of the elastic tissue fibers is clearly demonstrated. A to C, Verhoeff elastic tissue stain ×250, reduced by 30%.

2) The potential role of vasoconstriction in immediate recoil (16) may have been attenuated by the destruction of myocytes. In this regard, Jenkins and Spears (17) has noted that coronary vasoconstriction is completely inhibited with laser heating of the vessel. In our study, the extent of myocyte necrosis was directly related to temperature, with the entire media being involved at 70°C.

3) Thermal alteration of protein structure may be another

factor resulting in the attenuation of immediate recoil. Structural protein and collagen are denatured at 60° to 70°C (18) and previous studies have demonstrated that heat can rearrange collagen substructure (19,20). The resultant remodeling of vessel microstructure may be the basis for the decreased recoil and the improved dilation found in this study. As cooling occurs while the balloon remains inflated, reforming collagen bonds may lock the vessel wall into this new dilated state and prevent immediate recoil.

4) It has recently been demonstrated that radiofrequency balloon heating significantly increases compliance of the vessel wall in an in vitro model utilizing porcine peripheral arteries (21). The pathologic basis for this observation may be the denaturation of proteins, alteration of elastic tissue and necrosis of myocytes demonstrated by this study. The resultant decrease in resistance of the vessel wall to stretch (i.e., vascular softening) may facilitate dilation.

5) Finally, the temperature-dependent compaction and thinning of the arterial wall may have also partially contributed to the increased lumen size.

Comparison with laser balloon angioplasty. Low pressure, radiofrequency balloon angioplasty differs from laser balloon angioplasty, the only other extensively evaluated thermal balloon technique, in several important ways. Laser angioplasty imparts energy to the vessel wall through spectral absorption, its interaction with the vessel therefore being, to a large extent, dependent on the optical properties of the tissue (22,23). In contrast, radiofrequency balloon angioplasty imparts energy to the vessel through thermal conduction with the transfer of energy being dependent on the thermal conductive properties of the vascular tissue.

The depth to which the vessel wall is affected may also differ significantly with these two techniques. Depth of penetration with laser energy is dependent on the laser dose employed and the degree of energy absorption and reflection. At laser doses designed to heat vascular tissue to temperatures of 80° to 100°C, Jenkins and Spears (17) have demonstrated tissue damage at a depth of 1 to 6 mm. With radiofrequency balloon angioplasty, the depth of penetration is dependent on the balloon/vessel wall temperature gradient and the thermal conductive properties of the vessel wall. In this study, when the temperature was confined to ≤60°C, the maximal depth of tissue damage was 360 μm, never extending into the adventitia. Depth of penetration may be important when considering the possibility of late aneurysm formation as this is associated with transmural damage (24).

Low temperature radiofrequency angioplasty presumably will not desiccate thrombus or seal intimal flaps, both of which are important mechanisms of laser balloon angioplasty (22). The desiccation of thrombus requires temperatures high enough to vaporize water, and work with laser angioplasty has demonstrated that tissue welding requires a temperature of at least 80°C (25).

Study limitations. There are several important limitations of this study. 1) The experiments were performed with normal, nonatherosclerotic vessels. As a result, we could not study the effect of radiofrequency heating on remodeling atheromatous plaque or determine whether the technique would cause a significant dilation in an atheromatous vessel. However, recent studies by Lee et al. (26) and by Deutsch et al. (27), do suggest that radiofrequency balloon angioplasty is more efficacious than conventional balloon angioplasty in human postmortem atherosclerotic vessels.

2) Although this study compared the use of heated and nonheated balloon dilations, direct comparison with conventional balloon angioplasty is limited by our use of oversized balloons and low inflation pressures. Typically, conventional balloon angioplasty employs a balloon/vessel diameter ratio of 1.0 and inflation pressures ranging between 6 and 12 atm. Because we used nonatheromatous vessels, oversizing of the balloon was necessary to effect vascular dilation. Because this balloon attains nominal size at 2 atm, this pressure was chosen to dilate the vessels as atraumatically as possible while still guaranteeing full balloon inflation.

3) The generally low incidence of dissections, possibly due to the absence of plaque in this nonatherosclerotic model, makes it difficult to determine if low pressure, radiofrequency angioplasty has any effect upon the occurrence of dissection. This issue may be better addressed with atherosclerotic vessels, which are more prone to dissection with balloon dilation.

4) This study did not include a long-term follow-up phase, thereby precluding evaluation of such important issues as restenosis and aneurysm formation.

Conclusions. This study of normal porcine peripheral arteries has demonstrated that the addition of low temperature, radiofrequency heating to low pressure balloon dilation results in a significantly greater lumen dilation than is achieved without such heating. This enhanced dilation was observed with both single and multiple inflations. The basis for this enhanced dilation may be increased myocyte necrosis, alteration of the elastic tissue or thermal alteration of structural proteins. The potential superiority of low pressure, radiofrequency angioplasty over conventional nonthermal angioplasty needs to be further tested in atheromatous vessels.

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