Use of Therapeutic Ultrasound in Percutaneous Coronary Angioplasty

Experimental In Vitro Studies and Initial Clinical Experience

Robert J. Siegel, MD; Julian Gunn, MD; Arif Ahsan, MD; Michael C. Fishbein, MD; Robert J. Bowes, MD; David Oakley, MD; Clare Wales, RN; Wolfgang Steffen, MD; Stephen Campbell, MD; Henry Nita, MS; Timothy Mills, PhD; Paul Silverton, MD; Richard K. Myler, MD; David C. Cumberland, MD

Background
Previous studies have shown the feasibility of peripheral arterial ultrasound angioplasty.

Methods and Results
In this report, we describe the use of percutaneous therapeutic ultrasound for coronary angioplasty. In vitro, 11 postmortem, atherosclerotic occluded coronary arteries were obtained to assess catheter-delivered ultrasound for arterial recanalization as well as for assessment of the size of particulate debris. Clinically, coronary ultrasound angioplasty was performed in 19 patients (mean age, 56 years) to assess safety and feasibility for the treatment of obstructive coronary atherosclerosis. Three patients with unstable angina and 16 with exercise-induced myocardial ischemia were treated with a prototype 4.6F coronary catheter ultrasound ablation device with a 1.7-mm diameter ball tip. The ultrasound coronary catheter delivered ultrasound energy at 19.5 kHz, with a power output of 16 to 20 W at the transducer. Energy is delivered in a pulsed mode with a 50% duty cycle of 30 milliseconds. Patients were treated for a mean of 493 seconds (range, 130 to 890) with intracoronary ultrasound ablation. All lesions were treated with adjunctive balloon angioplasty. All 11 postmorten coronary occlusions were recanalized, and 99% of the particulates generated were <10 μm in diameter. We found that after ultrasound, mean (±SD) coronary arterial stenosis fell from 80±12% to 60±18% (P<.001) and to 26±11% (P<.001) after adjunctive balloon angioplasty. Mean pressures required to achieve full balloon inflation were 2.7 atm (range, 1 to 5.5) with a median of 3.0-mm balloon size (2.5 to 3.5). No ultrasound-related complications were identified.

Conclusions
Intracoronary ultrasound plaque ablation appears to be safe. Our findings suggest that catheter-delivered high-intensity, low-frequency ultrasound may be useful for lesion debulking and enhancing arterial distensibility, allowing balloon dilation at relatively low pressures. (Circulation. 1994;89:1587-1592.)

Key Words • atherosclerosis • ultrasound • angioplasty

Catheter-delivered high-intensity, low-frequency ultrasound energy has been shown experimentally to recanalize guide wire–resistant fibrous and calcific atherosclerotic occlusions,1-4 to rapidly dissolve arterial thrombi,5,6 and to induce vasodilation in vitro and in vivo.6 The microscopic particulate debris generated during plaque ablation and thrombus dissolution are small and comparable to the particulates from other clinically used modalities.1,5,6 Clinical studies in humans have demonstrated that this technique can be used safely and effectively for peripheral angioplasty.5,10

Studies using a recently developed coronary ultrasound probe system have shown that this device can be used to dissolve thrombotic canine coronary occlusions, that the delivered ultrasound energy results in coronary vasodilation, and that there is no ultrasound-induced arterial damage.11 This report describes the initial clinical studies performed to assess if percutaneous catheter-delivered high-intensity, low-frequency ultrasound is safe and feasible in the treatment of obstructive coronary atherosclerosis.

Methods

In Vitro Study

Ultrasound Angioplasty System

The ultrasound probe system (Baxter-Edwards Healthcare Corporation, Bentley Laboratories, Europe BV, Uden, The Netherlands) consists of an electrical generator, a piezoelectric transducer, and a 4.6F-diameter catheter ensheathing a titanium wire probe that transmits the ultrasound energy. The piezoelectric crystals in the transducer convert electrical energy into mechanical motion at a frequency of 19.5 kHz (19 500 cycles per second). The amplitude of longitudinal motion of the probe tip during a cycle is from 15 to 30 μm. The ultrasound coronary catheter, of rapid exchange design, is 145 cm long and has a 1.7-mm ball tip, a distal infusion lumen, and a lumen for an 0.014- or 0.018-in. coronary guide wire. This catheter fits through an 8F guide catheter. The ultrasound catheter is flushed with heparinized saline at 10 mL/min to prevent heating of the probe during the transmission of ultrasound. The ultrasound energy is administered in 15-second bursts, with a 5-second off-time. The power output at the transducer is 16 to 20 W in a pulsed mode, with a 50% duty cycle of 30 milliseconds.

Postmortem Studies on Human Coronary Arteries

In vitro studies were performed on 11 occluded human coronary arterial segments. The coronary arteries were ex-
cised from nine different human hearts at the time of autopsy. Six coronary arterial segments were fixed in 10% neutral buffered formalin and five were stored for 1 week at 4°C. Nine of 11 arterial segments were heavily calcified radiographically and by gross and histological examination. The criteria for selection of the postmortem human coronary arteries were that the unactivated ultrasound probe was impalpable across the occlusions. The occlusion length was assessed by guide wire passage from a proximal site and then from the distal end of the artery. The mean length of the occlusion was 3.2±1.6 cm. For the in vitro studies, the activated ultrasound probe was advanced using firm pressure (approximately 100 to 200 g force as assessed by a dynamometer) (PK Neuses Inc, Arlington Heights, Ill) in 15-second intervals with 10 mL/min of saline flush.

The effluent from each of the 11 recanalized arterial segments was collected, and particulates were studied with an electronic particle counter of the resistive-pulse type (model FN, Coulter Electronics, Hialeah, Fla). Each specimen was sufficiently diluted (Isoton, Coulter Diagnostics, Hialeah, Fla) both to provide adequate specimen volume (0.5 mL per size range study) and to eliminate coincidence coincidences by achieving measured particulate concentrations below 10⁻⁷/L. The counter was calibrated using polystyrene latex spheres (PolySciences, Inc, Warrington, Pa) and commercial control material (4Cplus, Coulter Diagnostics). In the configuration that we use, the instrument measures particle volume (V) per over a range from 0.3 to approximately 2×10⁻⁷ FL. The sensitivity in this interval is 10⁴ particles per liter. Note that this is expressed in SI units; for comparison given in conventional units, this corresponds to only 0.001 particle per microliter. For convenience, we present our data assuming the particles can be considered approximately spherical, and we can thus express their diameter (D) as D=(6V/π)¹/³. We have previously described this technique in detail² and the validity of this spherical approximation elsewhere.³ As assessed by the resistive pulse method, particles 2.5 to 80 μm in diameter are detected.

**Clinical Study**

**In Vivo Study**

With prior ethical committee approval, 19 symptomatic patients with obstructive single-artery coronary artery disease consented to undergo percutaneous ultrasound angioplasty as part of their coronary balloon angioplasty procedure. The indication for angioplasty was symptomatic coronary artery disease manifested by angina at rest (n=3) or exercise-induced myocardial ischemia (n=16). There were 8 lesions in the proximal or mid left anterior descending coronary artery and 11 lesions in the midportion of the right coronary artery. At baseline, the mean (±SD) diameter stenosis was 80±12%, with a mean length of 18 mm (range, 4 to 78). The minimal lumen diameter was 0.6±0.3 mm, and the reference vessel diameters ranged from 2.5 to 3.5 mm. There were 6 type A, 10 type B, and 3 type C lesions as classified by American College of Cardiology/American Heart Association criteria.⁴ The mean duration of ultrasound administration was 439 seconds (range, 138 to 890).

The performance of clinical ultrasound angioplasty is similar to standard coronary balloon angioplasty. After an 8F introducer sheath is placed in the femoral artery, patients are given 10,000 U of heparin intravenously. Standard 8F guiding catheters are used for ultrasound and adjunctive balloon angioplasty. Angiograms are performed at baseline after 200 μg of intracoronary nitroglycerin, after ultrasound exposure, after repeat nitroglycerin (200 μg intracoronary), after balloon angioplasty, and again after nitroglycerin (200 μg intracoronary). The smallest luminal diameter within the stenosis as well as a normal reference segment are measured using a Philips digital quantitative angiographic system. Distal vessels are carefully evaluated for embolization. Subsequently, all patients have undergone adjunctive balloon angioplasty. Eighteen of 19 patients underwent repeat coronary angiography 18 to 24 hours after the angioplasty procedure to evaluate the acute results. Patients were discharged 24 hours after angiography on 75 mg of aspirin daily in addition to their standard medications.

**Statistical Analysis**

Comparison of angiographic diameter stenoses was performed using a two-sided, paired Student’s t test. A P value <.05 was considered significant. Data are expressed ±SD.

**Results**

**In Vitro Findings**

Application of the prototype coronary ultrasound probe recanalized 11 of 11 occlusions, 10 of which were calcific. The rate of recanalization was 10±5 mm per minute. Fig 1A is a radiograph of a calcified, occluded, postmortem human right coronary artery. Figs 1B and 1C demonstrate the histological findings after ultrasound recanalization of arterial occlusions at two different sites. The arterial lumen appears relatively circular and smooth. The arterial wall is heavily calcified, and there is no evidence of thermal damage. These histological findings after ultrasound recanalization were typical for all of the 11 postmortem vessels studied in vitro.

Fig 2 is a graph displaying the particle size distribution for the 11 recanalized atherosclerotic coronary arteries. As measured by the resistive pulse method, >99% of the particulates are ≤10 μm in diameter.

**Clinical Findings**

Ultrasound angioplasty in patients reduced the stenosis in 17 of 19 coronary lesions treated. Fig 3 shows the reduction in the stenosis of the left anterior descending coronary artery of case 7. As measured by quantitative digital angiography, the percent stenosis was reduced from 71 to 57 after ultrasound angioplasty and to 43 after adjunctive balloon angioplasty. The mean percent reduction in stenosis for the group was from 80±12 to 60±18 (P<.0001), and the mean (±SD) minimum lumen diameter (MLD) increased from 0.6±0.3 mm to 1.1±0.5 mm (P<.001) after application of catheter-delivered ultrasound energy. Angiographically, the residual luminal contours were all smooth in appearance, with no clefts or haziness visible, and the arterial run-off was brisk.

In a single case (patient 3), there was a guiding catheter-induced dissection of a right coronary artery after use of the ultrasound catheter. Balloon dilatation failed in this case to restore arterial patency, but there were no clinical sequelae. All the other 18 patients underwent successful adjunctive balloon angioplasty, the final mean residual stenosis being 26±11% (P<.001), and the MLD increased to 2.4±0.5 mm (P<.001).

Specific attention was given to assess potential complications. There was no evidence of ultrasound-induced emboli, heart block, arterial dissection, perforation, vasospasm, or abrupt closure. There was no pain or significant ECG changes associated with the intracoronary delivery of ultrasound energy. While ultrasound was not seen to induce arterial vasodilation for the patients as a group, there was one case in which
ultrasound reversed vasospasm that was refractory to 700 μg of intracoronary nitroglycerin.

Pressures required to achieve full balloon inflation, ie, at which the stenosis yielded, were 2.7 atm (range, 1.0 to 5.5), with a median of 3.0-mm balloon size (2.5 to 3.5).

During the next 24 hours, all patients were asymptomatic, and there was no ECG evidence or enzymatic evidence of myocardial infarction in any patient. Angiographic follow-up at 18 to 24 hours demonstrated continued patency of all except one vessel (see Table). In the one patient with a previously totally occluded left anterior descending coronary artery, the artery silently reoccluded; patency was restored by repeat balloon angioplasty. For the other 17 patients, the mean MLD of 2.4 mm did not change 24 hours after angioplasty, but the arterial stenosis increased from 26±11% to 32±11% in the same period (P<.02). Administration of intracoronary nitroglycerin resulted in no significant overall increase in lumen diameter at any stage of the procedure or at 24 hours.

**Discussion**

This is the first clinical report on the use of catheter-delivered high-intensity, low-frequency ultrasound for the treatment of coronary arterial obstructions. For the patient group, mean stenosis fell by 20% and the MLD increased by 0.5 mm (P<.001). In 16 of 19 lesions treated by ultrasound, there was a fall in percent stenosis by >20% and/or an increase in MLD by 0.3 mm. This preliminary study showed that the procedure...
was safe despite prolonged exposure to ultrasound energy of up to 15 minutes (138 to 890 seconds). There was no evidence of arterial emboli, heart block, arterial perforation, dissection, or vasospasm, nor was there evidence of myocardial ischemia or infarction.

The in vitro data, using the same coronary ultrasound angioplasty system as used clinically, demonstrate the effectiveness of ultrasound energy for arterial recanalization: Namely, the unactivated probe in the in vitro studies was not able to cross the calcific coronary arterial occlusions. Subsequent activation of ultrasound energy resulted in probe passage and the generation of a smooth circular arterial lumen conforming to the shape of the ultrasound probe tip. These findings are consistent with previous studies and support the mechanistic role of ultrasound energy for the improvement of the arterial lumen diameter in clinical cases undergoing coronary ultrasound angioplasty.

During adjunctive balloon angioplasty after ultrasound exposure, it was noted that the mean balloon pressures to achieve full inflation, ie, the yield pressure of the underlying lesion, were relatively low at 2.7 atm (range, 1 to 5.5). These findings are consistent with our initial clinical observations in treating peripheral arteries: Namely, that after ultrasound application, there was only a slight "waist" or deformation of the inflated balloon, suggesting that the resistance of the lesions to pressure had been decreased. We subsequently found in vitro that after 2 minutes of ultrasound exposure to calcific atherosclerotic arteries, the arterial distensibility increased. This finding could have two potential implications. First, the "nondilatable," balloon-resistant lesion may become amenable to balloon dilation after ultrasound ablation. Second, if the barotrauma of high balloon inflation pressures is responsible for acute complications or promotes restenosis, a mechanical device to reduce balloon inflation pressure could theoretically have a favorable impact on coronary balloon angioplasty results.

We have previously noted arterial vasodilation after exposure to catheter-delivered ultrasound. However, in this intracoronary study in which patients were premedicated with intracoronary nitroglycerin, there was only one case with direct evidence of ultrasound-induced vasodilation. One patient had spasm at a severe right coronary artery stenosis that persisted despite 700 μg of intracoronary nitroglycerin but was reversed after 30 seconds of intracoronary ultrasound exposure, a finding consistent with our prior experience in peripheral arteries as well as in vitro studies. It is conceivable that the increase seen in the mean arterial stenosis from 26% to 32% at 24 hours reflects the disappearance of ultrasound-induced vasodilatory effects. Alternatively,
these findings may simply reflect the inherent recoil that may occur after a balloon angioplasty procedure.16

A current limitation of the coronary ultrasound ablation device is that the size of the lumen generated is restricted by the probe tip size. Approaches to achieve larger lumen size include the use of larger probe tips as well as increasing the ultrasound power output to augment plaque ablation.

At present, there are a number of interventional devices being tested in the coronary circulation to improve the results of balloon angioplasty.17-20 Ultrasound appears particularly promising because, as we predicted from previous experiments and clinical experience in peripheral arteries,10 no adverse reaction to prolonged ultrasound exposure occurred; also, ultrasound is potentially useful by enhancing arterial distensibility and possibly modifying the atherosclerotic plaque itself. The clinical usefulness of another known property of ultrasound, ie, thrombus dissolution,3-5,12 remains to be determined by further experience in patients with acute coronary syndromes.

Acknowledgments

This study was supported in part by a Research Grant from Baxter HealthCare Corporation. The authors are grateful to Stuart Dubin, MD, PhD, for his technical assistance in the measurement of particle size.

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R J Siegel, J Gunn, A Ahsan, M C Fishbein, R J Bowes, D Oakley, C Wales, W Steffen, S Campbell and H Nita

Circulation. 1994;89:1587-1592
doi: 10.1161/01.CIR.89.4.1587

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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