A Randomized Comparison of the Effects of Gradual Prolonged Versus Standard Primary Balloon Inflation on Early and Late Outcome

Results of a Multicenter Clinical Trial

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Background Observational studies have suggested that prolonged balloon inflation during coronary angioplasty is associated with a high clinical success rate. This randomized clinical trial sought to evaluate the impact of primary gradual and prolonged inflations versus standard short dilations in patients undergoing elective angioplasty.

Methods and Results In phase 1 of the study, patients were randomized to receive two to four standard (1 minute) dilations or one or two prolonged (15 minutes) dilations after a perfusion balloon had been placed across a single target lesion. Patients with unsuccessful angiographic appearance after phase 1 dilations had further dilations in phase 2. Patients were followed for 6 to 12 months after the procedure. Of 478 patients, 242 received a median of one prolonged dilatation of 15 minutes' duration, and 236 received three dilations for a median of 1 minute. Patients assigned to prolonged dilations had a higher success rate (≤50% residual visual stenosis) (95% versus 89%; P = .016), less severe residual stenosis by quantitative angiography (median [25th and 75th percentiles], 55% [26%, 42%] versus 38% [30%, 46%]; P = .001), and a lower rate of major dissections (3% versus 9%; P = .003) at the end of phase 1. A total of 114 patients had further dilations in phase 2—43 in the prolonged arm and 71 in the standard arm. The final procedural success rate was 98% with both primary dilatation strategies, which included additional maneuvers such as prolonged dilatations in the patients randomized to the primary standard dilatation. Overall, 330 of 416 patients (79%) who were discharged after a successful procedure without any in-hospital event (death, myocardial infarction, coronary artery bypass graft surgery, abrupt closure, or repeat angioplasty in target vessel) returned for follow-up angiography. The restenosis rate (>50% residual visual stenosis) was 44% (95% confidence interval, 37% to 52%) in the prolonged dilatation group and 44% (36% to 52%) in the standard dilatation group. The primary angiographic end point of failure at the end of phase 1, abrupt closure, or restenosis throughout the study period was similar in both groups (prolonged, 51%; standard, 49%; P = .62). The secondary end point of absence of clinical events (death, nonfatal myocardial infarction, coronary artery bypass graft surgery, or repeat angioplasty in target vessel) also was similar (prolonged, 66%; standard, 74%; P = .15).

Conclusions Primary gradual and prolonged dilatations caused less arterial trauma with a modestly larger arterial lumen compared with standard dilatations. This initial improvement in angiographic appearance did not lead to a significant reduction in restenosis or clinical adverse events during follow-up. (Circulation. 1994;90:1118-1125.)

Key Words • angioplasty • perfusion • clinical trials • restenosis

The impact of the rate and duration of balloon inflation during coronary angioplasty has not previously been evaluated in a prospective, controlled clinical trial. Although observational studies have suggested that prolonged balloon inflation has a high procedural success rate and few in-hospital complications, reports of its effect on restenosis have been conflicting.1-3 Until the introduction of the perfusion balloon, the ability to perform prolonged balloon inflations was limited by the ischemia that developed during the occlusion.4,5 With a perfusion balloon, prolonged dilatations of 15 minutes’ duration have been performed without the development of either myocardial ischemia or necrosis.6 Therefore, the perfusion balloon has made it possible to examine the importance of different inflation strategies on procedural and long-term outcomes after angioplasty.

This randomized clinical trial was performed to test the hypothesis that a primary gradual prolonged balloon inflation of 15 minutes’ duration was associated with a higher procedural success rate, fewer in-hospital complications, and a lower restenosis rate during a 6-month follow-up period compared with two to four standard 1-minute inflations.
Methods

Patients undergoing elective coronary angioplasty at 13 hospitals between April 1989 and August 1991 were consid-
ered for entry in the study. The protocol was approved by the institu-
tional review board at each clinical site, and all patients signed informed consent before the angioplasty procedure.
The clinical sites, investigators, and coordinators are listed in the “Appendix.” The study was conceived, conducted, and
managed at the Duke Coordinating Center independent from
the sponsor of the trial. There was no direct relation among
the coordinating center, primary investigators, and the sponsor
of the trial.

Inclusion and Exclusion Criteria

Patients were considered for eligibility in the study if they
had stable or unstable angina with at least one lesion (>50% diameter stenosis) in a native vessel suitable for angioplasty.
Patients were excluded if they had an acute myocardial
infarction within the 24 hours preceding the scheduled pro-
dure or if repeat angiography at 6 months was not possible.
Patients could be enrolled only once in the study. Patients
were also excluded if they had angiographic characteristics
that would limit the satisfactory placement or performance of
a perfusion balloon catheter for a prolonged dilatation: lesion of
>15 mm; major side branch, defined as ≥2.0 mm in
diameter, within 10 mm of the center of the target lesion; distal
lesion (>70 mm from the coronary ostium); target lesion
within 20 mm of a sharp (>45°) angulation; ostial stenosis
≥50% diameter in the target vessel; target vessel ≤2 mm in
diameter; lesion in or distal to saphenous vein grafts or
internal mammary artery grafts; 50% stenosis proximal to
the target lesion; tandem lesion (≥50% stenosis within 15 mm
of the target lesion); or angulated lesion (>45°).

A screening log was kept during a 1-year period at the two
highest enrolling sites (Duke University and University of
Ottawa). During this period, 1687 patients were screened for
participation in the trial, and 162 (10%) were enrolled. Of the
excluded patients at the two sites, 76% were not suitable for
randomization because of the angiographic criteria (major side
branch, 18%; total occlusion or lesion length >15 mm, 14%
lesion too distal or target vessel <2.5 mm, 8%; lesion in bypass
grafts, 8%; tandem lesion, 6%; ostial lesion or too angulated
lesion, 6%; too tortuous, 4%; or multiple angiographic criteria,
12%). Clinical criteria excluded 15% of patients (prior enroll-
ment in another randomized trial, 8%; angioplasty for acute
myocardial infarction, 3%; previous enrollment in the trial,
2%; or refused consent, 2%). The remaining 9% of patients
were not randomized because of other technical reasons in 8%
and unable to cross after predilatation in 1%.

Definitions of Baseline Characteristics

The following definitions were used. Hypertension was
defined as a sustained diastolic blood pressure of >90 mm Hg
or documented physician diagnosis and treatment. Type I
diabetes was defined as insulin-dependent diabetes. Type II
diabetes was defined as insulin-resistant diabetes treated with
oral hypoglycemic agents. History of smoking was defined as
current cigarette smokers. Prior myocardial infarction was
defined as a history of hospitalization for treatment of myo-
cardial infarction. Prior cardiac surgery was defined as a
history of any coronary artery, including valvular and coronary
to-artery bypass graft surgery. Unstable angina was defined as
present in patients with rest pain or post-coronary infar-
ction chest pain within 7 days of infarction. Congestive cardiac
failure was defined when appropriate symptoms and signs of
heart failure were present.

Angioplasty Protocol and Procedure

All patients were pretreated with aspirin (325 mg/d) and
persantine (75 mg TID) for at least 24 hours before the proce-
dure. Heparin was administered at the beginning of each pro-
dure after arterial and venous access had been established.
Activated clotting time (ACT) was used to ensure adequate
heparinization with an ACT of >300 seconds before any balloon
inflation. Angioplasty was performed via the femoral approach
using 8F arterial sheaths and guide catheters.

A schematic outline of the basic study design is shown in Fig
1. A perfusion balloon catheter (PBC) was used in both arms
of the study to test the different inflation strategies. The Stack
Perfusion Balloon Catheter (Advanced Cardiovascular Sys-
tems) of appropriate size (balloon-to-artery ratio of 1.1 to 1.0)
was advanced across the lesion over a 0.018-in. exchangeable
guide wire. After placement of the perfusion balloon, patients
were randomized to either standard or prolonged dilatation in
the first phase (phase 1) of the study.

If it was not possible to place the perfusion balloon or if the
angioplasty operator believed that the lesion was too tight for
easy perfusion balloon placement, a brief (1 minute) predila-
tation using a 2.0-mm standard balloon was permitted. A
predilatation was performed in 69 of 547 patients (13%).
These patients were prespecified by the protocol to be ana-
lyzed separately because it was not possible to test the
hypothesis of a primary prolonged dilatation in this cohort.

Standard Dilatation

Patients assigned to standard dilatation received 2 to 4
dilations of 1 minute each. The perfusion balloon was
inflated over 20 seconds to a maximum of 6 atm. Heparin (5000
U) was administered during the first standard dilatation through
the central lumen of the PBC.

Prolonged Dilatation

Patients assigned to prolonged dilatations had 1 or 2 pro-
longed dilatations of 15 minutes each. The inflation was
performed gradually by increasing the atmospheric pressure by 1 unit every 30 seconds until maximally inflated at 6 atm. Heparin was administered through the central lumen every 3 minutes at a dose of 1000 U (500 U/mL) for a total of 5000 U during the initial prolonged inflation. During second or subsequent prolonged dilatations, the heparin dose was reduced to 500 U every 3 minutes.

All patients had repeat coronary angiographic injections at the end of phase 1. Successfully treated patients (≤50% stenosis) had no further dilatations and received routine postangioplasty management. Patients with a >50% diameter residual stenosis or lesions complicated by a major dissection, as determined by the angioplasty operator performing the procedure, went on to phase 2 for further dilatations.

Management in Phase 2

Further dilatations in phase 2 were performed at the discretion of the angioplasty operator. Progressive occlusive dissections were treated by prolonged dilatations of 20 to 30 minutes. Other persistent lesions were treated in the manner deemed most suitable by the angioplasty operator. Use of intracoronary stents was discouraged during the study, although they could be inserted during phase 2 at the discretion of the angioplasty operator. Repeat angiographic injections were performed at the end of phase 2.

Coronary Angiography and Assessment

Coronary angiography was performed in near 90° orthogonal views before perfusion balloon angioplasty, at the end of phase 1, and at the end of the procedure in all patients. Intracoronary nitroglycerin (0.1 to 0.3 mg) was given before each set of injections. Repeat coronary angiography was performed by protocol at 6 months or for recurrent ischemia or abrupt closure either in-hospital or during the 6-month follow-up period. Angiographic injections were performed replicating the orthogonal views used during the initial procedure.

Cineangiograms were read in the core angiographic laboratory by two angioplasty operators blinded to the treatment assignment. Coronary luminal diameter narrowing was graded visually by an ordinal scale (0%, <25%, 25%, 50%, 75%, 95%, or 100%) as previously described.7 Lesion morphology was classified according to the American College of Cardiology/American Heart Association (ACC/AHA) classification,8 and coronary flow was graded by the Thrombolysis in Myocardial Infarction (TIMI) classification.9 Morphological classification assessed at the end of phase 1 and at the end of the procedure included the presence or absence of major or minor dissections as previously described.10 Major dissection was defined as a luminal or extraluminal linear or spiral tear of the arterial wall characterized by marked extraluminal contrast accumulation and with delayed washout of contrast.

Quantitative Coronary Angiography

All cineangiograms were attempted for analysis by an automated edge-detection digital angiographic system (ARTREK version 10 software, ADAC Laboratories).11 Percent diameter stenosis before the procedure, at the end of phase 1, at the end of the procedure, and during the follow-up was calculated as the mean value from two orthogonal views. It was possible to obtain good-quality digital images in 97% (462 of 478) of patients before angioplasty, in 95% (455 of 478) at the end of phase 1, and in 96% (472 of 478) at the end of the procedure. Digital images were obtained in 96% (306 of 320) of patients returning for follow-up angiography.

Clinical Follow-up

All patients received standard management after successful angioplasty. Intravenous heparin was used at the discretion of the investigator. The median (25th and 75th percentiles) duration of heparin use was similar in the two treatment arms (standard, 17 [12, 19] hours; prolonged, 16 [12, 19] hours). A standard 12-lead ECG was obtained 24 hours after the procedure. Serial measurements of serum creatine kinase (CK) and CK-MB were performed twice during the first 24 hours.

The following complications were noted: death from any cause, nonfatal myocardial infarction, coronary artery bypass graft surgery (emergency or elective), abrupt closure in the target vessel, repeat angioplasty in the target vessel, and recurrent ischemia. The definition for myocardial infarction was any two of the following: chest pain lasting >30 minutes, new Q waves or ST elevation (>1 mV) in at least two contiguous leads on the ECG, or a more than twofold increase in CK-MB above baseline to an abnormal level. The definition of emergency coronary artery bypass graft surgery included all patients sent to such surgery the same day as their perfusion balloon angioplasty. The definition for recurrent ischemia was chest pain of <20 minutes associated with new ECG changes. The definition of abrupt closure was angiographic documentation of TIMI grade 0 or 1 flow. During follow-up, all patients received aspirin (325 mg/d) and concomitant medical therapy as clinically indicated.

All patients who survived to hospital discharge were followed for at least 6 months and as long as 1 year after discharge. Repeat coronary angiography was performed at 6 months after hospital discharge in 320 of 416 patients who had a successful procedure (success phase 1 or 2) and no in-hospital complications (death, myocardial infarction, coronary artery bypass graft surgery, or repeat angioplasty). The reason for lack of angiographic follow-up in 96 patients was patient refusal in 73 patients, medical contraindication in 9, lost to follow-up in 6, and other technical reasons in 8. Six-month follow-up also included clinical assessment of functional status (Canadian cardiovascular grade for angina), interim complications (death, nonfatal myocardial infarction, unstable angina, coronary artery bypass graft surgery, or repeat angioplasty), and exercise ECG. Patients with failed angioplasty or coronary artery bypass graft surgery had clinical follow-up within 1 year of randomization.

Statistical Analysis

The randomization was stratified only by clinical site. Permeated block randomization was used to maintain chronological balance in the number of patients allocated to each treatment arm. Patients were randomized after the PBC was placed across the lesion but before starting the inflation.

Continuous variables are summarized using the median and the 25th and 75th percentiles. All primary treatment comparisons were performed according to the “intention-to-treat” principle.

The primary end point was the presence of >50% visual stenosis at the target lesion either at the end of phase 1, during hospitalization, or during follow-up (up to 1 year) as determined by the angiographic core laboratory. Visual assessment of the stenosis was used because it was available in all patients undergoing angiography, whereas quantitative angiography was not, as previously described. The occurrence of >50% lesion in the target vessel at any one of these points was counted as a failure, whereas the absence of >50% lesion at all time points was considered a success. Only patients (n = 371) who had in-hospital or follow-up repeat angiography during the study period were included in this analysis. The primary end point was analyzed by logistic regression techniques. Treatment comparisons were performed unadjusted and also adjusted for baseline disease factors known to priori to influence angiographic failure. These factors included unstable angina, hypertension, diabetes mellitus, lesion location, or lesion morphology (type A, B, or C) according to the ACC/AHA classification.5

The secondary end point, defined as clinical failure, was a rank-ordered composite end point that was hierarchical and in
which patients were counted with the worst outcome that they experienced. Listed in order of severity, the outcome categories consisted of death, nonfatal myocardial infarction, coronary artery bypass graft surgery, repeat angioplasty in the target vessel, and no clinical event. Ordinal logistic regression techniques were used to assess the treatment differences both unadjusted as well as adjusted for selected baseline characteristics. Six patients lost to follow-up were excluded from this analysis.

Other prespecified secondary comparisons of treatment strategy were performed using specific components of the end points above, including failure at the end of phase 1, major dissection at the end of phase 1, residual percent diameter stenosis at the end of phase 1 adjusted for preprocedure percent stenosis, angiographic failure through hospital discharge (failure at the end of phase 1, abrupt closure, repeat angioplasty of target vessel, coronary artery bypass graft surgery, or death), and restenosis rate (defined as >50% visual stenosis of target lesion after initially successful \([\leq 50\% \text{ stenosis}]\) procedure). The above analyses were performed using logistic regression techniques, with the exception of percent diameter stenosis, which was determined by generalized linear modeling techniques. Analyses were performed using the SAS statistical software.

The trial was designed to provide adequate statistical power to detect a 35% reduction in the primary end point (>50% angiographic stenosis as defined above) in the patients without any predilatation, assuming that this end point would occur in approximately 40% of patients enrolled in the standard dilatation arm. Assuming that only 85% of eligible patients would actually return for their follow-up angiographic study, 438 patients (219 in each arm) were required to achieve 80% power based on \(\alpha=0.05\). The enrollment was further increased to 478 patients to also provide 80% power for detecting the anticipated reduction from 8% to 2% in the secondary end point of angiographically determined failure at the end of phase 1.

Results

A total of 478 patients had a primary dilatation using the perfusion balloon to test the two dilatation strategies as outlined in the hypothesis. Two hundred forty-two patients were randomized to receive the prolonged dilatation, and 236 were randomized to receive the standard dilatation.

Baseline clinical and angiographic characteristics in the two groups were generally similar, as shown in Table 1. However, the target artery was more frequently the right coronary artery in patients randomized to prolonged dilatation (48% versus 39%). Conversely, more patients with the left anterior descending coronary artery as a target were treated in the standard arm (44% versus 36%). The majority of lesions being treated in the study were type B lesions (63%), and a restenotic lesion was the target in 78 patients (16%).

The procedure information is shown in Table 2. The compliance to the phase 1 dilatations in the standard arm was 100%. For patients assigned to the prolonged dilatation, 92% had at least one dilatation lasting >10 minutes during phase 1. The reason for inability to perform the assigned prolonged dilatation in 19 patients was ischemia in the coronary distribution of balloon inflation in 15 patients and other technical reasons in 4 patients. The average longest dilatation during phase 1 in the 19 patients was 5.2 minutes. The median visual stenosis at the end of phase 1 in patients with prolonged

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Standard (n=236)</th>
<th>Prolonged (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>56 (49, 65)</td>
<td>57 (49, 65)</td>
</tr>
<tr>
<td>Age &gt;75 y</td>
<td>7 (3%)</td>
<td>9 (4%)</td>
</tr>
<tr>
<td>Male, n</td>
<td>181 (77%)</td>
<td>179 (74%)</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>95 (40%)</td>
<td>89 (37%)</td>
</tr>
<tr>
<td>Type I diabetes, n</td>
<td>2 (1%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Type II diabetes, n</td>
<td>28 (12%)</td>
<td>26 (11%)</td>
</tr>
<tr>
<td>History of smoking, n</td>
<td>182 (77%)</td>
<td>182 (76%)</td>
</tr>
<tr>
<td>Prior myocardial infarction, n</td>
<td>108 (46%)</td>
<td>124 (51%)</td>
</tr>
<tr>
<td>Prior cardiac surgery, n</td>
<td>4 (2%)</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Unstable angina, n</td>
<td>131 (57%)</td>
<td>142 (60%)</td>
</tr>
<tr>
<td>Congestive heart failure, n</td>
<td>7 (3%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>No. of diseased vessels (≥75% diameter stenosis)†</td>
<td>148 (63%)</td>
<td>155 (64%)</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>75 (30%)</td>
<td>76 (31%)</td>
</tr>
<tr>
<td>Left anterior descending coronary artery</td>
<td>168 (71%)</td>
<td>163 (67%)</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>103 (44%)</td>
<td>88 (36%)</td>
</tr>
<tr>
<td>Visual percent diameter stenosis, %‡</td>
<td>41 (17%)</td>
<td>38 (16%)</td>
</tr>
<tr>
<td>TIMI grade flow†</td>
<td>0 (0%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>1 (1%)</td>
<td>2 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>2 (5%)</td>
<td>11 (5%)</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>3 (94%)</td>
<td>221 (94%)</td>
<td>226 (94%)</td>
</tr>
<tr>
<td>Lesion type‡</td>
<td>A (32%)</td>
<td>90 (38%)</td>
</tr>
<tr>
<td>B (67%)</td>
<td>153 (67%)</td>
<td>140 (60%)</td>
</tr>
<tr>
<td>C (1%)</td>
<td>1 (1%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Restenosis lesion</td>
<td>47 (21%)</td>
<td>31 (13%)</td>
</tr>
</tbody>
</table>

TIMI indicates Thrombolysis in Myocardial Infarction trial. *Values are given as medians (25th and 75th percentiles). †As determined visually by the core angiographic laboratory. §American College of Cardiology/American Heart Association classification. See "Methods" for definitions.

primary dilatation was 25% (<25%, 25%) and with standard dilatation was 25% (<25%, 50%). Patients assigned to prolonged dilatation had a higher success rate (visual stenosis of ≥50%) at the end of phase 1 (95%) compared with patients assigned to
standard dilatations (89%) (P<.016). The primary prolonged dilatation gave rise to fewer major dissections at the end of phase 1 (3%) compared with standard dilatations (9%; P<.003).

A total of 114 patients required further dilatations in phase 2, 71 patients in the standard dilatation arm, and 43 in the prolonged arm (Table 2). The balloon size increased in both groups during phase 2. The median dilatation time was longer in the second phase in patients assigned to primary standard dilatations, whereas the inflation pressure increased in patients assigned to primary prolonged dilatations. The success rate of the 114 patients treated in phase 2 was 96% for those in the standard dilatation arm and 91% for those in the prolonged dilatation arm. The final procedural success rate (including phase 1 and phase 2) was 98% with both primary dilatation strategies. The rate of major dissections was also similar in both groups at the end of the procedure (standard dilatation arm, 6%; prolonged dilatation arm, 4%).

Complications occurring during both phases of the procedure and during hospitalization were rare and are shown in Table 3. In hospital, 9 patients (4%) randomized to standard dilatation had either abrupt closure, myocardial infarction, repeat angioplasty of the target vessel, or coronary artery bypass graft surgery compared with 13 patients (5%) assigned to prolonged dilatation. The angiographic failures (defined as either failure at the end of phase 1, abrupt closure, repeat angioplasty of target vessel, or coronary artery bypass graft surgery) in the prolonged dilatation arm was 9% compared with 13% in the standard arm (P=.15) during the hospitalization.

The median time from angioplasty to follow-up angiogram was 6.2 (5.6, 7.3) months in both groups. The clinical outcomes during the follow-up period were similar in both groups and are shown in Table 3. Overall, 320 of 416 patients (77%) discharged after a successful procedure in the absence of any in-hospital event returned for follow-up angiography. The restenosis rate (visual diameter stenosis of >50%) was 44% (64 of 145; 95% confidence interval, 36% to 52%) in the standard dilatation group and 44% (77 of 174; 95% confidence interval, 37% to 52%) in the prolonged dilatation group (P=.88). The restenosis rate with either primary dilatation strategy was similar in patients who were enrolled with a restenotic lesion.

Table 2. Procedural Information for Phase 1 and Phase 2

<table>
<thead>
<tr>
<th></th>
<th>Standard (n=236)</th>
<th>Prolonged (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum balloon size, mm</td>
<td>3 (3, 3.5)</td>
<td>3 (3, 3.5)</td>
</tr>
<tr>
<td>No. of dilatations</td>
<td>3 (2, 4)</td>
<td>1 (1, 2)</td>
</tr>
<tr>
<td>Dilation time, min</td>
<td>1 (1, 1)</td>
<td>15 (15, 15.1)</td>
</tr>
<tr>
<td>Maximum atmospheric pressure</td>
<td>6 (6, 8)</td>
<td>6 (6, 6)</td>
</tr>
</tbody>
</table>

Values are given as medians (25th and 75th percentiles).

Table 3. Clinical Outcomes for Both Patient Groups

<table>
<thead>
<tr>
<th></th>
<th>Standard (n=236)</th>
<th>Prolonged (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural events (phases 1 and 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient occlusion</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>VT or VF arrest</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stent</td>
<td>2 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Emergency CABG</td>
<td>3 (1%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Patients with any procedural event*</td>
<td>4 (2%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>In-hospital events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent ischemia</td>
<td>3 (1%)</td>
<td>13 (5%)</td>
</tr>
<tr>
<td>Acute reclosure of target lesion</td>
<td>3 (1%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4 (2%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Repeat PTCA of target vessel</td>
<td>3 (1%)</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>CABG</td>
<td>4 (2%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patients with any in-hospital event*</td>
<td>9 (4%)</td>
<td>13 (5%)</td>
</tr>
<tr>
<td>Postdischarge events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>3 (1%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>CABG</td>
<td>13 (6%)</td>
<td>13 (6%)</td>
</tr>
<tr>
<td>Repeat PTCA of target vessel</td>
<td>39 (17%)</td>
<td>53 (22%)</td>
</tr>
<tr>
<td>Patients with any postdischarge event*</td>
<td>47 (20%)</td>
<td>62 (26%)</td>
</tr>
</tbody>
</table>

VT indicates ventricular tachycardia; VF, ventricular fibrillation; CABG, coronary artery bypass graft surgery; and PTCA, percutaneous transluminal coronary angioplasty.

*Number of patients with at least one event.
Each patient may have multiple events.

Fig 2. Cumulative distribution curves of pretreatment and post-phase 1 diameter stenoses of target lesion as measured by quantitative coronary angiography in patients randomized to gradual, prolonged dilatation or standard dilatation. Pretreatment and post-phase 1 digital images were available in 462 and 455 patients, respectively. The percent diameter stenosis at the end of phase 1 was less severe (P=.001) in patients with primary prolonged dilatations compared with standard dilatations when adjusting for pretreatment diameter stenosis.
The percent diameter stenosis as determined by quantitative coronary angiography is shown in Figs 2 and 3. The median diameter stenosis before randomization was similar in both groups (prolonged, 68% [61%, 76%]; standard, 70% [62%, 76%]). At the end of phase 1, the percent diameter stenosis was less severe in patients assigned to prolonged dilatations (35% [26%, 42%]) compared with patients assigned to standard dilatations (38% [30%, 46%], P=.001) when adjusted for preangioplasty stenosis. The final percent diameter stenosis was similar in both primary dilatation strategies (prolonged, 32% [25%, 39%]; standard, 35% [27%, 43%]; P=.23). The follow-up diameter stenosis was also similar in both groups (prolonged, 49% [35%, 67%]; standard, 47% [33%, 65%]).

The primary end point of angiographic failure at the end of phase 1, abrupt closure, or angiographic restenosis throughout the study period was similar in both groups (standard, 49%; prolonged, 51%; P=62). Adjusting the primary end point by accounting for baseline characteristics, lesion location, and lesion type did not affect the outcome (χ², .1, P=.75). The secondary end point of absence of clinical events (death, nonfatal myocardial infarction, coronary artery bypass graft surgery, or repeat angioplasty of target vessel) throughout the study period was similar in both groups (standard, 74%; prolonged, 66%; P=.15).

Discussion

This randomized trial comparing two primary dilatation strategies using a perfusion balloon found no difference in the overall angiographic outcomes or clinical events within 1 year of the initial procedure. Although the gradual prolonged dilatation strategy was associated with a better angiographic appearance during the first phase compared with the use of standard dilatations, the use of prolonged dilatations in the second phase of the procedure achieved a similar high procedural success rate (98%) in both groups. With an equally high procedural success rate, it is not surprising that the clinical event rates during the follow-up period were also similar in both dilatation strategies.

The use of a prolonged balloon inflation was associated with fewer major dissections during the initial phase of the procedure, a finding that supports an association between prolonged dilatations and less arterial trauma. Furthermore, prolonged dilatations have been used successfully to treat major dissections to achieve stable angiographic appearances after standard angioplasty. The use of longer dilatation times in the second phase of the procedure allowed the success rate to increase from 89% to 98% in patients assigned to an initial standard dilatation strategy.

A primary gradual prolonged dilatation led to a modest reduction in the residual percent diameter stenosis. This finding was supported by congruent observations by visual assessment and by quantitative angiography. The difference of 3% diameter stenosis between the two dilatation strategies is small but similar to the difference of 7% diameter stenosis observed in the randomized trial of atherectomy versus standard balloon angioplasty (CAVEAT). These modest differences in residual stenosis are not associated with any prolonged clinical benefit as documented in the present study and in the CAVEAT experience.

The restenosis rate in this study with prolonged dilatation (44%) was similar to those rates observed with standard balloon angioplasty16-18 and with previous perfusion balloon angioplasty experience. Recent observations by Kuntz and colleagues19 have suggested that the residual luminal narrowing after percutaneous intervention is the major predictor of restenosis during follow-up. The modest differences between standard and prolonged dilatations at the end of the procedure observed in the present study suggest that this is not sufficient to reduce restenosis rates (see Fig 3). Furthermore, the absence of a major dissection at the end of the procedure has previously been suggested to be associated with a higher rate of restenosis.20 The small difference in the rate of major dissections (6% versus 4%) at the end of procedure was not sufficient in the present study to alter the rate of restenosis in the two treatment arms.

There are several limitations to the present study. It must be emphasized that the study attempted to evaluate inflation strategies and not the device per se. The perfusion balloon was used in both arms of the study, and therefore this trial cannot be used to judge results that would have occurred if the perfusion balloon could not be easily placed. Newer perfusion balloons with lower crossing profiles have become available since the completion of the study, which could allow for perfusion balloon angioplasty to be performed in more complex coronary anatomy. Because the same catheter with the same balloon material was used in both arms of the study, no comparison can be made with other materials and their effect on the incidence of major dissection and procedural success rate. 19, 21 Although many of the patients enrolled in the present study were young with predominantly one-vessel coronary artery disease and normal left ventricular function, the majority also had some high-risk features known to be harbingers of a high clinical and procedural adverse event rate after standard angioplasty, including unstable angina or more
complex target lesion morphology (type B AHA/ACC classification).10,22
In conclusion, the present randomized trial of inflation strategies using a perfusion balloon has shown a high procedural success rate and few clinical adverse events irrespective of the initial inflation strategy used. The primary prolonged dilatation caused less arterial trauma with less major dissections and a moderately larger arterial luminal narrowing during the early phase of the procedure compared with a standard dilatation strategy. The initial standard dilatation strategy was enhanced with longer dilatations during the second phase of the procedure. The initial improvement in arterial appearance after prolonged dilatations did not lead to a significant reduction in clinical adverse events or restenosis during follow-up. The use of prolonged inflations during balloon angioplasty either primarily or as dissection repair may be sufficient to achieve high procedural success rates with an acceptable incidence of adverse clinical events and restenosis.

Acknowledgment

This work was supported by a grant from Advanced Cardiovascular Systems, Santa Clara, Calif.

Appendix

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Circulation. 1994;89:1118-1125
doi: 10.1161/01.CIR.89.3.1118

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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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