Morphologic changes in the pulmonary arteries after percutaneous balloon angioplasty for pulmonary arterial stenosis

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ABSTRACT The pathologic appearance of pulmonary arteries subjected to balloon dilation was studied in four subjects with stenosis of pulmonary arteries. Nine vessels were dilated. Successful dilation in seven vessels was accompanied by intimal disruption and tearing of the media. In one vessel, at the site of a previous surgical procedure, dilation could not be accomplished. Histologically, this vessel was encased by reactive fibrous tissue, which may have precluded successful dilation. In one case, simultaneous rupture of the dilating balloon and the left pulmonary artery occurred. Morphologic examination could not adequately explain the cause of vessel rupture. Among the six vessels successfully dilated and studied 4 to 14 months after the dilation, the postdilation luminal diameter had been maintained. Tears in the intima and media as seen histologically had been filled in by scar tissue. In one artery a dilated segment distal to a residual obstruction revealed marked intimal proliferation. Circulation 71, No. 2, 195–201, 1985.

THE MORPHOLOGIC changes in human vessels after balloon angioplasty are not well defined. Dotter and Judkins' described the first transluminal angioplasty procedure in 1964. Later, percutaneous transluminal balloon angioplasty was introduced. The new technique was used initially to treat obstructive arterial disease derived from atherosclerosis and has since been applied to treat many causes of vascular obstruction of various types and in many vessels of the body.

Although balloon dilation of stenotic pulmonary arteries is being increasingly used clinically, we are unaware of any published reports dealing with pathologic findings after this procedure in patients with pulmonary arterial stenosis.

The purpose of this report is to define the gross and histologic sequelae of transluminal balloon angioplasty performed in nine pulmonary arterial branches among four children in whom death occurred from various causes.

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CLINICAL INVESTIGATION

Materials and methods

The four patients were part of a group of 25 children at the University of Minnesota who underwent balloon dilation angioplasty for hypoplastic or stenotic pulmonary arteries.

Protocol for dilation angioplasty. Before recommendation of balloon angioplasty of a pulmonary artery, the criteria described by Lock et al.² were followed. The diameter of the hypoplastic or stenotic pulmonary artery was measured directly from biplane cineangiograms. A polyethylene balloon catheter with an inflatable diameter three to four times that of the narrowed segment was introduced into the affected pulmonary arterial segment and inflated to 1 atmosphere of pressure. The catheter was manipulated until the stenotic segment indented the balloon. The balloon was then inflated to a pressure of 7 to 8 atmospheres and maintained for 30 sec.

Assessment of effects of dilation angioplasty. The anatomic and hemodynamic effects of balloon angioplasty were assessed by one or more of the following: (1) direct measurement of the diameter of the narrowed segment angiographically before and after dilation, (2) assessment of the gradient across the stenotic segment or segments before and after balloon dilation, and (3) lung scan assessment of blood flow to the lung served by the dilated vessel or vessels before and after balloon dilation.

Case summaries

Patient 1. In this female patient, cyanosis was apparent in infancy. Cardiac catheterization revealed hypoplasia of the right and left pulmonary arteries with systemic pressures in the right ventricle. The intracardiac structures appeared normal. At 32 months of age the patient underwent successful balloon angioplasty dilation of the right pulmonary artery (table 1). At 35 months of age, dilation of the left pulmonary artery was performed in which a 12 mm dilating balloon was inflated to 9 atmospheres in the left lower pulmonary artery. Simultaneous rupture of the balloon and the left lower pulmonary artery occurred. The child exsanguinated and died despite massive transfusions and an emergency thoracotomy.
TABLE 1
Clinical results of balloon dilation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at dilation</th>
<th>Pulmonary artery dilated</th>
<th>Interval between dilation and death</th>
<th>Balloon size (mm)</th>
<th>Diameter of dilated vessel by angio (mm)</th>
<th>Systolic gradient across dilated vessel (mm Hg)</th>
<th>Result</th>
<th>Anatomic diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32 mo</td>
<td>Right</td>
<td>3 mo</td>
<td>10</td>
<td>2.9</td>
<td>65</td>
<td>20</td>
<td>Successful dilation</td>
</tr>
<tr>
<td></td>
<td>35 mo</td>
<td>Left</td>
<td>2 hr</td>
<td>12</td>
<td>4.0</td>
<td>—</td>
<td>—</td>
<td>Ruptured during dilation; patient died</td>
</tr>
<tr>
<td>2</td>
<td>28 mo</td>
<td>Left</td>
<td>3 days</td>
<td>12</td>
<td>4.0</td>
<td>75</td>
<td>35</td>
<td>Successful dilation</td>
</tr>
<tr>
<td>3</td>
<td>7 yr, 4 mo</td>
<td>Left</td>
<td>14 mo</td>
<td>8</td>
<td>2.7</td>
<td>75</td>
<td>35</td>
<td>Successful dilation</td>
</tr>
<tr>
<td></td>
<td>7 yr, 4 mo</td>
<td>Left lower</td>
<td>14 mo</td>
<td>8</td>
<td>2.5</td>
<td>75</td>
<td>35</td>
<td>Successful dilation</td>
</tr>
<tr>
<td></td>
<td>7 yr, 6 mo</td>
<td>Intermediate branch, right</td>
<td>12 mo</td>
<td>7</td>
<td>2.2</td>
<td>25</td>
<td>5</td>
<td>Successful dilation</td>
</tr>
<tr>
<td>4</td>
<td>6 mo</td>
<td>Right, proximal</td>
<td>12 mo</td>
<td>10</td>
<td>2.0</td>
<td>25</td>
<td>10</td>
<td>Successful dilation</td>
</tr>
<tr>
<td>5</td>
<td>6 mo</td>
<td>Left</td>
<td>9 mo</td>
<td>8</td>
<td>3.4</td>
<td>25</td>
<td>10</td>
<td>Successful dilation</td>
</tr>
</tbody>
</table>

*Intraoperative dilation.

Gross autopsy findings included right ventricular hypertrophy and left hemithorax. The pulmonary arterial branches displayed generalized hypoplasia. The intimal surface of the successfully dilated right pulmonary artery was rough and gray. There was a healed linear fissure that extended obliquely along the length of the right pulmonary artery. Several strands of tissue crossed this fissure (figure 1). The wall of the left pulmonary artery was thin throughout its length, and there was a fresh transmural tear in the posterior wall of the left lower pulmonary artery 1 cm distal to its origin from the parent artery.

Microscopic sections of a nondilated segment of a pulmonary artery displayed an irregular intimal thickening composed of collagen and elastic fibers. The media was remarkable for its thickness and paucity of elastic fibers and had a muscular rather than an elastic configuration.

A segment of the right pulmonary artery (figure 2) that had been successfully dilated 4 months earlier displayed an irregular intima, thick in some parts and very thin in others. The thick segments of intima were composed of collagen and elastic tissue. The media was interrupted at one of the vessel, and the defect was filled in by a scar of collagen and elastic fibers. The adventitia was abnormally thick and fibrotic. The transluminal strand illustrated in figure 1 contained parallel elastic fibers and was interpreted as representing a fragment of intima and media that had previously been split by the angioplasty.

Histologic examination of the left pulmonary artery in the region of the recent balloon angioplasty demonstrated several tears in the intima and a transmural rupture. There was extensive adventitial hemorrhage.

**Patient 2.** A diagnosis of tetralogy of Fallot with pulmonary valvular atresia was made when this female patient was 5 days old. A Gore-tex shunt (4 mm) was placed between the ascending aorta and the main pulmonary artery. Hemodynamic studies repeated when the patient was 28 months old revealed the Gore-tex shunt to be open. Severe stenoses of the right ventricular infundibulum, pulmonary valve, and left pulmonary artery were also shown. At operation it was believed that the channel of the left pulmonary artery could not be satisfactorily widened by placement of a patch. Therefore intraoperative balloon dilation was performed (table 1) with a 12 mm balloon inflated to 7 atmospheres for 30 sec. The tetralogy of Fallot was then totally repaired and the Gore-tex shunt was closed. The patient left the operating room in satisfactory condition and was extubated on the first postoperative day. On the third postoperative day a severe bradycardia occurred and progressed to cardiac arrest; resuscitation was unsuccessful.

At autopsy the heart displayed the tetralogy of Fallot, for which total correction had been performed 3 days before death. Additionally, a nonobstructive hourglass type of partial cor triatriatum was present. A surgically placed pericardial patch...
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FIGURE 1. Patient 1. The heart viewed from the front. The main, right, and left pulmonary arteries have been opened. The right pulmonary artery (RPA) was successfully dilated 4 months earlier. There is a long linear split in the posterior wall of the right pulmonary artery (black arrows) extending from the origin of the vessel to its bifurcation. Two strands of tissue bridge the split and represent remnants of torn intima and media. The dilated distal right pulmonary artery wall is very thin (white arrows). MPA = main pulmonary artery.

Patient 3. This male infant was cyanotic at birth. At 8 months of age, tetralogy of Fallot and stenoses of the pulmonary arterial branches were diagnosed. A left Blalock-Taussig shunt was performed, and the child’s condition improved. At 3½ years of age, cardiac catheterization revealed multiple stenoses of the right and left pulmonary arteries. For this reason the child was not deemed a candidate for total correction of the tetralogy of Fallot, and a palliative Gore-tex (5 mm) graft was placed between the aorta and the main pulmonary artery.

When the patient was 7 years 4 months old, percutaneous

FIGURE 2. Patient 1. Photomicrograph of cross section of the right pulmonary artery at the site of the bridging tag of tissue illustrated in figure 1. Successful balloon dilation had occurred 4 months previously. The tissue tag extends into the lumen and is composed of torn intima and media. The media to the left is relatively normal, and that to the lower right is thinned. The media at the level of the tissue tag is disrupted and filled in with scar tissue. (Elastic tissue stain; original magnification ×30.)

widened the right ventricular outflow tract. The right and left pulmonary arteries were hypoplastic.

Histologic examination of the nondilated right pulmonary artery showed the structure of the wall to be normal. The left pulmonary artery, which had been successfully dilated by intraoperative balloon angioplasty 3 days before death, displayed medial thinning and tearing of medial elastic tissue, as well as transmedial rupture (figure 3). Although blood extended into the media, between media and adventitia, and into the adventitia, no extravascular hemorrhage had taken place.

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FIGURE 3. Patient 2. a, Cross section of the proximal left pulmonary artery 3 days after successful intraoperative dilation. The intima and media at left have split. The outer half of the media at bottom has pulled away. Blood has dissected into the media, between the media and adventitia and into the adventitia. b, Cross section of the distal left pulmonary artery. The media at left has split and elements of this layer have retracted. There is hemorrhagic dissection into and through the media at top and gross hemorrhage into the adventitia. (a and b, elastic tissue stain; original magnification ×25).

balloon dilation was successfully performed on the proximal segment of the left pulmonary artery and on the left lower pulmonary artery (table 1). In addition, balloon pulmonary valvuloplasty was performed. Two months later the intermediate branch of the right pulmonary artery was successfully dilated. The proximal segment of the right pulmonary artery could not be dilated, although an appropriately sized balloon was placed in that segment and expanded with a pressure of 11 atmospheres. Obstruction in the proximal segment of the right pulmonary artery persisted. One year later a patch graft was placed in the right pulmonary artery, and the Blalock-Taussig shunt was closed. The patient died on the first postoperative day.

Autopsy confirmed the clinical diagnosis of tetralogy of Fallot with central pulmonary arterial dysplasia and hypoplasia. The pulmonary valve was grossly disrupted by the previous balloon valvuloplasty. Fragments of the valvular cusps were attached to the commissures.

The left main pulmonary artery, which had been successfully dilated 14 months previously, contained a strand of tissue crossing the lumen. The intima was rough (figure 4). We consider this strand to represent a piece of arterial wall that had separated when the balloon dilation was done 14 months earlier. On microscopic examination the left lower pulmonary artery had areas of thinned media alternating with near-normal media. The intima was hypertrophied. The thickened adventitia was composed of dense collagen.

A nondilated, hypoplastic segment of the left pulmonary artery showed a moderately thickened intima composed mainly of smooth muscle fibers and normal-appearing media and adventitia.

The intermediate branch of the right pulmonary artery had been successfully dilated 12 months previously. Histologic examination of this vessel showed absence of normal media in about 25% of the circumference of the vessel. The medial defect had healed with deposits of dense collagenous tissue (figure 5, a). There was prominent intimal proliferation composed of both collagen and elastic fibers. The thickened adventitia was composed mainly of collagen.

Unsuccessful dilation of the proximal segment of the right pulmonary artery at the level of the Blalock-Taussig anastomosis had been attempted 12 months earlier. Histologically, the intima of this segment was grossly irregular, suggesting earlier fragmentation. The media was intact. There was dense scarring of the adventitia and periadventitia (figure 5, b).

Patient 4. This male infant was evaluated at 3 weeks of age for cyanosis. With the aid of cardiac catheterization, diagnoses of tetralogy of Fallot and complete atrioventricular canal were made. A Gore-tex (3.7 mm) central shunt was placed between the aorta and the main pulmonary artery. At 6 months of age, cardiac catheterization revealed a functioning central shunt. The right and left pulmonary arteries were found to be narrow at their origins from the main pulmonary artery (table 1). For this condition, balloon dilation of the origins of the right and left pulmonary arteries was accomplished intraoperatively. Comparison of angiograms obtained before and after balloon dilation indicated that the diameter of the narrowed segment of each pulmonary artery was doubled. A pulmonary valvotomy was also performed at this operation. The child did poorly after surgery, and evidence of pulmonary edema persisted.

At 10 months of age, cardiac catheterization revealed cor triatriatum. At operation, tissue thought to be the membrane of a
cor triatriatum was resected, but pulmonary venous obstruction persisted. Therefore, 1 month later the patient underwent reoperation and additional tissue was resected. The child’s condition did not improve and he died at 15 months of age.

Autopsy findings confirmed the presence of a persistent common atrioventricular canal with a functional single atrium. The right ventricular infundibulum was stenotic. The pulmonary valve was bicuspid and dysplastic. The aortico pulmonary shunt was patent.

The diameter of the origin of the right pulmonary artery was 6 mm (6.6 mm on postdilation angiography). The diameter of the origin of the left pulmonary artery was 5 mm (5.7 mm on postdilation angiography). The intimas of the right and left pulmonary arteries at their origins were roughened. Microscopically, both arteries had areas of prior medial rupture that had healed by the formation of collagen and scattered elastic fibers. Additionally, stenosis involved the left lower pulmonary vein and the right lower pulmonary vein at their junctions with the left atrium.

Results

Clinical assessment of balloon dilation. Balloon dilation angioplasty of the left lower pulmonary artery in patient 1 was unsuccessful, since the artery ruptured during dilation. Balloon dilation angioplasty of the proximal right pulmonary artery in patient 3 was not successful.

Angiographic measurement of the stenotic segments before and after dilation showed significant increase in the diameter of each of the other seven dilated pulmonary arteries (table 1). Systolic pressure gradients across the dilated site were measured in five of the arteries, and the gradient fell significantly in each. In two of the cases in which results were evaluated by lung perfusion scan, blood flow to the lung served by a dilated vessel was shown to have increased significantly in each.

Anatomic features of the undilated pulmonary arteries. The underlying histologic appearance of the hypoplastic or stenotic pulmonary arteries was different in each case. The pulmonary arteries in patient 1 had intimal proliferation and medial hypertrophy. There was a
paucity of elastic fibers in the media. Patient 2 exhibited hypoplasia of the central pulmonary arteries. Histologically, the intima, media, and adventitia appeared normal. In patient 3 the arteries displayed a diffuse hypoplasia with a moderate amount of intimal proliferation. The media was normal. In patient 4 the media was thickened but the vessel otherwise appeared normal.

**Mechanisms of successful balloon dilation in seven pulmonary arteries.** One pulmonary artery from patient 1, one from patient 2, three from patient 3, and two from patient 4 were successfully dilated, suggesting that in these four patients, the differences in underlying histologic appearance did not significantly interfere with achieving successful dilation.

In each of the seven successfully dilated vessels, intimal interruption was evident. All seven had histologic evidence of significant medial tears, and in five the medial tear extended through to the adventitia. The adventitia remained intact in all seven successfully dilated arteries.

At the site of the transmedial tear, the media and intima separated in a wedge-shaped fashion, leaving a gap that represented up to 25% of the wall circumference. These gaps, produced by separation of contiguous intima and media and covered by stretched adventitia, were responsible for the increased luminal cross-sectional area.

**Mechanisms of healing.** In the six vessels evaluated after 4 or more months, separation of the intima from the media and tears of the media had healed with deposits of dense collagen and varying amounts of elastic fibers. In patient 3, in the intermediate branch of the right pulmonary artery the intima reconstituted itself as a thick layer of fibrous tissue. This was the only successfully dilated vessel distal to a persistent severe obstruction. The intima remained fragmented in the other vessels with intimal fibrous thickening in the predilation state. In the seven successfully dilated arteries that were evaluated late, adventitial fibrous thickening produced by dense collagen fibers and some elastic tissue fibers was present. In the two vessels evaluated shortly after dilation, hemorrhage was prominent in the adventitial layer.

**Causes of failure.** The proximal right pulmonary artery in patient 3 was narrowed at the site of a previous Blalock-Taussig shunt and was too rigid to be dilated. Histologically, this vessel showed intimal fibrous proliferation, a normal media, and pronounced collagenous thickening of the adventitia and periadventitia. The intima of this vessel had been torn in numerous places by the balloon dilation; however, the media and adventitia remained intact, and the width of the vessel was unchanged. We can postulate that the thickened, dense periadventitia formed a nondilatable cast around the vessel. Moreover, multiple intimal fractures in this vessel did not increase luminal cross-sectional areas.

The cause of rupture of the left pulmonary artery in patient 1 is of concern but cannot be positively identified. There was a paucity of elastic tissue in the media of some of the vessels of this patient, but the amount of elastic tissue in the media in the left pulmonary artery near the site of rupture appeared normal. A possibility is that rupture of the dilating balloon focused dilating pressure at one site, thus causing rupture of the artery.

**Discussion**

Successful balloon dilation of seven pulmonary arterial branches in this report was in each instance associated with histologic evidence of medial disruption (transmedial tears in five arteries).

In an experimental study, Lock et al. created bilateral branch pulmonary arterial stenosis in newborn lambs. Balloon angioplasty was performed on nine long-term survivors. Angiographically, luminal diameter at the stenotic site was increased in all (mean increase 53%). Histologic examination of the dilated area in four lambs killed within 2 days after dilation revealed tears through the entire thickness of the intima and media in each. Blood had dissected into the media and between the media and adventitia. The tears did not extend through the adventitia. No aneurysms had formed.

Five lambs were killed later. In these the postdilation luminal diameter had been maintained. Structural interruptions of the intima and media had been reconstituted mainly by scar tissue.

Disruption of the media has been observed after balloon angioplasty of other nonatherosclerotic arterial stenoses. Resected specimens of aorta with coarctation from six children were experimentally dilated within 2 hr of surgical resection. Five specimens were dilated to 8 atmospheres of pressure and had an 80% to 100% increase in internal diameter. Histologically, tears extended into the media in four of the five specimens and completely through the media in three of these.

Lock et al. created experimental coarctation of the aorta in 13 lambs and subjected the resulting stenosis to balloon dilation. The site of balloon dilation was examined within the first 48 hr after dilation in seven lambs. In six cases tears separated the intima from the media, and the separation extended into the media. There was significant intramedial hemorrhage with
separation of medial elements. In seven other lambs killed 8 weeks to 1 year after dilation the dilated luminal diameter had been maintained. The intima was intact in each. Medial tears and separation of medial elements caused by earlier dilation had healed by scar formation. There were no aneurysms.

The cause(s) of luminal widening after balloon dilation of atherosclerotic coronary arteries remains undefined.

Baughman et al. performed balloon angioplasty on coronary arteries from 12 human cadavers. The angiographically determined transluminal diameter increased in 50 of 54 sites of dilation (93%). This increase in diameter was caused by disruption and tearing of the intima and media.

Histologic evidence of intimal and medial rupture as the means of luminal expansion has been shown to occur in dilation of human femoral and coronary arteries in vivo as well as in balloon dilation of cadaver coronary arteries, renal arteries, and canine aortas. On the other hand, other studies have failed to show medial tears or disruption secondary to dilation.

Medial tearing and separation of the torn sections of media forms the basis of enlargement of nonatherosclerotic arteries undergoing balloon dilation angioplasty. Some studies suggest that this same mechanism underlies the enlargement of atherosclerotic arteries during balloon dilation angioplasty.

References